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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	05/25/2021	11013729	16326.0018FPWO	6655

23552 7590 05/05/2021

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 321 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Pratibha S. Pilgaonkar, Mumbai, INDIA;
TOWA Pharmaceutical Europe, S.L. Unipersonal, Barcelona, SPAIN;
Maharukh T. Rustomjee, Mumbai, INDIA;
Anilkumar S. Gandhi, Mumbai, INDIA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 04/26/2021

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
04/26/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

Corrected ***Notice of Allowability***	**Application No.** 14/379,613	**Applicant(s)** Pilgaonkar et al.	
	Examiner LYNDSEY M BECKHARDT	**Art Unit** 1613	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Notice of Allowance mailed 04/07/2021.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☑ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☑ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/LMB/ Examiner, Art Unit 1613	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613

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MSN Exhibit 1002
Page 3 of 680

Continuation of 3. The allowed claim(s) is/are: 21,23,26,30,32,35-37 and 39-48

Corrected Notice of Allowability

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

Claims 21, 23, 26, 30, 32 and 40-48 are allowable. The restriction requirement of Groups I-III and species 1-4, as set forth in the Office action mailed on 06/02/2015, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Specifically, the restriction requirement of Groups I-III and species of organic acid, excipient, treatment and method of making is withdrawn. Claims 33-37, and 39, directed to a method of making and method of use are no longer withdrawn from consideration because the claim(s) requires all the limitations of an allowable claim.

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with E. Joseph Gess on 03/25/2021.

The application has been amended as follows:

Claim 33. (Cancelled)

Claim 34. (Cancelled)

Claim 35. A process for the preparation of the composition according to claim 23, comprising the step of mixing the first type of particles and the second type of particles with the at least one ~~at least one~~ pharmaceutically acceptable excipient.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: Pursuant to the Patent Board Decision on 01/12/2021, the instant invention is considered novel and unobvious over the closet prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 21, 23, 26, 30, 32, 35-37 and 39-48 are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY MARIE BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached on Monday, Tuesday and Thursday 7:30 to 3pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LMB/

Examiner, Art Unit 1613

/ANDREW S ROSENTHAL/
Primary Examiner, Art Unit 1613

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K31/4439 OR A61K9/14 OR A61K9/1617 OR A61K9/1652 OR A61K9/4833 OR A61K9/5026 OR A61K9/5042 OR A61K9/5084 OR A61K9/5089 OR A61P7/02	03/31/2021	LMB

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**
	No Classified Search		

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

/LMB/	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613

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MSN Exhibit 1002
Page 9 of 680

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

Search Notes		
Search Notes	**Date**	**Examiner**
East (keyword and Inventor) see attached	9/24/2015	LMB
Google (keyword) see attached East search terms	9/24/2015	LMB
East (keyword and Inventor) see attached	3/7/2016	LMB
Google (keyword) see attached East search terms	3/7/2016	LMB
East (keyword and Inventor) see attached	7/25/2017	LMB
East (keyword and Inventor) see attached	01/08/2018	LMB
East (keyword and Inventor) see attached	11/08/2018	LMB
Google (keyword) see attached East search terms	11/08/2018	LMB
East (keyword and Inventor) see attached	05/20/2019	LMB
East (keyword and Inventor) see attached	03/31/2021	LMB
CPC search (keyword limited) see attached	03/31/2021	LMB
Google (keyword) see attached	03/31/2021	LMB

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	East (keyword.clm.) see attached	03/31/2021	LMB

/LMB/	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613

IPR2025-01107
MSN Exhibit 1002
Page 10 of 680

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

CPC						
Symbol					Type	Version
A61K	/	31	/	4439	F	2013-01-01
A61K	/	9	/	1617	I	2013-01-01
A61K	/	9	/	1652	I	2013-01-01
A61K	/	9	/	5026	I	2013-01-01
A61K	/	9	/	5084	I	2013-01-01
A61K	/	9	/	5089	I	2013-01-01
A61K	/	9	/	14	I	2013-01-01
A61K	/	9	/	4833	I	2013-01-01
A61K	/	9	/	5042	I	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
	/		/					

/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613	20 April 2021	Total Claims Allowed:	
(Assistant Examiner)	(Date)	18	
/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613	21 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20210419A

IPR2025-01107
MSN Exhibit 1002
Page 11 of 680

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	31	/	4439	
A61K9/16	/	9	/	16	
A61K9/50	/	9	/	50	
A61K9/14	/	9	/	14	
A61K9/48	/	9	/	48	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613	20 April 2021	Total Claims Allowed:	
(Assistant Examiner)	(Date)	18	
/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613	21 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20210419A

IPR2025-01107
MSN Exhibit 1002
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	**Art Unit**
	LYNDSEY M BECKHARDT	1613

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19		28		37		46				
	2		11		20		29		38		47				
	3		12		21		30		39		48				
	4		13		22		31		40						
	5		14		23		32		41						
	6		15		24		33		42						
	7		16		25		34		43						
	8		17		26		35		44						
	9		18		27		36		45						

/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613	20 April 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	18	
/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613	21 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20210419A

IPR2025-01107
MSN Exhibit 1002
Page 13 of 680

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MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

Courtesy Reminder for
Application Serial No: 14/379,613

Attorney Docket No: 16326.0018FPWO
Customer Number: 23552
Date of Electronic Notification: 04/07/2021

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:
USPTO23552@merchantgould.com

To view your correspondence online or update your email addresses, please visit us anytime at **https://ppair-my.uspto.gov/pair/PrivatePair.**
If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov or call 1-866-217-9197.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23552 7590 04/07/2021
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

TITLE OF INVENTION: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/07/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
BECKHARDT, LYNDSEY MARIE	1613	424-490000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Melissa M. Hayworth
2 E. Joseph Gess
3 Daniel R. Evans

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: TOWA Pharmaceutical Europe, S.L. Unipersonal

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Barcelona, Spain

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ☒ Corporation or other private group entity ❑ Government

4a. Fees submitted: ☒ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 132725

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Melissa M. Hayworth/ Date 9 April 2021

Typed or printed name Melissa M. Hayworth Registration No. 45774

IPR2025-01107
MSN Exhibit 1002
Page 15 of 680

Electronic Patent Application Fee Transmittal

Application Number:	14379613
Filing Date:	19-Aug-2014
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Filer:	Melissa M. Hayworth/Lisa Kenney
Attorney Docket Number:	16326.0018FPWO

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1200**

Electronic Acknowledgement Receipt	
EFS ID:	42414024
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	09-APR-2021
Filing Date:	19-AUG-2014
Time Stamp:	14:07:57
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1200
RAM confirmation Number	E202149E09163170
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	16326-0018FPWO_Issue_Fee_Transmittal.PDF	1466350 7f728dcbc1f1c102cd78225e6dd5c50916b55d46	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30874 b4c65e8e6c7b179c2b11f80de1da121ff26b5ea4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1497224		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Pilgoankar et al.	Examiner:	Lyndsey M. Beckhardt
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.:	23552	Confirmation No.:	6655
Title:	Oral Pharmaceutical Compositions of Dabigatran Etexilate		

STATEMENT OF SUBSTANCE OF INTERVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Attention: Commissioner for Patents

In response to the Interview Summary mailed on 7 April 2021, Applicant offers the following statement of substance. Applicant notes that the telephonic interview was conducted 31 March 2021 with Applicant's representative E. Joseph Gess.

After the Patent Board Decision dated 12 January 2021 reversing the Examiner's outstanding rejections, the Examiner called to discuss rejoining withdrawn claims and allowing the present application. Applicant's representative agreed to a minor amendment to claim 35 to correct a typographical error.

With regard to method of treatment claims 33 and 34, the Examiner improperly insisted that these claims be amended to remove "preventing venous thromboembolic events in adult patients who have undergone hip replacement surgery", alleging that this amendment was necessary to overcome a 112 first paragraph issue. However, as pointed out to the Examiner during the interview, dabigatran is approved by the FDA with an indication of "[f]or the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery." A copy of the current dabigatran prescribing information is attached hereto to complete the record. Accordingly, Applicant strenuously disagrees that there is any issue under 35 U.S.C. §112 with regard to claims 33 and 34 as were pending.

Merely to expedite allowance of the other claims, Applicant agreed to cancel claims 33 and 34. Applicant expressly reserves the right to file a continuation application directed to this

subject matter. However, Applicant notes that the current allowed claims relate to the novel composition comprising dabigatran, and thus, cover its use for any methods of treatment.

Applicant further notes that a Notice of Allowance and Fees Due was mailed 7 April 2021. The allowed claims are claims 21, 23, 26, 30, 32, 35-37 and 39-48 – as indicated in the "Conclusion" on page 3 of the Notice of Allowability. However, the Continuation Sheet improperly recites that the allowed claims are 21, 23, 26, 30, 32, 35-37 and 39-45 and on page 2 of the Notice of Allowability under "Election/Restrictions" it is indicated that claims 21, 23, 26, 30, 32 and 40-48 are allowable. For clarification of the record, the allowed claims are claims 21, 23, 26, 30, 32, 35-37 and 39-48 – as indicated in the "Conclusion" on page 3 of the Notice of Allowability, and Applicant is proceeding on this basis.

If there are any remaining questions or concerns regarding the present application or this paper, Applicant requests that the Examiner telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

Date: 9 April 2021

/Melissa M. Hayworth/
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IPR2025-01107
MSN Exhibit 1002
Page 21 of 680

FULL PRESCRIBING INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. If anticoagulation with PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4, 2.5, 2.6) and Warnings and Precautions (5.1)]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of PRADAXA and neuraxial procedures is not known**

***[see Warnings and Precautions (5.3)]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation

PRADAXA is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

1.2 Treatment of Deep Venous Thrombosis and Pulmonary Embolism

PRADAXA is indicated for the treatment of deep venous thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days.

1.3 Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism

PRADAXA is indicated to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have been previously treated.

1.4 Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery

PRADAXA is indicated for the prophylaxis of deep vein thrombosis and pulmonary embolism, in patients who have undergone hip replacement surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Indication	Dosage	
Reduction in Risk of Stroke and Systemic Embolism in Non-valvular AF	CrCl >30 mL/min:	150 mg twice daily
	CrCl 15 to 30 mL/min:	75 mg twice daily
	CrCl <15 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl 30 to 50 mL/min with concomitant use of P-gp inhibitors:	Reduce dose to 75 mg twice daily if given with P-gp inhibitors dronedarone or systemic ketoconazole.
	CrCl <30 mL/min with concomitant use of P-gp inhibitors:	Avoid co-administration
Treatment of DVT and PE **Reduction in the Risk of Recurrence of DVT and PE**	CrCl >30 mL/min:	150 mg twice daily
	CrCl ≤30 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl <50 mL/min with concomitant use of P-gp inhibitors:	Avoid co-administration
Prophylaxis of DVT and PE Following Hip Replacement Surgery	CrCl >30 mL/min:	110 mg for first day, then 220 mg once daily
	CrCl ≤30 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl <50 mL/min with concomitant use of P-gp inhibitors:	Avoid co-administration

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of PRADAXA is 150 mg taken orally, twice daily. For patients with severe renal impairment (CrCl 15-30 mL/min), the recommended dose of PRADAXA is 75 mg twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Dosing recommendations for patients with a CrCl <15 mL/min or on dialysis cannot be provided.

Treatment of Deep Venous Thrombosis and Pulmonary Embolism
For patients with CrCl >30 mL/min, the recommended dose of PRADAXA is 150 mg taken orally, twice daily, after 5-10 days of parenteral anticoagulation. Dosing recommendations for patients with a CrCl ≤30 mL/min or on dialysis cannot be provided *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
For patients with CrCl >30 mL/min, the recommended dose of PRADAXA is 150 mg taken orally, twice daily after previous treatment. Dosing recommendations for patients with a CrCl ≤30 mL/min or on dialysis cannot be provided *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
For patients with CrCl >30 mL/min, the recommended dose of PRADAXA is 110 mg taken orally 1-4 hours after surgery and after hemostasis has been achieved, then 220 mg taken once daily for 28-35 days. If PRADAXA is not started on the day of surgery, after hemostasis has been achieved initiate treatment with 220 mg once daily. Dosing recommendations for patients with a CrCl ≤30 mL/min or on dialysis cannot be provided *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.2, 12.3)]*.

2.2 Dosing Adjustments
Assess renal function prior to initiation of treatment with PRADAXA. Periodically assess renal function as clinically indicated (i.e., more frequently in clinical situations that may be associated with a decline in renal function) and adjust therapy accordingly. Discontinue PRADAXA in patients who develop acute renal failure while on PRADAXA and consider alternative anticoagulant therapy.

Generally, the extent of anticoagulation does not need to be assessed. When necessary, use aPTT or ECT, and not INR, to assess for anticoagulant activity in patients on PRADAXA *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
In patients with moderate renal impairment (CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole can be expected to produce dabigatran exposure similar to that observed in severe renal impairment. Reduce the dose of PRADAXA to 75 mg twice daily *[see Warnings and Precautions (5.5), Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Dosing recommendations for patients with CrCl ≤30 mL/min cannot be provided. Avoid use of concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
Dosing recommendations for patients with CrCl ≤30 mL/min or on dialysis cannot be provided. Avoid use of concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.3) and Clinical Pharmacology (12.2, 12.3)]*.

2.3 Instructions to Patients
Instruct patients to swallow the capsules whole. PRADAXA should be taken with a full glass of water. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure *[see Clinical Pharmacology (12.3)]*.

If a dose of PRADAXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of PRADAXA should not be doubled to make up for a missed dose.

2.4 Converting from or to Warfarin
When converting patients from warfarin therapy to PRADAXA, discontinue warfarin and start PRADAXA when the INR is below 2.0.

When converting from PRADAXA to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:
- For CrCl ≥50 mL/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing PRADAXA.
- For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA.
- For CrCl <15 mL/min, no recommendations can be made.

Because PRADAXA can increase INR, the INR will better reflect warfarin's effect only after PRADAXA has been stopped for at least 2 days *[see Clinical Pharmacology (12.2)]*.

2.5 Converting from or to Parenteral Anticoagulants
For patients currently receiving a parenteral anticoagulant, start PRADAXA 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For patients currently taking PRADAXA, wait 12 hours (CrCl ≥30 mL/min) or 24 hours (CrCl <30 mL/min) after the last dose of PRADAXA before initiating treatment with a parenteral anticoagulant *[see Clinical Pharmacology (12.3)]*.

2.6 Discontinuation for Surgery and Other Interventions
If possible, discontinue PRADAXA 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

If surgery cannot be delayed, there is an increased risk of bleeding *[see Warnings and Precautions (5.2)]*. This risk of bleeding should be weighed against the urgency of intervention *[see Warnings and Precautions (5.1, 5.3)]*. Use a specific reversal agent (idarucizumab) in case of emergency surgery or urgent procedures when reversal of the anticoagulant effect of dabigatran is needed. Refer to the idarucizumab prescribing information for additional information. Restart PRADAXA as soon as medically appropriate.

3 DOSAGE FORMS AND STRENGTHS

150 mg capsules with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a white opaque body imprinted in black with "R150".

110 mg capsules with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted in black with "R110".

75 mg capsules with a white opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a white opaque body imprinted in black with "R75".

4 CONTRAINDICATIONS

PRADAXA is contraindicated in patients with:

- Active pathological bleeding *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.
- History of a serious hypersensitivity reaction to PRADAXA (e.g., anaphylactic reaction or anaphylactic shock) *[see Adverse Reactions (6.1)]*.
- Mechanical prosthetic heart valve *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including PRADAXA, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant and restart PRADAXA as soon as medically appropriate *[see Dosage and Administration (2.4, 2.5, 2.6)]*.

5.2 Risk of Bleeding

PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue PRADAXA in patients with active pathological bleeding *[see Dosage and Administration (2.2)]*.

Risk factors for bleeding include the concomitant use of other drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs). PRADAXA's anticoagulant activity and half-life are increased in patients with renal impairment *[see Clinical Pharmacology (12.2)]*.

Reversal of Anticoagulant Effect:

A specific reversal agent (idarucizumab) for dabigatran is available when reversal of the anticoagulant effect of dabigatran is needed:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding

Hemodialysis can remove dabigatran; however the clinical experience supporting the use of hemodialysis as a treatment for bleeding is limited *[see Overdosage (10)]*. Prothrombin complex concentrates, or recombinant Factor VIIa may be considered but their use has not been evaluated in clinical trials. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of dabigatran. Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

To reduce the potential risk of bleeding associated with the concurrent use of dabigatran and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of dabigatran *[see Clinical Pharmacology (12.3)]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of dabigatran is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

5.4 Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves

The safety and efficacy of PRADAXA in patients with bileaflet mechanical prosthetic heart valves was evaluated in the RE-ALIGN trial, in which patients with bileaflet mechanical prosthetic heart valves (recently implanted or implanted more than three months prior to enrollment) were randomized to dose adjusted warfarin or 150 mg, 220 mg, or 300 mg of PRADAXA twice a day. RE-ALIGN was terminated early due to the occurrence of significantly more thromboembolic events (valve thrombosis, stroke, transient ischemic attack, and myocardial infarction) and an excess of major bleeding (predominantly post-operative pericardial effusions requiring intervention for hemodynamic compromise) in the PRADAXA treatment arm as compared to the warfarin treatment arm. These bleeding and thromboembolic events were seen both in patients who were initiated on PRADAXA post-operatively within three days of mechanical bileaflet valve implantation, as well as in patients whose valves had been implanted more than three months prior to enrollment. Therefore, the use of PRADAXA is contraindicated in patients with mechanical prosthetic valves *[see Contraindications (4)]*.

The use of PRADAXA for the prophylaxis of thromboembolic events in patients with atrial fibrillation in the setting of other forms of valvular heart disease, including the presence of a bioprosthetic heart valve, has not been studied and is not recommended.

5.5 Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure

The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided *[see Clinical Pharmacology (12.3)]*.

P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran *[see Clinical Pharmacology (12.3)]*. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
Reduce the dose of PRADAXA to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with PRADAXA in patients with moderate renal impairment (CrCl 30-50 mL/min). Avoid use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) *[see Drug Interactions (7.1) and Use in Specific Populations (8.6)]*.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Avoid use of PRADAXA and concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Drug Interactions (7.2) and Use in Specific Populations (8.6)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
Avoid use of PRADAXA and concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Drug Interactions (7.3) and Use in Specific Populations (8.6)]*.

5.6 Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome
Direct-acting oral anticoagulants (DOACs), including PRADAXA, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple-positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:

- Increased Risk of Thrombotic Events after Premature Discontinuation *[see Warnings and Precautions (5.1)]*
- Risk of Bleeding *[see Warnings and Precautions (5.2)]*
- Spinal/Epidural Anesthesia or Puncture *[see Warnings and Precautions (5.3)]*
- Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves *[see Warnings and Precautions (5.4)]*
- Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome *[see Warnings and Precautions (5.6)]*

The most serious adverse reactions reported with PRADAXA were related to bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
The RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study provided safety information on the use of two doses of PRADAXA and warfarin *[see Clinical Studies (14.1)]*. The numbers of patients and their exposures are described in Table 1. Limited information is presented on the 110 mg dosing arm because this dose is not approved.

Table 1 Summary of Treatment Exposure in RE-LY

	PRADAXA 110 mg twice daily	PRADAXA 150 mg twice daily	Warfarin
Total number treated	5983	6059	5998
Exposure			
> 12 months	4936	4939	5193
> 24 months	2387	2405	2470
Mean exposure (months)	20.5	20.3	21.3
Total patient-years	10,242	10,261	10,659

Drug Discontinuation in RE-LY
The rates of adverse reactions leading to treatment discontinuation were 21% for PRADAXA 150 mg and 16% for warfarin. The most frequent adverse reactions leading to discontinuation of PRADAXA were bleeding and gastrointestinal events (i.e., dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea).

Bleeding [see Warnings and Precautions (5.2)]

Table 2 shows the number of adjudicated major bleeding events during the treatment period in the RE-LY study, with the bleeding rate per 100 subject-years (%). Major bleeding is defined as bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells, bleeding at a critical site or with a fatal outcome. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 2 Adjudicated Major Bleeding Events in Treated Patients[a]

Event	PRADAXA 150 mg N = 6059 n (%/year[b])	Warfarin N = 5998 n (%/year[b])	PRADAXA 150 mg vs. Warfarin HR (95% CI)
Major Bleeding[c]	350 (3.47)	374 (3.58)	0.97 (0.84, 1.12)
Intracranial Hemorrhage (ICH)[d]	23 (0.22)	82 (0.77)	0.29 (0.18, 0.46)
Hemorrhagic Stroke[e]	6 (0.06)	40 (0.37)	0.16 (0.07, 0.37)
Other ICH	17 (0.17)	46 (0.43)	0.38 (0.22, 0.67)
Gastrointestinal	162 (1.59)	111 (1.05)	1.51 (1.19, 1.92)
Fatal Bleeding[f]	7 (0.07)	16 (0.15)	0.45 (0.19, 1.10)
ICH	3 (0.03)	9 (0.08)	0.35 (0.09, 1.28)
Non-intracranial[g]	4 (0.04)	7 (0.07)	0.59 (0.17, 2.02)

[a]Patients during treatment or within 2 days of stopping study treatment. Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories.
[b]Annual event rate per 100 pt-years = 100 * number of subjects with event/subject-years. Subject-years is defined as cumulative number of days from first drug intake to event date, date of last drug intake + 2, death date (whatever occurred first) across all treated subjects divided by 365.25. In case of recurrent events of the same category, the first event was considered.
[c]Defined as bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site or with fatal outcome.
[d]Intracranial bleed included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.
[e]On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14 Clinical Studies.
[f]Fatal bleed: Adjudicated major bleed as defined above with investigator reported fatal outcome and adjudicated death with primary cause from bleeding.
[g]Non-intracranial fatal bleed: Adjudicated major bleed as defined above and adjudicated death with primary cause from bleeding but without symptomatic intracranial bleed based on investigator's clinical assessment.

There was a higher rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg than in patients receiving warfarin (6.6% vs. 4.2%, respectively).

The risk of major bleeds was similar with PRADAXA 150 mg and warfarin across major subgroups defined by baseline characteristics (see Figure 1), with the exception of age, where there was a trend towards a higher incidence of major bleeding on PRADAXA (hazard ratio 1.2, 95% CI: 1.0 to 1.5) for patients ≥75 years of age.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Pilgoankar et al.	Examiner:	Lyndsey M. Beckhardt
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.:	23552	Confirmation No.:	6655
Title:	Oral Pharmaceutical Compositions of Dabigatran Etexilate		

STATEMENT OF SUBSTANCE OF INTERVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Attention: Commissioner for Patents

In response to the Interview Summary mailed on 7 April 2021, Applicant offers the following statement of substance. Applicant notes that the telephonic interview was conducted 31 March 2021 with Applicant's representative E. Joseph Gess.

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If there are any remaining questions or concerns regarding the present application or this paper, Applicant requests that the Examiner telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

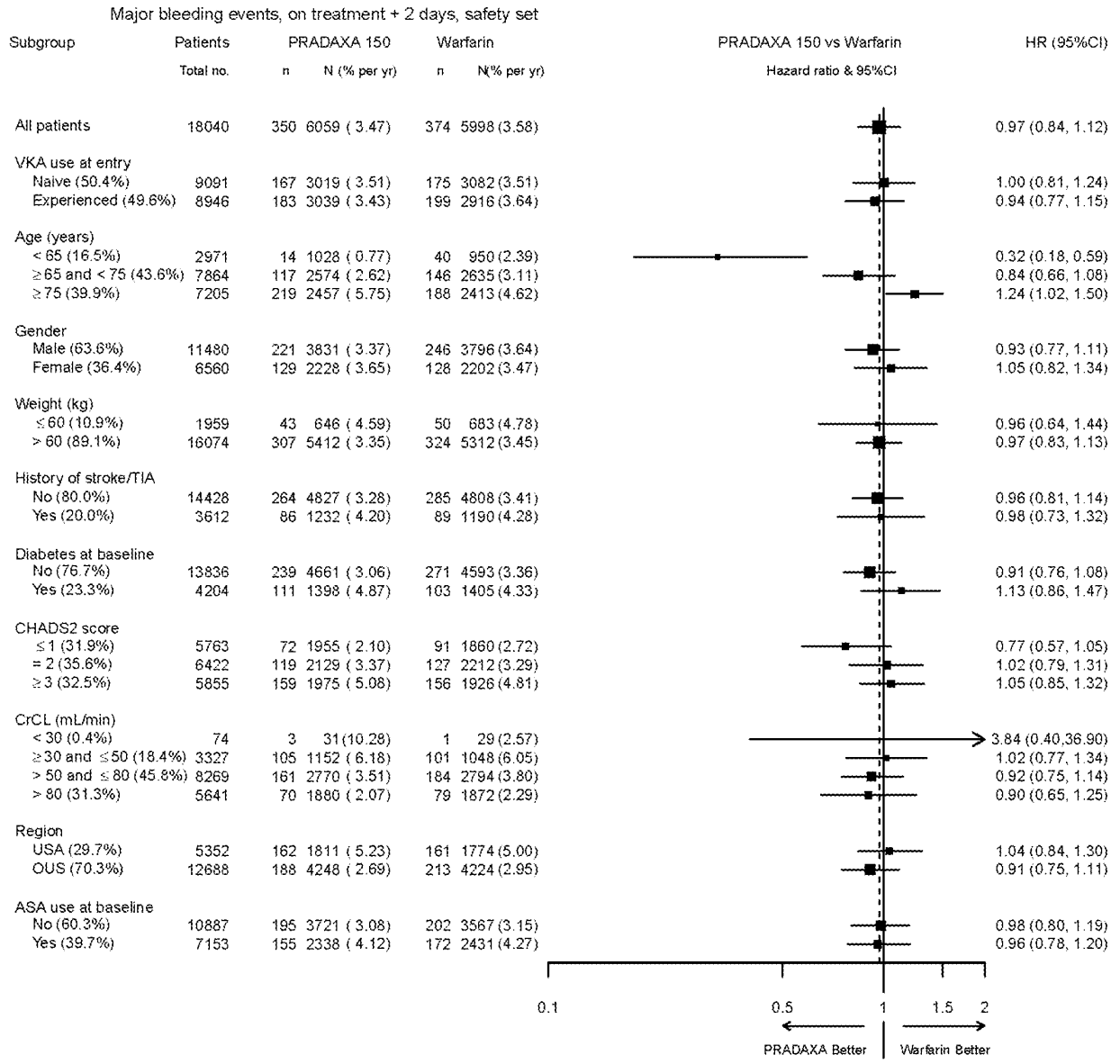
Date: 9 April 2021

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Figure 1 Adjudicated Major Bleeding by Baseline Characteristics Including Hemorrhagic Stroke Treated Patients



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Gastrointestinal Adverse Reactions

Patients on PRADAXA 150 mg had an increased incidence of gastrointestinal adverse reactions (35% vs. 24% on warfarin). These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and gastrointestinal ulcer).

Hypersensitivity Reactions

In the RE-LY study, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in <0.1% of patients receiving PRADAXA.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism

PRADAXA was studied in 4387 patients in 4 pivotal, parallel, randomized, double-blind trials. Three of these trials were active-controlled (warfarin) (RE-COVER, RE-COVER II, and RE-MEDY), and one study (RE-SONATE) was placebo-controlled. The demographic characteristics were similar among the 4 pivotal studies and between the treatment groups within these studies. Approximately 60% of the treated patients were male, with a mean age of 55.1 years. The majority of the patients were white (87.7%), 10.3% were Asian, and 1.9% were black with a mean CrCl of 105.6 mL/min.

Bleeding events for the 4 pivotal studies were classified as major bleeding events if at least one of the following criteria applied: fatal bleeding, symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding), bleeding causing a fall in hemoglobin level of 2.0 g/dL (1.24 mmol/L or more, or leading to transfusion of 2 or more units of whole blood or red cells).

RE-COVER and RE-COVER II studies compared PRADAXA 150 mg twice daily and warfarin for the treatment of deep vein thrombosis and pulmonary embolism. Patients received 5-10 days of an approved parenteral anticoagulant therapy followed by 6 months, with mean exposure of 164 days, of oral only treatment; warfarin was overlapped with parenteral therapy. Table 3 shows the number of patients experiencing bleeding events in the pooled analysis of RE-COVER and RE-COVER II studies during the full treatment including parenteral and oral only treatment periods after randomization.

Table 3 Bleeding Events in RE-COVER and RE-COVER II Treated Patients

	Bleeding Events-Full Treatment Period Including Parenteral Treatment		
	PRADAXA 150 mg twice daily N (%)	**Warfarin N (%)**	**Hazard Ratio (95% CI)[c]**
Patients	**N=2553**	**N=2554**	
Major bleeding event[a]	37 (1.4)	51 (2.0)	0.73 (0.48, 1.11)
Fatal bleeding	1 (0.04)	2 (0.1)	
Bleeding in a critical area or organ	7 (0.3)	15 (0.6)	
Fall in hemoglobin ≥2 g/dL or transfusion ≥2 units of whole blood or packed red blood cells	32 (1.3)	38 (1.5)	
Bleeding sites for MBE[b]			
Intracranial	2 (0.1)	5 (0.2)	
Retroperitoneal	2 (0.1)	1 (0.04)	
Intraarticular	2 (0.1)	4 (0.2)	
Intramuscular	2 (0.1)	6 (0.2)	
Gastrointestinal	15 (0.6)	14 (0.5)	
Urogenital	7 (0.3)	14 (0.5)	
Other	8 (0.3)	8 (0.3)	
Clinically relevant non-major bleeding	101 (4.0)	170 (6.7)	0.58 (0.46, 0.75)
Any bleeding	411 (16.1)	567 (22.7)	0.70 (0.61, 0.79)

Note: MBE can belong to more than one criterion.
[a]Patients with at least one MBE.
[b]Bleeding site based on investigator assessment. Patients can have more than one site of bleeding.
[c]Confidence interval

The rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg in the full treatment period was 3.1% (2.4% on warfarin).

The RE-MEDY and RE-SONATE studies provided safety information on the use of PRADAXA for the reduction in the risk of recurrence of deep vein thrombosis and pulmonary embolism.

RE-MEDY was an active-controlled study (warfarin) in which 1430 patients received PRADAXA 150 mg twice daily following 3 to 12 months of oral anticoagulant regimen. Patients in the treatment studies who rolled over into the RE-MEDY study had a combined treatment duration of up to more than 3 years, with mean exposure of 473 days. Table 4 shows the number of patients experiencing bleeding events in the study.

Table 4 Bleeding Events in RE-MEDY Treated Patients

	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI)[c]
Patients	**N=1430**	**N=1426**	
Major bleeding event[a]	13 (0.9)	25 (1.8)	0.54 (0.25, 1.16)
Fatal bleeding	0	1 (0.1)	
Bleeding in a critical area or organ	7 (0.5)	11 (0.8)	
Fall in hemoglobin ≥2 g/dL or transfusion ≥2 units of whole blood or packed red blood cells	7 (0.5)	16 (1.1)	
Bleeding sites for MBE[b]			
Intracranial	2 (0.1)	4 (0.3)	
Intraocular	4 (0.3)	2 (0.1)	
Retroperitoneal	0	1 (0.1)	
Intraarticular	0	2 (0.1)	
Intramuscular	0	4 (0.3)	
Gastrointestinal	4 (0.3)	8 (0.6)	
Urogenital	1 (0.1)	1 (0.1)	
Other	2 (0.1)	4 (0.3)	
Clinically relevant non-major bleeding	71 (5.0)	125 (8.8)	0.56 (0.42, 0.75)
Any bleeding	278 (19.4)	373 (26.2)	0.71 (0.61, 0.83)

Note: MBE can belong to more than one criterion.
[a]Patients with at least one MBE.
[b]Bleeding site based on investigator assessment. Patients can have more than one site of bleeding.
[c]Confidence interval

In the RE-MEDY study, the rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg was 3.1% (2.2% on warfarin).

RE-SONATE was a placebo-controlled study in which 684 patients received PRADAXA 150 mg twice daily following 6 to 18 months of oral anticoagulant regimen. Patients in the treatment studies who rolled over into the RE-SONATE study had combined treatment duration up to 9 months, with mean exposure of 165 days. Table 5 shows the number of patients experiencing bleeding events in the study.

Table 5 Bleeding Events in RE-SONATE Treated Patients

	PRADAXA 150 mg twice daily N (%)	Placebo N (%)	Hazard Ratio (95% CI)[c]
Patients	**N=684**	**N=659**	
Major bleeding event[a]	2 (0.3)	0	
Bleeding in a critical area or organ	0	0	
Gastrointestinal[b]	2 (0.3)	0	
Clinically relevant non-major bleeding	34 (5.0)	13 (2.0)	2.54 (1.34, 4.82)
Any bleeding	72 (10.5)	40 (6.1)	1.77 (1.20, 2.61)

Note: MBE can belong to more than one criterion.
[a]Patients with at least one MBE.
[b]Bleeding site based on investigator assessment. Patients can have more than one site of bleeding.
[c]Confidence interval

In the RE-SONATE study, the rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg was 0.7% (0.3% on placebo).

Clinical Myocardial Infarction Events
In the active-controlled VTE studies, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA [20 (0.66 per 100 patient-years)] than in those who received warfarin [5 (0.17 per 100 patient-years)]. In the placebo-controlled study, a similar rate of non-fatal and fatal clinical myocardial infarction was reported in patients who received PRADAXA [1 (0.32 per 100 patient-years)] and in those who received placebo [1 (0.34 per 100 patient-years)].

Gastrointestinal Adverse Reactions
In the four pivotal studies, patients on PRADAXA 150 mg had a similar incidence of gastrointestinal adverse reactions (24.7% vs. 22.7% on warfarin). Dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) occurred in patients on PRADAXA in 7.5% vs. 5.5% on warfarin, and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage) occurred at 3.0% vs. 1.7%, respectively.

Hypersensitivity Reactions
In the 4 pivotal studies, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in 0.1% of patients receiving PRADAXA.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
PRADAXA was studied in 5476 patients, randomized and treated in two double-blind, active-controlled non-inferiority trials (RE-NOVATE and RE-NOVATE II). The demographic characteristics were similar across the two studies and between the treatment groups within these studies. Approximately 45.3% of the treated patients were male, with a mean age of 63.2 years. The majority of the patients were white (96.1%), 3.6% were Asian, and 0.3% were black with a mean CrCl of 92 mL/min.

Bleeding events for the RE-NOVATE and RE-NOVATE II studies were classified as major bleeding events if at least one of the following criteria applied: fatal bleeding, symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or retroperitoneal bleeding), bleeding causing a fall in hemoglobin level of 2.0 g/dL (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells, requiring treatment cessation or leading to re-operation.

The RE-NOVATE study compared PRADAXA 75 mg taken orally 1-4 hours after surgery followed by 150 mg once daily, PRADAXA 110 mg taken orally 1-4 hours after surgery followed by 220 mg once daily and subcutaneous enoxaparin 40 mg once daily initiated the evening before surgery for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who had undergone hip replacement surgery. The RE-NOVATE II study compared PRADAXA 110 mg taken orally 1-4 hours after surgery followed by 220 mg once daily and subcutaneous enoxaparin 40 mg once daily initiated the evening before surgery for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who had undergone hip replacement surgery. In the RE-NOVATE and RE-NOVATE II studies, patients received 28-35 days of PRADAXA or enoxaparin with median exposure of 33 days. Tables 6 and 7 show the number of patients experiencing bleeding events in the analysis of RE-NOVATE and RE-NOVATE II.

Table 6 Bleeding Events in RE-NOVATE Treated Patients

	PRADAXA 220 mg N (%)	**Enoxaparin N (%)**
Patients	**N=1146**	**N=1154**
Major bleeding event	23 (2.0)	18 (1.6)
Clinically relevant non-major bleeding	48 (4.2)	40 (3.5)
Any bleeding	141 (12.3)	132 (11.4)

Table 7 Bleeding Events in RE-NOVATE II Treated Patients

	PRADAXA 220 mg N (%)	**Enoxaparin N (%)**
Patients	**N=1010**	**N=1003**
Major bleeding event	14 (1.4)	9 (0.9)
Clinically relevant non-major bleeding	26 (2.6)	20 (2.0)
Any bleeding	98 (9.7)	83 (8.3)

In the two studies, the rate of major gastrointestinal bleeds in patients receiving PRADAXA and enoxaparin was the same (0.1%) and for any gastrointestinal bleeds was 1.4% for PRADAXA 220 mg and 0.9% for enoxaparin.

Gastrointestinal Adverse Reactions
In the two studies, the incidence of gastrointestinal adverse reactions for patients on PRADAXA 220 mg and enoxaparin was 39.5% and 39.5%, respectively. Dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) occurred in patients on PRADAXA 220 mg in 4.1% vs. 3.8% on enoxaparin, and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage) occurred at 0.6% vs. 1.0%, respectively.

Hypersensitivity Reactions
In the two studies, drug hypersensitivity (such as urticaria, rash, and pruritus) was reported in 0.3% of patients receiving PRADAXA 220 mg.

Clinical Myocardial Infarction Events
In the two studies, clinical myocardial infarction was reported in 2 (0.1%) of patients who received PRADAXA 220 mg and 6 (0.3%) of patients who received enoxaparin.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of PRADAXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post approval use of PRADAXA: angioedema, thrombocytopenia, esophageal ulcer, alopecia, neutropenia, agranulocytosis.

7 DRUG INTERACTIONS

7.1 Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided *[see Clinical Pharmacology (12.3)]*.

P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran *[see Clinical Pharmacology (12.3)]*. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

In patients with moderate renal impairment (CrCl 30-50 mL/min), reduce the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitors dronedarone or systemic ketoconazole. The use of the P-gp inhibitors verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor does not require a dose adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

The concomitant use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

7.2 Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Avoid use of PRADAXA and P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

7.3 Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
In patients with CrCl ≥50 mL/min who have concomitant administration of P-gp inhibitors such as dronedarone or systemic ketoconazole, it may be helpful to separate the timing of administration of dabigatran and the P-gp inhibitor by several hours. The concomitant use of PRADAXA and P-gp inhibitors in patients with CrCl <50 mL/min should be avoided *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6) and Clinical Pharmacology (12.2, 12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on PRADAXA use in pregnant women are insufficient to determine drug-associated risks for adverse developmental outcomes. There are risks to the mother associated with untreated venous thromboembolism in pregnancy and a risk of hemorrhage in the mother and fetus associated with the use of anticoagulants *(see Clinical Considerations)*. In pregnant rats treated from implantation until weaning, dabigatran increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition at an exposure 2.6 times the human exposure. At a similar exposure, dabigatran decreased the number of implantations when rats were treated prior to mating and up to implantation (gestation Day 6). Dabigatran administered to pregnant rats and rabbits during organogenesis up to exposures 8 and 13 times the human exposure, respectively, did not induce major malformations. However, the incidence of delayed or irregular ossification of fetal skull bones and vertebrae was increased in the rat *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnancy confers an increased risk for thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

Fetal/Neonatal adverse reaction

Use of anticoagulants, including PRADAXA, may increase the risk of bleeding in the fetus and neonate. Monitor neonates for bleeding *[see Warnings and Precautions (5.2)]*.

Labor or delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. PRADAXA use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider discontinuation or use of shorter acting anticoagulant as delivery approaches *[see Warnings and Precautions (5.2, 5.3)]*.

Data

Animal Data

Dabigatran has been shown to decrease the number of implantations when male and female rats were treated at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at MRHD of 300 mg/day based on area under the curve [AUC] comparisons) prior to mating and up to implantation (gestation Day 6). Treatment of pregnant rats after implantation with dabigatran at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Dabigatran administered to pregnant rats and rabbits during organogenesis up to maternally toxic doses of 200 mg/kg (8 and 13 times the human exposure, respectively, at a MRHD of 300 mg/day based on AUC comparisons) did not induce major malformations, but increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat.

Death of offspring and mother rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at a dose of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons).

8.2 Lactation

Risk Summary

There are no data on the presence of dabigatran in human milk, the effects on the breastfed child, or on milk production. Dabigatran and/or its metabolites were present in rat milk. Breastfeeding is not recommended during treatment with PRADAXA.

8.4 Pediatric Use

Safety and effectiveness of PRADAXA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the RE-LY study, 82% were 65 and over, while 40% were 75 and over. The risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups *[see Warnings and Precautions (5), Adverse Reactions (6.1), and Clinical Studies (14.1)]*.

8.6 Renal Impairment

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation

No dose adjustment of PRADAXA is recommended in patients with mild or moderate renal impairment *[see Clinical Pharmacology (12.3)]*. Reduce the dose of PRADAXA in patients with severe renal impairment (CrCl 15-30 mL/min) *[see Dosage and Administration (2.1, 2.2) and Clinical Pharmacology (12.3)]*. Dosing recommendations for patients with CrCl <15 mL/min or on dialysis cannot be provided.

Adjust dose appropriately in patients with renal impairment receiving concomitant P-gp inhibitors *[see Warnings and Precautions (5.5), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Patients with severe renal impairment (CrCl ≤30 mL/min) were excluded from RE-COVER.

Dosing recommendations for patients with CrCl ≤30 mL/min or on dialysis cannot be provided. Avoid use of PRADAXA with concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
Patients with severe renal impairment (CrCl <30 mL/min) were excluded from RE-NOVATE and RE-NOVATE II.

Dosing recommendations for patients with CrCl <30 mL/min or on dialysis cannot be provided.

Avoid use of PRADAXA with concomitant P-gp inhibitors in patients with CrCl <50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.3) and Clinical Pharmacology (12.2, 12.3)]*.

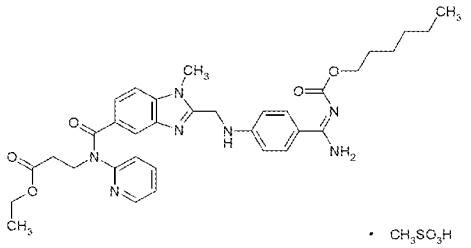
10 OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding. A specific reversal agent (idarucizumab) is available.

Dabigatran is primarily eliminated by the kidneys with a low plasma protein binding of approximately 35%. Hemodialysis can remove dabigatran; however, data supporting this approach are limited. Using a high-flux dialyzer, blood flow rate of 200 mL/min, and dialysate flow rate of 700 mL/min, approximately 49% of total dabigatran can be cleared from plasma over 4 hours. At the same dialysate flow rate, approximately 57% can be cleared using a dialyzer blood flow rate of 300 mL/min, with no appreciable increase in clearance observed at higher blood flow rates. Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen. The effect of dialysis on dabigatran's plasma concentration would be expected to vary based on patient specific characteristics. Measurement of aPTT or ECT may help guide therapy *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

11 DESCRIPTION

The chemical name for dabigatran etexilate mesylate, a direct thrombin inhibitor, is β-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate. The empirical formula is $C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$ and the molecular weight is 723.86 (mesylate salt), 627.75 (free base). The structural formula is:



Dabigatran etexilate mesylate is a yellow-white to yellow powder. A saturated solution in pure water has a solubility of 1.8 mg/mL. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol.

PRADAXA capsules are supplied in 75 mg, 110 mg, and 150 mg strengths for oral administration. Each capsule contains dabigatran etexilate mesylate as the active ingredient: 150 mg dabigatran etexilate (equivalent to 172.95 mg dabigatran etexilate mesylate), 110 mg dabigatran etexilate (equivalent to 126.83 mg dabigatran etexilate mesylate), or 75 mg dabigatran etexilate (equivalent to 86.48 mg dabigatran etexilate mesylate) along with the following inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shell is composed of carrageenan, hypromellose, potassium chloride, titanium dioxide, black edible ink, and FD&C Blue No. 2 (150 mg and 110 mg capsules only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

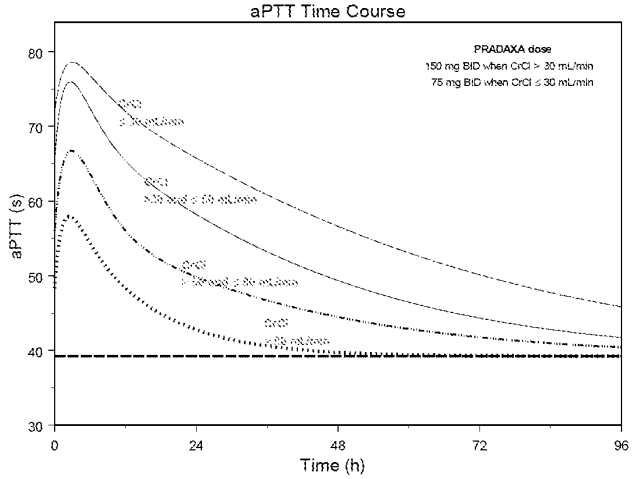
Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

12.2 Pharmacodynamics

At recommended therapeutic doses, dabigatran etexilate prolongs the coagulation markers such as aPTT, ECT, and TT. INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring.

The aPTT test provides an approximation of PRADAXA's anticoagulant effect. The average time course for effects on aPTT, following approved dosing regimens in patients with various degrees of renal impairment is shown in Figure 2. The curves represent mean levels without confidence intervals; variations should be expected when measuring aPTT. While advice cannot be provided on the level of recovery of aPTT needed in any particular clinical setting, the curves can be used to estimate the time to get to a particular level of recovery, even when the time since the last dose of PRADAXA is not precisely known. In the RE-LY trial, the median (10^{th} to 90^{th} percentile) trough aPTT in patients receiving the 150 mg dose was 52 (40 to 76) seconds.

Figure 2 Average Time Course for Effects of Dabigatran on aPTT, Following Approved PRADAXA Dosing Regimens in Patients with Various Degrees of Renal Impairment*



*Simulations based on PK data from a study in subjects with renal impairment and PK/aPTT relationships derived from the RE-LY study; aPTT prolongation in RE-LY was measured centrally in citrate plasma using PTT Reagent Roche Diagnostics GmbH, Mannheim, Germany. There may be quantitative differences between various established methods for aPTT assessment.

The degree of anticoagulant activity can also be assessed by the ecarin clotting time (ECT). This test is a more specific measure of the effect of dabigatran than activated partial thromboplastin time (aPTT). In the RE-LY trial, the median (10^{th} to 90^{th} percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 to 103) seconds.

In orthopedic hip surgery patients, maximum aPTT response (Emax) to dabigatran and baseline aPTT were higher shortly after surgery than at later time points (e.g. ≥3 days after surgery).

Cardiac Electrophysiology
No prolongation of the QTc interval was observed with dabigatran etexilate at doses up to 600 mg.

12.3 Pharmacokinetics
Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Pharmacokinetics described here refer to the sum of dabigatran and its glucuronides. Dabigatran displays dose-proportional pharmacokinetics in healthy subjects and patients in the range of doses from 10 to 400 mg.

Absorption
The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3 to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. After oral administration of dabigatran etexilate in healthy volunteers, C_{max} occurs at 1 hour post-administration in the fasted state. Coadministration of PRADAXA with a high-fat meal delays the time to C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran; PRADAXA may be administered with or without food.

The oral bioavailability of dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell compared to the intact capsule formulation. PRADAXA capsules should therefore not be broken, chewed, or opened before administration.

Distribution
Dabigatran is approximately 35% bound to human plasma proteins. The red blood cell to plasma partitioning of dabigatran measured as total radioactivity is less than 0.3. The volume of distribution of dabigatran is 50 to 70 L. Dabigatran pharmacokinetics are dose proportional after single doses of 10 to 400 mg. Given twice daily, dabigatran's accumulation factor is approximately two.

Elimination
Dabigatran is eliminated primarily in the urine. Renal clearance of dabigatran is 80% of total clearance after intravenous administration. After oral administration of radiolabeled dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The half-life of dabigatran in healthy subjects is 12 to 17 hours.

Metabolism
After oral administration, dabigatran etexilate is converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is subject to conjugation forming pharmacologically active acyl glucuronides. Four positional isomers, 1-O, 2-O, 3-O, and 4-O-acylglucuronide exist, and each accounts for less than 10% of total dabigatran in plasma.

Renal Impairment
An open, parallel-group single-center study compared dabigatran pharmacokinetics in healthy subjects and patients with mild to moderate renal impairment receiving a single dose of PRADAXA 150 mg. Exposure to dabigatran increases with severity of renal function impairment (Table 8). Similar findings were observed in the RE-LY, RE-COVER and RE-NOVATE II trials.

Table 8 Impact of Renal Impairment on Dabigatran Pharmacokinetics

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in C_{max}	$t_{1/2}$ (h)
Normal	≥ 80	1x	1x	13
Mild	50-80	1.5x	1.1x	15
Moderate	30-50	3.2x	1.7x	18
Severe[+]	15-30	6.3x	2.1x	27

[+]Patients with severe renal impairment were not studied in RE-LY, RE-COVER and RE-NOVATE II. Dosing recommendations in subjects with severe renal impairment are based on pharmacokinetic modeling *[see Dosage and Administration (2.1, 2.2) and Use in Specific Populations (8.6)]*.

Hepatic Impairment

Administration of PRADAXA in patients with moderate hepatic impairment (Child-Pugh B) showed a large inter-subject variability, but no evidence of a consistent change in exposure or pharmacodynamics.

Drug Interactions

A summary of the effect of coadministered drugs on dabigatran exposure is shown in Figures 3.1 and 3.2.

In the orthopedic hip surgery patients, limited clinical data with P-gp inhibitors is available.

Figure 3.1 **Effect of P-gp Inhibitor or Inducer (rifampicin) Drugs on Peak and Total Exposure to Dabigatran (Cmax and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perpetrator and Dabigatran Etexilate Dose and Dosing Frequency are given as well as the Time of Perpetrator Dosing in Relation to Dabigatran Etexilate Dose (Time Difference)**

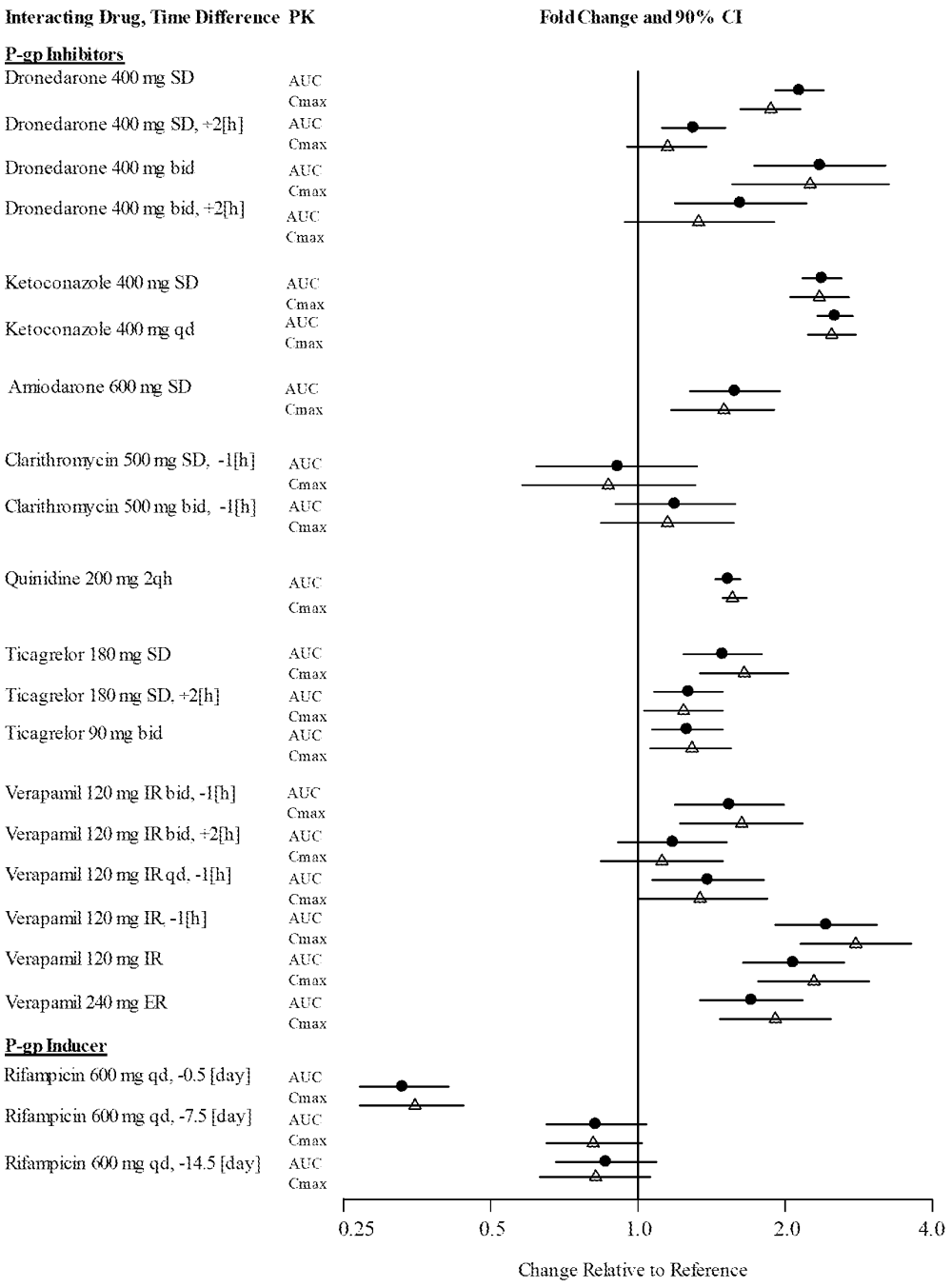
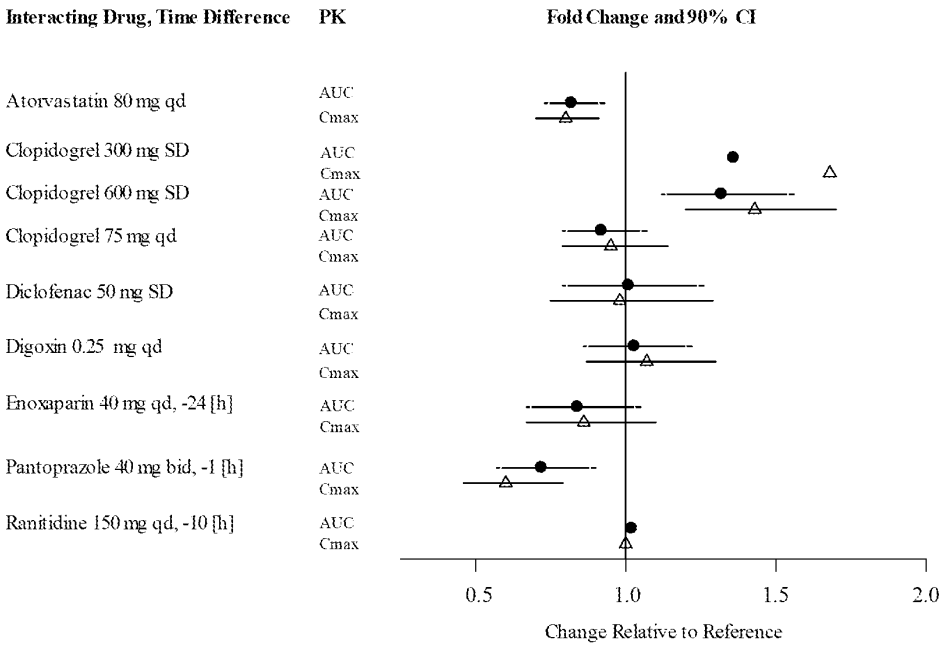


Figure 3.2 Effect of Non-P-gp Inhibitor or Inducer, Other Drugs, on Peak and Total Exposure to Dabigatran (Cmax and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perpetrator and Dabigatran Etexilate Dose and Dosing Frequency are given as well as the Time of Perpetrator Dosing in Relation to Dabigatran Etexilate Dose (Time Difference)



In RE-LY, dabigatran plasma samples were also collected. The concomitant use of proton pump inhibitors, H2 antagonists, and digoxin did not appreciably change the trough concentration of dabigatran.

Impact of Dabigatran on Other Drugs
In clinical studies exploring CYP3A4, CYP2C9, P-gp and other pathways, dabigatran did not meaningfully alter the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole, or ranitidine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dabigatran was not carcinogenic when administered by oral gavage to mice and rats for up to 2 years. The highest doses tested (200 mg/kg/day) in mice and rats were approximately 3.6 and 6 times, respectively, the human exposure at MRHD of 300 mg/day based on AUC comparisons.

Dabigatran was not mutagenic in *in vitro* tests, including bacterial reversion tests, mouse lymphoma assay and chromosomal aberration assay in human lymphocytes, and the *in vivo* micronucleus assay in rats.

In the rat fertility study with oral gavage doses of 15, 70, and 200 mg/kg, males were treated for 29 days prior to mating, during mating up to scheduled termination, and females were treated 15 days prior to mating through gestation Day 6. No adverse effects on male or female fertility were observed at 200 mg/kg or 9 to 12 times the human exposure at MRHD of 300 mg/day based on AUC comparisons. However, the number of implantations decreased in females receiving 70 mg/kg, or 3 times the human exposure at MRHD based on AUC comparisons.

14 CLINICAL STUDIES

14.1 Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation

The clinical evidence for the efficacy of PRADAXA was derived from RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy), a multi-center, multi-national, randomized parallel group trial comparing two blinded doses of PRADAXA (110 mg twice daily and 150 mg twice daily) with open-label warfarin (dosed to target INR of 2 to 3) in patients with non-valvular, persistent, paroxysmal, or permanent atrial fibrillation and one or more of the following additional risk factors:

- Previous stroke, transient ischemic attack (TIA), or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure, ≥ New York Heart Association Class 2
- Age ≥75 years
- Age ≥65 years and one of the following: diabetes mellitus, coronary artery disease (CAD), or hypertension

The primary objective of this study was to determine if PRADAXA was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke (ischemic and hemorrhagic) and systemic embolism. The study was designed to ensure that PRADAXA preserved more than 50% of warfarin's effect as established by previous randomized, placebo-controlled trials of warfarin in atrial fibrillation. Statistical superiority was also analyzed.

A total of 18,113 patients were randomized and followed for a median of 2 years. The patients' mean age was 71.5 years and the mean $CHADS_2$ score was 2.1. The patient population was 64% male, 70% Caucasian, 16% Asian, and 1% black. Twenty percent of patients had a history of a stroke or TIA and 50% were Vitamin K antagonist (VKA) naïve, defined as less than 2 months total lifetime exposure to a VKA. Thirty-two percent of the population had never been exposed to a VKA. Concomitant diseases of patients in this trial included hypertension 79%, diabetes 23%, and CAD 28%. At baseline, 40% of patients were on aspirin and 6% were on clopidogrel. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%.

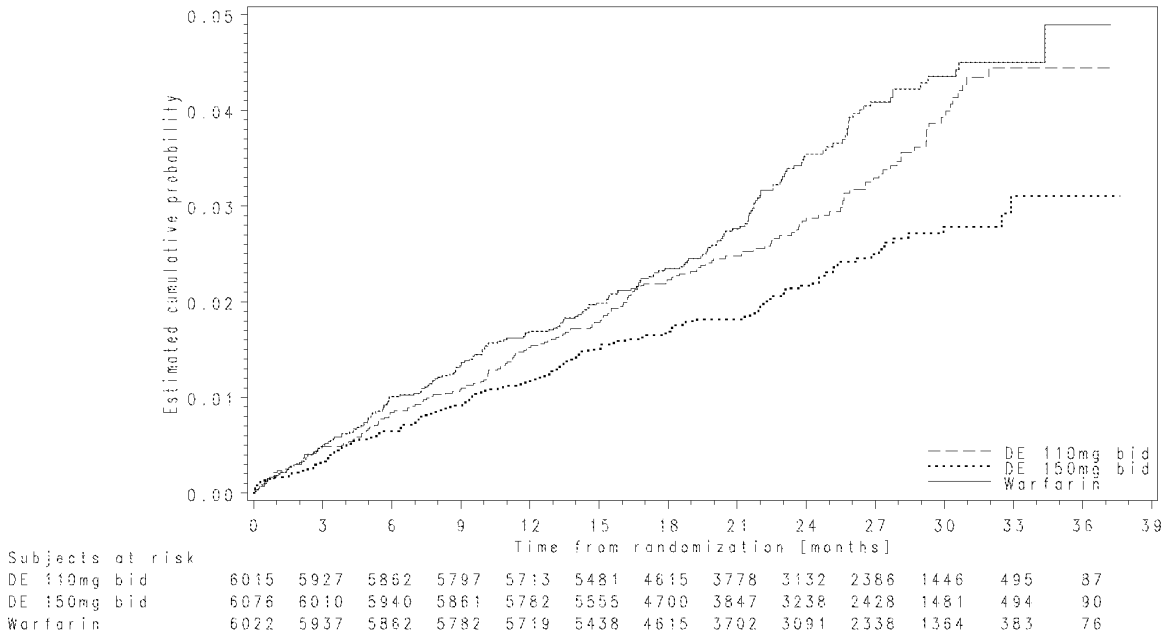
Relative to warfarin and to PRADAXA 110 mg twice daily, PRADAXA 150 mg twice daily significantly reduced the primary composite endpoint of stroke and systemic embolism (see Table 9 and Figure 4).

Table 9 First Occurrence of Stroke or Systemic Embolism in the RE-LY Study*

	PRADAXA 150 mg twice daily	PRADAXA 110 mg twice daily	Warfarin
Patients randomized	6076	6015	6022
Patients (% per yr) with events	135 (1.12%)	183 (1.54%)	203 (1.72%)
Hazard ratio vs. warfarin (95% CI)	0.65 (0.52, 0.81)	0.89 (0.73, 1.09)	
P-value for superiority	0.0001	0.27	
Hazard ratio vs. PRADAXA 110 mg (95% CI)	0.72 (0.58, 0.91)		
P-value for superiority	0.005		

* Randomized ITT

Figure 4 Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism



The contributions of the components of the composite endpoint, including stroke by subtype, are shown in Table 10. The treatment effect was primarily a reduction in stroke. PRADAXA 150 mg twice daily was superior in reducing ischemic and hemorrhagic strokes relative to warfarin.

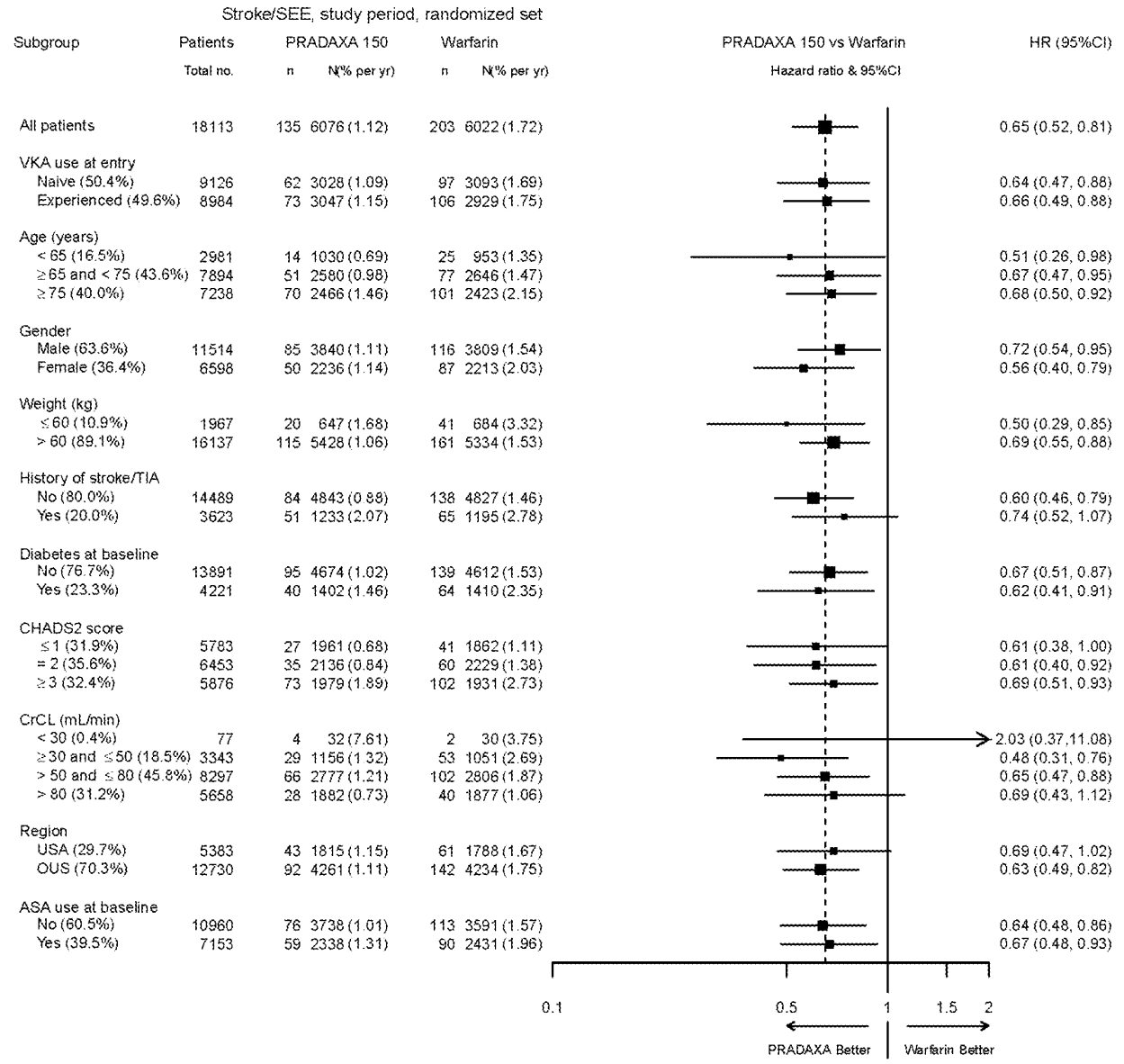
Table 10 Strokes and Systemic Embolism in the RE-LY Study

	PRADAXA 150 mg twice daily	Warfarin	Hazard ratio vs. warfarin (95% CI)
Patients randomized	6076	6022	
Stroke	123	187	0.64 (0.51, 0.81)
Ischemic stroke	104	134	0.76 (0.59, 0.98)
Hemorrhagic stroke	12	45	0.26 (0.14, 0.49)
Systemic embolism	13	21	0.61 (0.30, 1.21)

In the RE-LY trial, the rate of all-cause mortality was lower on dabigatran 150 mg than on warfarin (3.6% per year versus 4.1% per year). The rate of vascular death was lower on dabigatran 150 mg compared to warfarin (2.3% per year versus 2.7% per year). Non-vascular death rates were similar in the treatment arms.

The efficacy of PRADAXA 150 mg twice daily was generally consistent across major subgroups (see Figure 5).

Figure 5 Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics*



* Randomized ITT

Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

In RE-LY, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA (0.7 per 100 patient-years for 150 mg dose) than in those who received warfarin (0.6).

14.2 Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism

In the randomized, parallel group, double-blind trials, RE-COVER and RE-COVER II, patients with deep vein thrombosis and pulmonary embolism received PRADAXA 150 mg twice daily or warfarin (dosed to target INR of 2 to 3) following initial treatment with an approved parenteral anticoagulant for 5-10 days.

In RE-COVER, the median treatment duration during the oral only treatment period was 174 days. A total of 2539 patients (30.9% patients with symptomatic PE with or without DVT and 68.9% with symptomatic DVT only) were treated with a mean age of 54.7 years. The patient population was 58.4% male, 94.8% white, 2.6% Asian, and 2.6% black. The concomitant diseases of patients in this trial included hypertension (35.9%), diabetes mellitus (8.3%), coronary artery disease (6.5%), active cancer (4.8%), and gastric or duodenal ulcer (4.4%). Concomitant medications included agents acting on renin-angiotensin system (25.2%), vasodilators (28.4%), serum lipid-reducing agents (18.2%), NSAIDs (21%), beta-blockers (14.8%), calcium channel blockers (8.5%), ASA (8.6%), and platelet inhibitors excluding ASA (0.6%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 60% in RE-COVER study.

In RE-COVER II, the median treatment duration during the oral only treatment period was 174 days. A total of 2568 patients (31.8% patients with symptomatic PE with or without DVT and 68.1% with symptomatic DVT only) were treated with a mean age of 54.9 years. The patient population was 60.6% male, 77.6% white, 20.9% Asian, and 1.5% black. The concomitant diseases of patients in this trial included hypertension (35.1%), diabetes mellitus (9.8%), coronary artery disease (7.1%), active cancer (3.9%), and gastric or duodenal ulcer (3.8%). Concomitant medications included agents acting on renin-angiotensin system (24.2%), vasodilators (28.6%), serum lipid-reducing agents (20.0%), NSAIDs (22.3%), beta-blockers (14.8%), calcium channel blockers (10.8%), ASA (9.8%), and platelet inhibitors excluding ASA (0.8%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 57% in RE-COVER II study.

In studies RE-COVER and RE-COVER II, the protocol specified non-inferiority margin (2.75) for the hazard ratio was derived based on the upper limit of the 95% confidence interval of the historical warfarin effect. PRADAXA was demonstrated to be non-inferior to warfarin (dosed to target INR of 2 to 3) (Table 11) based on the primary composite endpoint (fatal PE or symptomatic non-fatal PE and/or DVT) and retains at least 66.9% (RE-COVER) and 63.9% (RE-COVER II) of the historical warfarin effect, respectively.

Table 11 Primary Efficacy Endpoint for RE-COVER and RE-COVER II – Modified ITT[a] Population

	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard ratio vs. warfarin (95% CI)
RE-COVER	**N=1274**	**N=1265**	
Primary Composite Endpoint[b]	34 (2.7)	32 (2.5)	1.05 (0.65, 1.70)
Fatal PE[c]	1 (0.1)	3 (0.2)	
Symptomatic non-fatal PE[c]	16 (1.3)	8 (0.6)	
Symptomatic recurrent DVT[c]	17 (1.3)	23 (1.8)	
RE-COVER II	**N=1279**	**N=1289**	
Primary Composite Endpoint[b]	34 (2.7)	30 (2.3)	1.13 (0.69, 1.85)
Fatal PE[c]	3 (0.2)	0	
Symptomatic non-fatal PE[c]	9 (0.7)	15 (1.2)	
Symptomatic recurrent DVT[c]	30 (2.3)	17 (1.3)	

[a]Modified ITT analyses population consists of all randomized patients who received at least one dose of study medication.
[b]Number of patients with one or more event.
[c]Number of events. For patients with multiple events each event is counted independently.

In the randomized, parallel group, double-blind, pivotal trial, RE-MEDY, patients received PRADAXA 150 mg twice daily or warfarin (dosed to target INR of 2 to 3) following 3 to 12 months of treatment with anticoagulation therapy for an acute VTE. The median treatment duration during the treatment period was 534 days. A total of 2856 patients were treated with a mean age of 54.6 years. The patient population was 61% male, and 90.1% white, 7.9% Asian and 2.0% black. The concomitant diseases of patients in this trial included hypertension (38.6%), diabetes mellitus (9.0%), coronary artery disease (7.2%), active cancer (4.2%), and gastric or duodenal ulcer (3.8%). Concomitant medications included agents acting on renin-angiotensin system (27.9%), vasodilators (26.7%), serum lipid reducing agents (20.6%), NSAIDs (18.3%), beta-blockers (16.3%), calcium channel blockers (11.1%), aspirin (7.7%), and platelet inhibitors excluding ASA (0.9%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 62% in the study.

In study RE-MEDY, the protocol specified non-inferiority margin (2.85) for the hazard ratio was derived based on the point estimate of the historical warfarin effect. PRADAXA was demonstrated to be non-inferior to warfarin (dosed to target INR of 2 to 3) (Table 12) based on the primary composite endpoint (fatal PE or symptomatic non-fatal PE and/or DVT) and retains at least 63.0% of the historical warfarin effect. If the non-inferiority margin was derived based on the 50% retention of the upper limit of the 95% confidence interval, PRADAXA was demonstrated to retain at least 33.4% of the historical warfarin effect based on the composite primary endpoint.

Table 12 Primary Efficacy Endpoint for RE-MEDY – Modified ITT[a] Population

	PRADAXA 150 mg twice daily N=1430 N (%)	Warfarin N=1426 N (%)	Hazard ratio vs. warfarin (95% CI)
Primary Composite Endpoint[b]	26 (1.8)	18 (1.3)	1.44 (0.78, 2.64)
Fatal PE[c]	1 (0.07)	1 (0.07)	
Symptomatic non-fatal PE[c]	10 (0.7)	5 (0.4)	
Symptomatic recurrent DVT[c]	17 (1.2)	13 (0.9)	

[a]Modified ITT analyses population consists of all randomized patients who received at least one dose of study medication.
[b]Number of patients with one or more event.
[c]Number of events. For patients with multiple events each event is counted independently.

In a randomized, parallel group, double-blind, pivotal trial, RE-SONATE, patients received PRADAXA 150 mg twice daily or placebo following 6 to 18 months of treatment with anticoagulation therapy for an acute VTE. The median treatment duration was 182 days. A total of 1343 patients were treated with a mean age of 55.8 years. The patient population was 55.5% male, 89.0% white, 9.3% Asian, and 1.7% black. The concomitant diseases of patients in this trial included hypertension (38.8%), diabetes mellitus (8.0%), coronary artery disease (6.0%), history of cancer (6.0%), gastric or duodenal ulcer (4.5%), and heart failure (4.6%). Concomitant medications included agents acting on renin-angiotensin system (28.7%), vasodilators (19.4%), beta-blockers (18.5%), serum lipid reducing agents (17.9%), NSAIDs (12.1%), calcium channel blockers (8.9%), aspirin (8.3%), and platelet inhibitors excluding ASA (0.7%). Based on the outcome of the primary composite endpoint (fatal PE, unexplained death, or symptomatic non-fatal PE and/or DVT), PRADAXA was superior to placebo (Table 13).

Table 13 Primary Efficacy Endpoint for RE-SONATE – Modified ITT[a] Population

	PRADAXA 150 mg twice daily N=681 N (%)	Placebo N=662 N (%)	Hazard ratio vs. placebo (95% CI)
Primary Composite Endpoint[b]	3 (0.4)	37 (5.6)	0.08 (0.02, 0.25) p-value <0.0001
Fatal PE and unexplained death[c]	0	2 (0.3)	
Symptomatic non-fatal PE[c]	1 (0.1)	14 (2.1)	
Symptomatic recurrent DVT[c]	2 (0.3)	23 (3.5)	

[a]Modified ITT analyses population consists of all randomized patients who received at least one dose of study medication.
[b]Number of patients with one or more events.
[c]Number of events. For patients with multiple events each event is counted independently.

14.3 Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery

In the randomized, parallel group, double-blind, non-inferiority trials, RE-NOVATE and RE-NOVATE II patients received PRADAXA 75 mg orally 1-4 hours after surgery followed by 150 mg daily (RE-NOVATE), PRADAXA 110 mg orally 1-4 hours after surgery followed by 220 mg daily (RE-NOVATE and RE-NOVATE II) or subcutaneous enoxaparin 40 mg once daily initiated the evening before surgery (RE-NOVATE and RE-NOVATE II) for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who have undergone hip replacement surgery.

Overall, in RE-NOVATE and RE-NOVATE II, the median treatment duration was 33 days for PRADAXA and 33 days for enoxaparin. A total of 5428 patients were treated with a mean age of 63.2 years. The patient population was 45.3% male, 96.1% white, 3.6% Asian, and 0.4 % black. The concomitant diseases of patients in these trials included hypertension (46.1%), venous insufficiency (15.4%), coronary artery disease (8.2%), diabetes mellitus (7.9%), reduced renal function (5.3%), heart failure (3.4%), gastric or duodenal ulcer (3.0%), VTE (2.7%), and malignancy (0.1%). Concomitant medications included cardiac therapy (69.7%), NSAIDs (68%), vasoprotectives (29.7%), agents acting on renin-angiotensin system (29.1%), beta-blockers (21.5%), diuretics (20.8%), lipid modifying agents (18.2%), any antithrombin/anticoagulant (16.0%), calcium channel blockers (13.6%), low molecular weight heparin (7.8%), aspirin (7.0%), platelet inhibitors excluding ASA (6.9%), other antihypertensives (6.7%), and peripheral vasodilators (2.6%).

For efficacy evaluation all patients were to have bilateral venography of the lower extremities at 3 days after last dose of study drug unless an endpoint event had occurred earlier in the study. In the primary efficacy analysis, PRADAXA 110 mg orally 1-4 hours after surgery followed by 220 mg daily was non-inferior to enoxaparin 40 mg once daily in a composite endpoint of confirmed VTE (proximal or distal DVT on venogram, confirmed symptomatic DVT, or confirmed PE) and all cause death during the treatment period (Tables 14 and 15). In the studies 2628 (76.5%) patients in RE-NOVATE and 1572 (78.9%) patients in RE-NOVATE II had evaluable venograms at study completion.

Table 14 Primary Efficacy Endpoint for RE-NOVATE

	PRADAXA 220 mg N (%)	Enoxaparin N (%)
Number of Patients[a]	**N=880**	**N= 897**
Primary Composite Endpoint	53 (6.0)	60 (6.7)
Risk difference (%) vs. enoxaparin (95% CI)	-0.7 (-2.9, 1.6)	
Number of Patients	**N=909**	**N=917**
Composite endpoint of major VTE[b] and VTE related mortality	28 (3.1)	36 (3.9)
Number of Patients	**N=905**	**N=914**
Proximal DVT	23 (2.5)	33 (3.6)
Number of Patients	**N=874**	**N=894**
Total DVT	46 (5.3)	57 (6.4)
Number of Patients	**N=1137**	**N=1142**
Symptomatic DVT	6 (0.5)	1 (0.1)
PE	5 (0.4)	3 (0.3)
Death	3 (0.3)	0

[a]Full Analysis Set (FAS): The FAS included all randomized patients who received at least one subcutaneous injection or one oral dose of study medication, underwent surgery and subjects for whom the presence or absence of an efficacy outcome at the end of the study was known, i.e., an evaluable negative venogram for both distal

and proximal DVT in both legs or any of the following: positive venography in one or both legs, or confirmed symptomatic DVT, PE, or death during the treatment period.
[b]VTE is defined as proximal DVT and PE

Table 15 Primary Efficacy Endpoint for RE-NOVATE II

	PRADAXA 220 mg N (%)	Enoxaparin N (%)
Number of Patients[a]	**N=792**	**N= 786**
Primary Composite Endpoint	61 (7.7)	69 (8.8)
Risk difference (%) vs. enoxaparin (95% CI)	-1.1 (-3.8, 1.6)	
Number of Patients	**N=805**	**N=795**
Composite endpoint of major VTE[b] and VTE related mortality	18 (2.2)	33 (4.2)
Number of Patients	**N=804**	**N=793**
Proximal DVT	17 (2.1)	31 (3.9)
Number of Patients	**N=791**	**N=784**
Total DVT	60 (7.6)	67 (8.5)
Number of Patients	**N=1001**	**N=992**
Symptomatic DVT	0	4 (0.4)
PE	1 (0.1)	2 (0.2)
Death	0	1 (0.1)

[a]Full Analysis Set (FAS): The FAS included all randomized patients who received at least one subcutaneous injection or one oral dose of study medication, underwent surgery and subjects for whom the presence or absence of an efficacy outcome at the end of the study was known, i.e., an evaluable negative venogram for both distal and proximal DVT in both legs or any of the following: positive venography in one or both legs, or confirmed symptomatic DVT, PE, or death during the treatment period.
[b]VTE is defined as proximal DVT and PE

16 HOW SUPPLIED/STORAGE AND HANDLING

PRADAXA 75 mg capsules have a white opaque cap imprinted with the Boehringer Ingelheim company symbol and a white opaque body imprinted with "R75". The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0355-09 Unit of use bottle of 60 capsules
- NDC 0597-0355-56 Blister package containing 60 capsules (10 x 6 capsule blister cards)

PRADAXA 110 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted with "R110". The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0108-54 Unit of use bottle of 60 capsules
- NDC 0597-0108-60 Blister package containing 60 capsules (10 x 6 capsule blister cards)

PRADAXA 150 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a white opaque body imprinted with "R150". The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0360-55 Unit of use bottle of 60 capsules
- NDC 0597-0360-82 Blister package containing 60 capsules (10 x 6 capsule blister cards)

Bottles
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Once opened, the product must be used within 4 months. Keep the bottle tightly closed. Store in the original package to protect from moisture.

Blisters
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package to protect from moisture.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Instructions for Patients

- Tell patients to take PRADAXA exactly as prescribed.
- Remind patients not to discontinue PRADAXA without talking to the health care provider who prescribed it.
- Keep PRADAXA in the original bottle to protect from moisture. Do not put PRADAXA in pill boxes or pill organizers.
- When more than one bottle is dispensed to the patient, instruct them to open only one bottle at a time.
- Instruct patient to remove only one capsule from the opened bottle at the time of use. The bottle should be immediately and tightly closed.
- Advise patients not to chew or break the capsules before swallowing them and not to open the capsules and take the pellets alone.
- Advise patients that the capsule should be taken with a full glass of water.

[see Boxed Warning, Dosage and Administration (2.3)]

Bleeding
Inform patients that they may bleed more easily, may bleed longer, and should call their health care provider for any signs or symptoms of bleeding *[see Warnings and Precautions (5.2)]*.

Instruct patients to seek emergency care right away if they have any of the following, which may be a sign or symptom of serious bleeding:

- Unusual bruising (bruises that appear without known cause or that get bigger)
- Pink or brown urine
- Red or black, tarry stools
- Coughing up blood
- Vomiting blood, or vomit that looks like coffee grounds

Instruct patients to call their health care provider or to get prompt medical attention if they experience any signs or symptoms of bleeding:

- Pain, swelling or discomfort in a joint
- Headaches, dizziness, or weakness
- Reoccurring nose bleeds
- Unusual bleeding from gums
- Bleeding from a cut that takes a long time to stop
- Menstrual bleeding or vaginal bleeding that is heavier than normal

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately *[see Boxed Warning]*.

Gastrointestinal Adverse Reactions
Instruct patients to call their health care provider if they experience any signs or symptoms of dyspepsia or gastritis:

- Dyspepsia (upset stomach), burning, or nausea
- Abdominal pain or discomfort
- Epigastric discomfort, GERD (gastric indigestion)

[see Adverse Reactions (6.1)]

Invasive or Surgical Procedures
Instruct patients to inform their health care provider that they are taking PRADAXA before any invasive procedure (including dental procedures) is scheduled *[see Dosage and Administration (2.6)]*.

Concomitant Medications
Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so their health care provider knows about other treatments that may affect bleeding risk (e.g., aspirin or NSAIDs) or dabigatran exposure (e.g., dronedarone or systemic ketoconazole) *[see Warnings and Precautions (5.2, 5.5)]*.

Prosthetic Heart Valves
Instruct patients to inform their health care provider if they will have or have had surgery to place a prosthetic heart valve *[see Warnings and Precautions (5.4)]*.

Pregnancy
Advise patients to inform their healthcare provider immediately if they become pregnant or intend to become pregnant during treatment with PRADAXA *[see Use in Specific Populations (8.1)]*.

Lactation
Advise patients not to breastfeed if they are taking PRADAXA *[see Use in Specific Populations (8.2)]*.

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Ridgefield, CT 06877 USA

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IT5060ANG062020

MEDICATION GUIDE
PRADAXA (pra dax a)
(dabigatran etexilate)
capsules

Read this Medication Guide before you start taking PRADAXA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about PRADAXA?

- People with atrial fibrillation (a type of irregular heartbeat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. PRADAXA lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking PRADAXA, you may have increased risk of forming a clot in your blood.

  Do not stop taking PRADAXA without talking to the doctor who prescribes it for you. Stopping PRADAXA increases your risk of having a stroke.

  PRADAXA may need to be stopped, if possible, prior to surgery or a medical or dental procedure. Ask the doctor who prescribed PRADAXA for you when you should stop taking it. Your doctor will tell you when you may start taking PRADAXA again after your surgery or procedure. If you have to stop taking PRADAXA, your doctor may prescribe another medicine to help prevent a blood clot from forming.

- PRADAXA can cause bleeding which can be serious, and sometimes lead to death. This is because PRADAXA is a blood thinner medicine that lowers the chance of blood clots forming in your body.
- **You may have a higher risk of bleeding if you take PRADAXA and**:
  - are over 75 years old
  - have kidney problems
  - have stomach or intestine bleeding that is recent or keeps coming back, or you have a stomach ulcer
  - take other medicines that increase your risk of bleeding, including:
    - aspirin or aspirin-containing products
    - long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
    - a medicine that contains warfarin sodium
    - a medicine that contains heparin
    - a medicine that contains clopidogrel bisulfate
    - a medicine that contains prasugrel
  - have certain kidney problems and also take a medicine that contains dronedarone or ketoconazole tablets.

    Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.
- PRADAXA can increase your risk of bleeding because it lessens the ability of your blood to clot. While you take PRADAXA:
  - you may bruise more easily
  - it may take longer for any bleeding to stop

  Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding:
  - unexpected bleeding or bleeding that lasts a long time, such as:
    - unusual bleeding from the gums
    - nose bleeds that happen often
    - menstrual bleeding or vaginal bleeding that is heavier than normal
  - bleeding that is severe or you cannot control
  - pink or brown urine
  - red or black stools (looks like tar)
  - bruises that happen without a known cause or get larger
  - cough up blood or blood clots
  - vomit blood or your vomit looks like “coffee grounds”
  - unexpected pain, swelling, or joint pain
  - headaches, feeling dizzy or weak

  Take PRADAXA exactly as prescribed. Do not stop taking PRADAXA without first talking to the doctor who prescribes it for you. Stopping PRADAXA may increase your risk of a stroke.

  PRADAXA may need to be stopped, if possible, for one or more days before any surgery, or medical or dental procedure. If you need to stop taking PRADAXA for **any reason**, talk to the doctor who prescribed PRADAXA for you to find out when you should stop taking it. Your doctor will tell you when to start taking PRADAXA again after your surgery or procedure.

- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like PRADAXA, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine.
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine.

  If you take PRADAXA and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots. Tell your doctor right away if you have back pain, tingling, numbness, muscle weakness (especially in your legs and feet), loss of control of the bowels or bladder (incontinence).

See "What are the possible side effects of PRADAXA?" for more information about side effects.

What is PRADAXA?

PRADAXA is a prescription blood thinner medicine that lowers the chance of blood clots forming in your body.
PRADAXA is used to:

- reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to blood clots forming and increase your risk of a stroke.
- treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism) and reduce the risk of them occurring again.
- to help prevent blood clots in the legs and lungs of people who have just had hip replacement surgery.

PRADAXA is not for use in people with artificial (prosthetic) heart valves.

It is not known if PRADAXA is safe and works in children.

Who should not take PRADAXA?

Do not take PRADAXA if you:

- currently have certain types of abnormal bleeding. Talk to your doctor before taking PRADAXA if you currently have unusual bleeding.
- have had a serious allergic reaction to PRADAXA. Ask your doctor if you are not sure.
- have ever had or plan to have a valve in your heart replaced

What should I tell my doctor before taking PRADAXA?

Before you take PRADAXA, tell your doctor if you:

- have kidney problems
- have ever had bleeding problems
- have ever had stomach ulcers
- have antiphospholipid syndrome (APS)
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if PRADAXA will harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with PRADAXA.
- are breastfeeding or plan to breastfeed. It is not known if PRADAXA passes into your breast milk. You and your doctor should decide if you will take PRADAXA or breastfeed.

Tell all of your doctors and dentists that you are taking PRADAXA. They should talk to the doctor who prescribed PRADAXA for you, before you have **any** surgery, or a medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some of your other medicines may affect the way PRADAXA works. Certain medicines may increase your risk of bleeding. See "**What is the most important information I should know about PRADAXA?**"

Especially tell your doctor if you take:

- a medicine that contains rifampin

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take PRADAXA?

- Your doctor will decide how long you should take PRADAXA. **Do not stop taking PRADAXA without first talking with your doctor. Stopping PRADAXA may increase your risk of having a stroke or forming blood clots.**
- **Take PRADAXA exactly as prescribed by your doctor.**
- Take PRADAXA capsules twice a day (approximately every 12 hours).
- If you miss a dose of PRADAXA, take it as soon as you remember. If your next dose is less than 6 hours away, skip the missed dose. Do not take two doses of PRADAXA at the same time.

- Swallow PRADAXA capsules whole. Do not break, chew, or empty the pellets from the capsule.
- You can take PRADAXA with or without food.
- You should take PRADAXA with a full glass of water.
- Do not run out of PRADAXA. Refill your prescription before you run out. If you plan to have surgery, or a medical or a dental procedure, tell your doctor and dentist that you are taking PRADAXA. You may have to stop taking PRADAXA for a short time. See "**What is the most important information I should know about PRADAXA?**".
- If you take too much PRADAXA, go to the nearest hospital emergency room or call your doctor.
- Call your doctor or healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your doctor or healthcare provider may need to check you.
- PRADAXA comes in a bottle or in a blister package.
- Only open 1 bottle of PRADAXA at a time. Finish your opened bottle of PRADAXA before opening a new bottle.
- After opening a bottle of PRADAXA, use within 4 months. See "**How should I store PRADAXA?**"
- When it is time for you to take a dose of PRADAXA, only remove your prescribed dose of PRADAXA from your open bottle or blister package.
- Tightly close your bottle of PRADAXA right away after you take your dose.

What are the possible side effects of PRADAXA?

PRADAXA can cause serious side effects, including:

- See "**What is the most important information I should know about PRADAXA?**"
- Allergic Reactions. In some people, PRADAXA can cause symptoms of an allergic reaction, including hives, rash, and itching. Tell your doctor or get medical help right away if you get any of the following symptoms of a serious allergic reaction with PRADAXA:
    - chest pain or chest tightness
    - swelling of your face or tongue
    - trouble breathing or wheezing
    - feeling dizzy or faint

Common side effects of PRADAXA include:

- indigestion, upset stomach, or burning
- stomach pain

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of PRADAXA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PRADAXA?

- Store PRADAXA at room temperature 68°F to 77°F (20°C to 25°C). After opening the bottle, use PRADAXA within 4 months. Safely throw away any unused PRADAXA after 4 months.
- **Keep PRADAXA in the original bottle or blister package to keep it dry (protect the capsules from moisture). Do not put PRADAXA in pill boxes or pill organizers.**
- **Tightly close your bottle of PRADAXA right away after you take your dose.**

Keep PRADAXA and all medicines out of the reach of children.

General information about the safe and effective use of PRADAXA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PRADAXA for a condition for which it was not prescribed. Do not give PRADAXA to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about PRADAXA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about PRADAXA that is written for health professionals.

For more information about PRADAXA, including current prescribing information and Medication Guide, go to www.pradaxa.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906, or scan the code below to go to www.pradaxa.com.

What are the ingredients in PRADAXA?

Active ingredient: dabigatran etexilate mesylate

Inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shell is composed of carrageenan, hypromellose, potassium chloride, titanium dioxide, black edible ink, and FD&C Blue No. 2 (150 mg and 110 mg capsules only).

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IT5060ANG062020

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: July 2020

Electronic Acknowledgement Receipt

EFS ID:	42413954
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	09-APR-2021
Filing Date:	19-AUG-2014
Time Stamp:	14:03:50
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant summary of interview with examiner	16326-0018FPWO-Substance_of_Interview-.PDF	19427957 13324eba7b90caaf5fd4240e9f3091ce3252c63f	no	29

Warnings:

Information:	
Total Files Size (in bytes):	19427957

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23552 7590 04/07/2021
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 04/07/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

TITLE OF INVENTION: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/07/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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MSN Exhibit 1002
Page 51 of 680

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23552 7590 04/07/2021
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

TITLE OF INVENTION: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/07/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
BECKHARDT, LYNDSEY MARIE	1613	424-490000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

IPR2025-01107
MSN Exhibit 1002
Page 52 of 680

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 04/07/2021

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
BECKHARDT, LYNDSEY MARIE	

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 04/07/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

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MSN Exhibit 1002
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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/379,613	Applicant(s) Pilgaonkar et al.	
	Examiner LYNDSEY M BECKHARDT	Art Unit 1613	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Patent Board Decision dated 01/12/2021.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☑ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☑ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 20210331.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/LMB/	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613

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Continuation of 3. The allowed claim(s) is/are: 21,23,26,30,32,35-37 and 39-45

Notice of Allowability

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

Claims 21, 23, 26, 30, 32 and 40-48 are allowable. The restriction requirement of Groups I-III and species 1-4, as set forth in the Office action mailed on 06/02/2015, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Specifically, the restriction requirement of Groups I-III and species of organic acid, excipient, treatment and method of making is withdrawn. Claims 33-37, and 39, directed to a method of making and method of use are no longer withdrawn from consideration because the claim(s) requires all the limitations of an allowable claim.

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with E. Joseph Gess on 03/25/2021.

The application has been amended as follows:

Claim 33. (Cancelled)

Claim 34. (Cancelled)

Claim 35. A process for the preparation of the composition according to claim 23, comprising the step of mixing the first type of particles and the second type of particles with the at least one ~~at least one~~ pharmaceutically acceptable excipient.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: Pursuant to the Patent Board Decision on 01/12/2021, the instant invention is considered novel and unobvious over the closet prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 21, 23, 26, 30, 32, 35-37 and 39-48 are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY MARIE BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached on Monday, Tuesday and Thursday 7:30 to 3pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LMB/
Examiner, Art Unit 1613

/ANDREW S ROSENTHAL/
Primary Examiner, Art Unit 1613

Examiner-Initiated Interview Summary	Application No. 14/379,613	Applicant(s) Pilgaonkar et al.		
	Examiner LYNDSEY M BECKHARDT	Art Unit 1613	AIA (First Inventor to File) Status No	Page 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
LYNDSEY M BECKHARDT	Examiner	Telephonic
E. Joseph Gess	Attorney of Record	

Date of Interview: 31 March 2021

Issues Discussed:

Proposed Amendment(s)

Examiner stated all previously withdrawn claims would be rejoined. Examiner proposed amending claims 33-34 to remove "preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery" to overcome 112 first paragraph issues. Applicant stated claims 33-34 should be canceled by Examiner's Amendment. Examiner stated the phrase at least one is repeated twice in instant claim 35 and would need to be corrected. Applicant agreed to remove one recitation of "at least one". Examiner stated a notice of Allowance would be sent.

/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K31/4439 OR A61K9/14 OR A61K9/1617 OR A61K9/1652 OR A61K9/4833 OR A61K9/5026 OR A61K9/5042 OR A61K9/5084 OR A61K9/5089 OR A61P7/02	03/31/2021	LMB

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**
	No Classified Search		

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

/LMB/	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

Search Notes		
Search Notes	**Date**	**Examiner**
East (keyword and Inventor) see attached	9/24/2015	LMB
Google (keyword) see attached East search terms	9/24/2015	LMB
East (keyword and Inventor) see attached	3/7/2016	LMB
Google (keyword) see attached East search terms	3/7/2016	LMB
East (keyword and Inventor) see attached	7/25/2017	LMB
East (keyword and Inventor) see attached	01/08/2018	LMB
East (keyword and Inventor) see attached	11/08/2018	LMB
Google (keyword) see attached East search terms	11/08/2018	LMB
East (keyword and Inventor) see attached	05/20/2019	LMB
East (keyword and Inventor) see attached	03/31/2021	LMB
CPC search (keyword limited) see attached	03/31/2021	LMB
Google (keyword) see attached	03/31/2021	LMB

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	East (keyword.clm.) see attached	03/31/2021	LMB

/LMB/	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

CPC						
Symbol					Type	Version
A61K	/	31	/	4439	F	2013-01-01
A61K	/	9	/	1617	I	2013-01-01
A61K	/	9	/	1652	I	2013-01-01
A61K	/	9	/	5026	I	2013-01-01
A61K	/	9	/	5084	I	2013-01-01
A61K	/	9	/	5089	I	2013-01-01
A61K	/	9	/	14	I	2013-01-01
A61K	/	9	/	4833	I	2013-01-01
A61K	/	9	/	5042	I	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
	/		/					

/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613	31 March 2021	Total Claims Allowed:	
(Assistant Examiner)	(Date)	18	
/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613	01 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20210331

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	31	/	4439	
A61K9/16	/	9	/	16	
A61K9/50	/	9	/	50	
A61K9/14	/	9	/	14	
A61K9/48	/	9	/	48	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613	31 March 2021	Total Claims Allowed:	
(Assistant Examiner)	(Date)	18	
/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613	01 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20210331

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	**Art Unit**
	LYNDSEY M BECKHARDT	1613

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19		28		37		46				
	2		11		20		29		38		47				
	3		12		21		30		39		48				
	4		13		22		31		40						
	5		14		23		32		41						
	6		15		24		33		42						
	7		16		25		34		43						
	8		17		26		35		44						
	9		18		27		36		45						

/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613	31 March 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	18	
/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613	01 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20210331

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S511	88	((("PILGAONKAR") near3 ("Pratibha")) OR (("RUSTOMJEE") near3 ("Maharukh")) OR (("GANDHI") near3 ("Anilkumar"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2021/03/24 08:44
S512	2	S511 and dabigatran	US-PGPUB; USPAT	ADJ	OFF	2021/03/24 08:47
S514	13	S511 and particles.clm.	US-PGPUB; USPAT	ADJ	OFF	2021/03/24 09:17
S513	7	S511 and particle.clm.	US-PGPUB; USPAT	ADJ	OFF	2021/03/24 09:17
S531	56,500	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 partide)	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:23
S530	2,477,829	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:23
S524	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2021/03/24 09:23
S523	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2021/03/24 09:23
S521	32	S519 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2021/03/24 09:23
S519	57	S515 or S516 or S517	US-PGPUB; USPAT; USOCR	OR	OFF	2021/03/24 09:23
S518	15	S515 or S516 or S517	USPAT	OR	OFF	2021/03/24 09:23
S566	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2021/03/24 09:24
S565	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2021/03/24 09:24
S563	32	S561 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2021/03/24 09:24
S561	57	S557 or S558 or S559	US-PGPUB; USPAT; USOCR	OR	OFF	2021/03/24 09:24

S560	15	S557 or S558 or S559	USPAT	OR	OFF	2021/03/24 09:24
S555	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2021/03/24 09:24
S553	0	("200600183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2021/03/24 09:24
S552	0	("200600183779").PN.	USPAT; USOCR	OR	OFF	2021/03/24 09:24
S551	0	("20060183779").PN.	USPAT; USOCR	OR	OFF	2021/03/24 09:24
S548	57	S545 or S546 or S547	US-PGPUB; USPAT; USOCR	OR	OFF	2021/03/24 09:24
S547	49	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24
S546	41	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24
S545	54	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24
S541	2,550,628	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend) same organic acid	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24
S540	7,856	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24
S539	52,756	(drug or active or pharmaceutical) same (particle or microsphere) same (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24
S537	2,644	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24
S536	2,644	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24
S534	10,734	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24

S532	9	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2021/03/24 09:24

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S572	8	dabigatran etexilate same particle$4.clm.	US-PGPUB; USPAT	ADJ	OFF	2021/03/24 10:21
S573	16	dabigatran etexilate.clm. and particle$4.clm.	US-PGPUB; USPAT	ADJ	OFF	2021/03/24 10:23
S576	33	acid near10 particle$4.clm. and dabigatran	US-PGPUB; USPAT	ADJ	OFF	2021/03/24 10:24
S575	0	acid near10 particle$4.clm. and dabiagran	US-PGPUB; USPAT	ADJ	OFF	2021/03/24 10:24
S574	18,766	acid near10 particle$4.clm.	US-PGPUB; USPAT	ADJ	OFF	2021/03/24 10:24

3/31/2021 1:03:37 PM
C:\Users\Ishaak\Documents\EAST\Workspaces\14379613.wsp

Web Search History

date, time	web site	search string
3/31/2021 1:15:04 PM	Google	dabigatran etexilate particles
3/31/2021 1:15:12 PM	Google	dabigatran etexilate and acid separated
3/31/2021 1:15:16 PM	Google	dabigatran etexilate and acid separattion
3/31/2021 1:15:19 PM	Google	dabigatran etexilate and acid separation
3/31/2021 1:15:35 PM	Google	dabigatran etexilate and acid particle
3/31/2021 1:15:46 PM	Google	separating acid particle oral formulation

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Bibliographic Data

Application No: 14/379,613

Foreign Priority claimed: (•) Yes ( ) No

35 USC 119 (a-d) conditions met: [✓] Yes [ ] No [ ] Met After Allowance

Verified and Acknowledged: /LYNDSEY M BECKHARDT/ Examiner's Signature [ ] Initials

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
08/19/2014	424	1613	16326.0018FPWO
RULE			

APPLICANTS

TOWA Pharmaceutical Europe, S.L. Unipersonal, Barcelona, SPAIN

INVENTORS

Pratibha S. Pilgaonkar, Mumbai, INDIA

Maharukh T. Rustomjee, Mumbai, INDIA

Anilkumar S. Gandhi, Mumbai, INDIA

CONTINUING DATA

This application is a 371 of PCT/EP2013/053426 02/21/2013

FOREIGN APPLICATIONS

INDIA IN461/MUM/2012 02/21/2012

IF REQUIRED, FOREIGN LICENSE GRANTED**

10/16/2014

STATE OR COUNTRY

INDIA

ADDRESS

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P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903
UNITED STATES

FILING FEE RECEIVED

$1,480

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 01/27/2021

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
BECKHARDT, LYNDSEY MARIE	

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
01/27/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PRATIBHA S. PILGAONKAR,
MAHARUKH T. RUSTOMJEE, and ANILKUMAR S. GANDHI

Appeal 2020-003706
Application 14/379,613
Technology Center 1600

Oral Hearing Held Virtually: January 7, 2021

Before ERIC B. GRIMES, JOHN E. SCHNEIDER, and
MICHAEL A. VALEK, *Administrative Patent Judges*.

A P P E A R A N C E S

ON BEHALF OF APPELLANT:

E. JOSEPH GESS, ESQUIRE
MERCHANT & GOULD P.C.
1900 Duke Street
Suite 600
Alexandria, Virginia 22314
(703) 684-2511

The above-entitled matter came on for hearing on Thursday, January 7, 2021, commencing at 10:14 a.m. EST, by video/by telephone.

P R O C E E D I N G S

MR. GESS: Hello, this is Joe Gess. And I am calling in with regard to appeal number 2020-003706.

JUDGE SCHNEIDER: Good morning, Counsel. This is Judge Schneider. We have on the panel today Judges Grimes and Valek. Again, as you mentioned, we're here for appeal number 2020-003706. Counsel, the panel is familiar with the records so you need not delve into the facts more than you certainly need to. You have 20 minutes. And would you please again state your name for the record.

MR. GESS: Okay. Good morning, I am Erich Joseph Gess. And I'll be providing the oral argument on behalf of the appellant this morning. We did file some slides, and each slide has a specific title and I will be referring to the slides during the hearing. This is an appeal from the final rejection of May 30th, U.S. serial number 14/379613. And the claims on appeal are found on pages 13 to 15 of the appeal brief filed December 6th.

Appellant is requesting a reversal of the examiner's final rejection on the basis that decided prior art does not suggest the claim composition to one of ordinary skill in the art. The primary reference, U.S. 779 publication, relates solely to a single multilayered particle designed specifically to meet the challenges of dabigatran etexilate. There's simply no suggestion in U.S. 779 to use two distinct particles, only

the single design particle is mentioned. Knowing the limitation --

JUDGE VALEK: Counsel, let me stop you for a second. This is Judge Valek. What about the Habib reference, the 891 publication? Why doesn't that evidence some motivation to take that single particle from the 779 publication and redistribute it, I guess, into two distinct particles, in your view?

MR. GESS: In my view, the 891 relates to a -- first of all, it relates to basically any type of active agent, not specifically the dabigatran. Okay? And that is one particle. The second particle is really an inert excipient, a fat wax particle. There's a big difference here in the fact that the 779 publication requires that there's certain layers in its one particle such that with when that particle enters the stomach an acid microclimate is created which will allow the dabigatran to be dissolved quickly and be absorbed quickly.

And this will allow the bioequivalence to be correct. Whereas in the 891, again the two particles are quite different, there's no interaction between them. Quite frankly, one skilled in the art taking a look at -- I don't know, they probably would never even consider the secondary reference because there is no interaction and it has nothing to do with what's happening in the 779 publication which deals specifically with the dabigatran.

Now, as well, you know, it's known that generally in the art modifying chemical pharmaceutical formulations are

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unpredictable. This is true especially when a particular configuration of the formulation is described in such a way as being necessary, such as here with the dabigatran. There should really be no motivation to even try something different without an expectation of success. So I don't think the combination is proper because another important reason is that in order to unravel the particle of the 779 publication you have to basically destroy the very essence of what was designed.

In order to deal with dabigatran, this particular particle was designed where you have these specific layers of a core layer of the acid, an insulating layer around the acid, and then the dabigatran on the other side of that insulated layer. They're very close in contact so that when it enters the stomach -- now the insulating layer is very critical in the sense that it maintains stability during storage; it keeps the core, the acid, separated from the active substance layer during storage.

But once it enters the stomach it allows immediate diffusion of the acid to the dabigatran to allow the dabigatran to dissolve and then get quickly absorbed in the stomach before it's passed on -- before anything is passed on to the small intestine. And this is very, very important --

JUDGE VALEK: Counsel, this is Judge Valek again. Why wouldn't one of skill in the art expect the same microclimate or acidic microclimate to be formed if you split the organic acid into a separate particle from the API as the examiner has done

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in this combination?

MR. BYRD: Well, it certainly wouldn't be -- is there a microclimate? They're separated. I mean, in one of the slides I have, the last slide, which is our plain composition of at least two distinct particles. The particles in there you see that's not layered, they're separate particles, they're not immediate in close contact. It is this close contact. I think the --

JUDGE VALEK: They're not -- counsel, this is Judge Valek again, they're not contiguous but your diagram here isn't necessarily to scale. I'm not sure that there would be this sort of floating in the air in an actual capsule. So is there anything -- is there anything to the fact that in, I guess, the 779 publication the layers are contiguous with each other as opposed to being separate in sort of the examiner's combination?

MR. GESS: Well, the -- in the 779, the crux of the entire invention are in those three layers: The core, the insulating, and then the active substance. And it talks about immediate diffusion. And this is, again, in order before things are passed on to the small intestine they want that microclimate to be immediate in terms of the action within the stomach. I think in the declaration, Franz -- the declaration we referred to which was filed, he talks about how this combination of layers, together, is what is critical to his invention. And that's what his invention is. They don't consider anything

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else. And they don't -- they consider the particle with this -- these layers, contiguous, so that when it enters the stomach there is immediate diffusion of the acid and then that is a quick dissolution and a quick absorption. Does that happen --

JUDGE GRIMES: Counsel, this is Judge Grimes. Can I ask a question about the Habib reference where you do have two separate particles?

MR. GESS: Yeah?

JUDGE GRIMES: In that case are the two particles intended to interact in some way in vivo after it's administered?

MR. GESS: No, they do not interact. In fact, the second particle that you have, which is a fat wax particle, is simply -- it creates a protective barrier. So that if one skilled in the art, if one is considering, the 779 is considering unravelling the various layers and they're looking at the Habib reference, what would they unravel? Well, what you have in Habib is the active and then you have this inert incipient with no interaction. That really goes to the optional protective coating that they talk about in 779 because that would perform the same function. So that would be one particle. That would be the same as the fat wax particle in Habib. And then that would leave the crux of the invention of 779 which is those three contiguous layers, the particle of those three contiguous layers which is so critical to the invention. If you start unravelling those three layers you're destroying the

concept of 779. And you can't do that.

MR. VALEK: Counsel, this is Judge Valek again. Isn't it even more than that? I feel like maybe you're even understating what Habib is teaching because it's teaching that fat wax is designed to prevent dissolution of the active ingredient. And isn't that sort of the opposite of what is being done in the bronze reference?

MR. GESS: It is -- it is a protective barrier to not allow any kind of solvent to get in. You know, the purpose of Habib of course is to avoid abuse with regard to opioids. So they don't want anyone dissolving out the particular active agent. But yes, it is different in that sense that here we are looking for dissolution, in Habib they are actually trying to have a protective barrier. But that also goes to the type of particles.

If you were to follow the teaching of Habib and what are the two particles that you would even try to take from the 779 patent, again, one would probably have to be a protective coating material, and the other, again, to try and maintain those three layers which are so critical in terms of creating the microclimate immediately with immediate diffusion because they're so close together. That's what the prior art came up with to try and deal with dabigatran.

And the secondary reference, you know, I think from the standpoint since it's dealing with particles which do not interact, it would not suggest separating components which must

interact, but rather it would suggest having particles which do not interact. Okay. So that in a sense would not suggest our plain composition. As you said as well, if you really look at Habib in terms of what they're trying to do, they're trying to prevent things from actually going in and dissolving. So from that aspect it's totally different and one skilled in the art probably would not even considered Habib in any event.

But again if you were to try and follow their teachings, you would not meet the claim composition even if you followed their teachings and tried to create different particles because you would want two particles that do not interact. You would not separate the acid and the active substance into separate particles following the teachings of Habib.

MR. VALEK: Okay. This is Judge Valek. That's fair enough. Do you have anything else to present, Counsel?

MR. GESS: Just that the -- you know, this proposed combination never be attempted by one of ordinary skill in the art. It required destroying the concept of the 779 publication in order to get our claimed composition. But even if one did attempt to unravel following the teachings of 891 you would not even get our claimed composition because again you would have to have particles that did not interact and you'd have to maintain the -- the critical core of the 779, which is the three layers, the core material, the acid layer and the insulating layer, and the active substance of dabigatran. And again this is all dealing with dabigatran. That's what this is about.

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And this 779 was designed specifically to overcome these issues of insolubility which goes to its adequate viability. And therefore that's why this is so important to have, according to the 779, the three layers. And that is not our claimed composition. We are successful with regard to having separated and having a different composition, a composition that is not disclosed in any of the prior art. And certainly based upon our discussion and the reasons we discussed, the proposed combination would certainly not suggest the claimed composition to one of ordinary skill in the art.

JUDGE SCHNEIDER: Thank you, Counsel. Judge Grimes, do you have any questions?

JUDGE GRIMES: No more questions for me.

JUDGE SCHNEIDER: Judge Valek, are you finished with your questioning?

JUDGE VALEK: Yes, no more from me. Thank you, Counsel.

JUDGE SCHNEIDER: Counsel, the case is submitted. The decision will issue in due course but before you hang up I'd like to ask the court reporter if he needs any spellings from you.

Thank you very much, Counsel. The case is submitted and thank you for your time this morning.

MR. GESS: Thank you.

(Off the record at 10:30 a.m.)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 01/12/2021

MERCHANT & GOULD P.C.
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EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
01/12/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PRATIBHA S. PILGAONKAR, MAHARUKH T. RUSTOMJEE, and ANILKUMAR S. GANDHI

Appeal 2020-003706
Application 14/379,613
Technology Center 1600

Before ERIC B. GRIMES, JOHN E. SCHNEIDER, and MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

Appellant[1] submits this appeal under 35 U.S.C. § 134(a) involving claims to compositions of two distinct types of particles and capsules containing the same, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.[2]

---

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies Esteve Pharmaceuticals, S.A., as the real party in interest. Appeal Br. 1. Herein, we refer to Appellant's Appeal Brief filed December 6, 2019 ("Appeal Br.") and Examiner's Answer mailed February 19, 2020 ("Ans.").

[2] An oral hearing was held on January 7, 2021. A transcript of the hearing will be made of record.

STATEMENT OF THE CASE

"Dabigatran is a potent, reversible, univalent direct thrombin inhibitor" that is "currently available as dabigatran etexilate mesylate (DEM) under the brand name Pradaxa®." Spec. 2:6–17. The Specification explains that "the aqueous solubility of DEM is strongly pH dependent with rather high solubility in acidic media and very poor solubility in neutral and basic media." *Id.* at 2:24–26. Moreover, while "DEM is stable in the solid state" it "undergoes degradation by hydrolytic pathways in the presence of moisture" and "is acid sensitive." *Id.* at 2:29–31.

The Specification explains that "[d]ue to these physicochemical and biopharmaceutical properties of DEM . . . attempts have been made to provide compositions of DEM that are stable and/or provide desirable *in vitro* release and bioavailability." One such approach is described in Brauns,[3] which, according to the Specification:

> describes pharmaceutical compositions of DEM for oral administration in the form of pellets comprising (a) substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids . . . and (b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material. The separating agent layer or insulating layer separates the acid core from the active substance containing layer. . . . Such layered pellets are later filled into hard capsules.

Spec. 3:1–10.

According to the Specification, Brauns' "process of preparing layered pellets is cumbersome, time consuming and uneconomical" and, therefore, a need exists for "alternate compositions of dabigatran etexilate that are stable,

[3] US 2006/0183779 A1, published Aug. 17, 2006 ("Brauns").

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easy or convenient to prepare," and which "provide the desired *in vitro* release and bioavailability." Spec. 3:10–12, 3:24–26. The Specification purports to provide such an alternate composition in a form of "a mixture of at least two types of particles . . . wherein a) the first type of particles comprise the active ingredient; [and] b) the second type of particles comprise at least one pharmaceutically acceptable organic acid." *See id.* at 3:28–35.

Claims 21, 23, 26, 30, 32, and 40–48 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Claim 21 is illustrative and reads as follows:

> 1. A composition comprising: a mixture of at least two distinct types of particles wherein
>
> a) the first type of particle comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic acids and inorganic acids: and
>
> b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

Appeal Br. 13.

Appellant seeks review of Examiner's rejection of claims 21, 23, 26, 30, 32, and 40–48 under 35 U.S.C. § 103 as unpatentable over Brauns in view of Habib[4] and PubChem.[5] Appeal Br. 3–12.

[4] US 2008/0069891 A1, published March 20, 2008 ("Habib").
[5] "Compound Summary for CID 9578572: Dabigatran Etexilate," available at https://pubchem.ncbi.nlm.nih.gov ("PubChem").

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The issue is: Does the preponderance of evidence of record support Examiner's conclusion that the cited prior art renders obvious the claimed compositions?

Analysis

Examiner finds that Brauns "teaches dabigatran etexilate and organic acids provide[] a significantly improved formulation" and describes a particle containing an organic acid core surrounded by "a separating layer followed by a layer containing the active substance."[6] Ans. 4. Examiner acknowledges that Brauns does not teach the drug and organic acid "in two distinct types of particles," as claimed. *Id.* at 8.

For that limitation, Examiner relies on Habib. Examiner determines Habib teaches a pharmaceutical composition that "comprises two particles, the first type containing the pharmaceutical agent and the second comprising fat/wax material." Ans. 8. According to Examiner, it would have been obvious to formulate the composition taught by Brauns "as two distinct particles as [Habib] teaches [a] pharmaceutical composition [that] comprise[s] two distinct types of particles, one of which includes a pharmaceutical agent" and Brauns "teaches the need for spatial separation of the organic acid and the active substance." *Id.*

Appellant argues that Examiner has not presented a sufficient prima facie showing because Brauns describes only a single, layered particle composition that achieves an acidic microenvironment through "immediate diffusion" of the acid layer into the active substance layer (*see* Appeal Br. 4–7) and there is no motivation or suggestion in the cited references to change

[6] Examiner relies on PubChem to establish that the active substance in Brauns is dabigatran etexilate. *See* Ans. 4.

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that composition to the "two distinct types of particles" recited in Appellant's claims. *See id.* at 9. In particular, Appellant points out that Habib "is not related at all to, or concerned with, the necessity of a close proximity between an acid and active ingredient to obtain a desired result, *i.e.*, an acidic environment that allows for diffusion." *Id.* Thus, urges Appellant, "[o]ne of skill in the art could not reasonably predict that the single layered particles of [Brauns] could be separated to form a composition" of two distinct particles as recited in Appellant's claims. *Id.* at 10.

We are persuaded by Appellant's argument and agree that Examiner has not articulated a sufficient rationale for combining the two particle composition taught in Habib to modify the single particle composition taught in Brauns. Habib is directed to an "abuse resistant drug formulation" (Habib, title) comprising "two particles" wherein "[t]he first particle comprises an API" and "[t]he second particle comprises a fat/wax material present in a an amount sufficient to inhibit administration abuse of the API from the first particle," e.g., if a capsule containing those particles is crushed, dissolved or injected. *Id.* ¶¶ 8, 20.

It is not clear why one of ordinary skill in the art would have considered Habib's abuse resistant formulations to be relevant to the layered particle compositions taught in Brauns. Indeed, Brauns teaches that an advantage of the "spatial separation of the organic acid and active substance by the insulating layer" in its layered particle composition is that it increases bioavailability by facilitating the creation of "an acid microclimate in which the active substance can dissolve" when acid from the core diffuses into the drug layer. Brauns ¶ 11. In contrast, the second particle in Habib's

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composition is intended to achieve the opposite result, i.e., to inhibit dissolution of the drug. *See* Habib ¶ 36 ("It is believed that the combination of particles according to the present invention produces a barrier relative to the active ingredient-containing particles against solvent access, thereby protecting and preserving the intended controlled release properties of the active particles.").

In view of these teachings, Examiner has not sufficiently explained why a skilled artisan would be motivated to combine Habib with Brauns to achieve a composition with the "two distinct types of particles" recited in Appellant's claims. For this reason, Examiner has not met the burden to establish a prima facie showing of obviousness. Accordingly, the rejection is not supported by the preponderance of the evidence and we, therefore, reverse.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
21, 23, 26, 30, 32, 40–48	103	Brauns, Habib, PubChem		21, 23, 26, 30, 32, 40–48

REVERSED

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/379,613	08/19/2014	1613	1480	16326.0018FPWO	19	1

CONFIRMATION NO. 6655

CORRECTED FILING RECEIPT

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903



Date Mailed: 12/23/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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Inventor(s)

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Anilkumar S. Gandhi, Mumbai, INDIA;

Applicant(s)

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Erich Gess--28510
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Daniel Evans--55868

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2013/053426 02/21/2013

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INDIA 461/MUM/2012 02/21/2012

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If Required, Foreign Filing License Granted: 10/16/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/379,613**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO

CONFIRMATION NO. 6655

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POA ACCEPTANCE LETTER

OC000000122179194

Date Mailed: 12/23/2020

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/18/2020.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/qnguyen/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.	23552	Confirmation No.	6655

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

REAL PARTY OF INTEREST – NOTIFICATION OF NAME CHANGE

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P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

The Patent Trial and Appeal Board is notified that the Real Party of Interest in U.S. Application 14/379,613 is now TOWA PHARMACEUTICAL EUROPE, S.L. UNIPERSONAL.

A change of name document has been filed with the USPTO Assignment Recordation Branch and a Request to Change Applicant under 37 C.F.R. § 1.46 (c) (2) also has been filed.

If there are any questions relating to this filing, Applicant requests the undersigned attorney be contacted.

Respectfully submitted,

Date: December 22, 2020

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23552
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Electronic Acknowledgement Receipt

EFS ID:	41471213
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	22-DEC-2020
Filing Date:	19-AUG-2014
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Application Type:	U.S. National Stage under 35 USC 371

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	16326-0018FPWO-Real_Party_of_Interest_Update.PDF	77444 49d979170f2066c604858b8cfac07f2bef3c2cff	no	1
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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
14/379,613	August 19, 2014

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☐ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

OR

☑ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☐ The address associated with the above-mentioned Customer Number

OR

☑ The address associated with Customer Number: 23552

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box).

Towa Pharmaceutical Europe, S.L. Unipersonal

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	
Name	David Reid		
Title	CEO		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.151, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/82C (07-13)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

No more than ten (10) patent practitioners total may be appointed as set forth below by name and registration number. This page need not be submitted if appointing the Patent Practitioner(s) associated with a Customer Number (see form PTO/AIA/82B):

Name	Registration Number
E. Joseph Gess	28510
Melissa M. Hayworth	45774
Daniel R. Evans	55868

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Towa Pharmaceutical Europe, S.L. Unipersonal

Application No./Patent No.: 14/379,613 Filed/Issue Date: August 19, 2014

Titled: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Towa Pharmaceutical Europe, S.L. Unipersonal, a Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 054665, Frame 0739, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Melissa M. Hayworth/	December 18, 2020
Signature	Date
Melissa M. Hayworth	45774
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/379,613	08/19/2014	1613	1480	16326.0018FPWO	19	1

CONFIRMATION NO. 6655

CORRECTED FILING RECEIPT

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

OC000000119273958

Date Mailed: 08/18/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Pratibha S. Pilgaonkar, Mumbai, INDIA;
Maharukh T. Rustomjee, Mumbai, INDIA;
Anilkumar S. Gandhi, Mumbai, INDIA;

Applicant(s)

~~DOSE Innova, S.L~~., Barcelona, SPAIN;

Power of Attorney: Towa Pharmaceutical Europe, S.L. Unipersonal
Erich Gess--28510
Melissa Hayworth--45774
Daniel Evans--55868

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2013/053426 02/21/2013

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
INDIA 461/MUM/2012 02/21/2012

Permission to Access Application via Priority Document Exchange: No

Permission to Access Search Results: No

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Pratibha	S.	PILGAONKAR	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Mumbai	Country of Residence	IN

Mailing Address of Inventor:

Address 1	221 Annexe Bldg.		
Address 2	Goregaon-Mulund Link Road		
City	Mumbai	**State/Province**	
Postal Code	400 078	**Country**	IN

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Maharukh	T.	RUSTOMJEE	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Mumbai	Country of Residence	IN

Mailing Address of Inventor:

Address 1	221 Annexe Bldg.		
Address 2	Goregaon-Mulund Link Road		
City	Mumbai	**State/Province**	IN
Postal Code	400 078	**Country**	IN

Inventor 3 Remove

Legal Name

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Anikumar	S.	GANDHI	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Mumbai	Country of Residence	IN

Mailing Address of Inventor:

Address 1	221 Annexe Bldg.		
Address 2	Goregaon-Mulund Link Road		
City	Mumbai	**State/Province**	
Postal Code	400 078	**Country**	IN

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	23552		
Email Address	mhayworth@merchantgould.com	Add Email	Remove Email

Application Information:

Title of the Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
Attorney Docket Number	16326.0018FPWO	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	23552		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Expired		[Remove]
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14379613	a 371 of international	PCT/EP2013/053426	2013-02-21

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Remove Access Code[i] (if applicable)
461/MUM/2012	IN	2012-02-21	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name: ~~DOSE Innova, S.L.~~ TOWA Pharmaceutical Europe, S.L. Unipersonal

Mailing Address Information For Applicant:

Address 1	Carrer de Sant Mari, 75-97 Polígon Industrial de		
Address 2	Carrer de Sant Mari, 75-97		
City	Barcelona	**State/Province**	
Country	ES	Postal Code	08107
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Melissa M. Hayworth/			Date (YYYY-MM-DD)	2020-12-18
First Name	Melissa	Last Name	Hayworth	Registration Number	45774

Additional Signature may be generated within this form by selecting the Add button.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IPR2025-01107
MSN Exhibit 1002
Page 111 of 680

Electronic Acknowledgement Receipt

EFS ID:	41438201
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	18-DEC-2020
Filing Date:	19-AUG-2014
Time Stamp:	18:14:59
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Req to correct/update/change appl name until pay issue fee	16326-0018FPWO-Request_Change-Applicant.PDF	80765 1b05d35694f5101c75363e702a5f23019746066e	no	1

Warnings:

Information:					
2	Req to correct/update/change appl name until pay issue fee	16326-0018FPWO-Dose-Towa_aia0041.PDF	204877 96cd60f52ebdffedee4bc66e34e5b244fe5bec84	no	2
Warnings:					
Information:					
3	Power of Attorney	16326-18FPWO_POA-TOWA_Signed.PDF	1337314 98eb47bc952e79a163075f4d0482cd5cd06c93fe	no	2
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
4	Assignee showing of ownership per 37 CFR 3.73	16326-0018FPWO_373c.PDF	118335 f46e97889e35cfcac6dbe9b530e9705c920e4edc	no	3
Warnings:					
Information:					
5	Request for Corrected Filing Receipt	16326-0018FPWO_Corrected_OFR_Dose-Towa.PDF	1203001 269ffc981dc33282d1484663f186d0767cca59bb	no	1
Warnings:					
Information:					
6	Application Data Sheet	16326-18FPWO-SADS_Dose-Towa.PDF	5149060 0a1819d2f547cb447b8dd3e5c00ce2804669b8e2	no	9
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
		Total Files Size (in bytes):	8093352		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.	23552	Confirmation No.	6655

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

REQUEST TO CHANGE APPLICANT UNDER 37 CFR § 1.46 (c)(2)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

It respectfully is requested that the Applicant name of the subject application be updated to reflect the current name.

Applicant's name has changed from Dose Innova, S.L. to Towa Pharmaceutical Europe, S.L. Unipersonal. A change of name document has been filed with the Assignment Branch. In support of the requested change of the Applicant's name submitted herewith are a Supplemental Application Data Sheet, PTO/AIA/41, a Statement Under 37 C.F.R. § 3.73(c), Power of Attorney, and a Corrected Official Filing Receipt.

It is believed that no fees are due with this submission. However, the Commissioner is hereby authorized to charge any deficiencies or credit any overpayment with respect to this patent application to deposit account number 13-2725 (Docket No. 16326.0018FPWO).

If there are any questions relating to this filing, Applicant requests the undersigned attorney be contacted.

Respectfully submitted,

Date: December 18, 2020

/Melissa M. Hayworth/
Melissa M. Hayworth
Registration No. 45774

Merchant & Gould PC
PO Box 2903
Minneapolis, MN 55402-0903
Telephone No.: 703.684.2522
Facsimile No.: 612.332.9081

23552
PATENT TRADEMARK OFFICE

Doc Code: R46C.REQ
Document Description: Request under 37 CFR 1.46(c) to correct, update or change the applicant.

PTO/AIA/41 (04-15)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST TO CORRECT OR UPDATE THE NAME OF THE APPLICANT UNDER 37 CFR 1.46(c)(1), OR CHANGE THE APPLICANT UNDER 37 CFR 1.46(c)(2)

(FOR USE ONLY IN APPLICATIONS FILED ON OR AFTER SEPTEMBER 16, 2012)

Application Number	14/379613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. Pilgaonkar
Art Unit	1613
Examiner Name	Lyndsey Marie Beckhardt
Practitioner Docket Number	16326.0018FPWO

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant hereby **requests that the name of the applicant be corrected or updated under 37 CFR 1.46(c)(1), or that the applicant be changed under 37 CFR 1.46(c)(2),** in the above-identified application. **Requests under 37 CFR 1.46(c)(1) or (c)(2) cannot be submitted after payment of the issue fee or if the application has been patented.**

Please check the applicable box(es) below.

☐ 1. This request is to **correct or update the name of the applicant** (**under 37 CFR 1.46(c)(1)**) and includes:

☐ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). A Corrected Web-based ADS may be used.

Note: Requests under 37 CFR 1.46(c)(1) may be filed to correct typographical errors in the name of the § 1.46 applicant, or for updating the name of the § 1.46 applicant (*i.e.*, where there is no change in the applicant itself but just in the applicant's name). See the Manual of Patent Examining Procedure (MPEP) section 605.01.

■ 2. This request is to **change the applicant** (**under 37 CFR 1.46(c)(2)**) and includes:

■ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) that identifies the changes with proper markings (underlining for insertions and strikethrough for deletions). A Corrected Web-based ADS may be used.

■ A Statement Under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent). See MPEP 325.

I am the

☐ applicant* ■ attorney or agent of record Registration number 45774 ☐ attorney or agent acting under 37 CFR 1.34 Registration number _____

Signature /Melissa M. Hayworth/

Typed or printed name Melissa M. Hayworth

Date 18 December 2020

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

☐ ** Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.36. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 12/18/2020

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
BECKHARDT, LYNDSEY MARIE	

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
12/18/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte Pratibha S. Pilgaonkar, *et al.*

Appeal 2020-003706
Application 14/379,613
Technology Center 1600

Before Deputy Clerk, Hearing Operations.

ORDER GRANTING REQUEST FOR TELEPHONIC HEARING

An oral hearing before a merits panel of the Patent Trial and Appeal Board has been scheduled to be included in the session of hearings commencing **Thursday, January 7, 2021 at 9:00 AM CT**. A Telephonic Oral Hearing has been granted.

This appeal hearing is set to be heard in a session of oral hearings beginning at **9:00 AM CT PTAB Hearings will provide Appellant with connection information prior to the hearing.** The Board will provide a court reporter and a transcript of the call will be entered into the record. All other expenses involved with the Telephonic Hearing, such as the cost of the call, must be borne by Appellant.

The panel will have access to all papers in Patents E2E. During the oral hearing, Appellant is advised to identify clearly and specifically all papers referenced (e.g., page of Appeal Brief; portions of a patent by column and line numbers) to ensure the clarity and accuracy of the court reporter's transcript. In addition, Appellant is advised to identify themselves each time they speak. Furthermore, the remote nature of the oral hearing may also result in an audio lag, and so Appellant is advised to observe a pause prior to speaking, so as to avoid speaking over others.

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MINNESOTA 55402-0903

The United States Patent and Trademark Office
PATENT TRIAL AND APPEAL BOARD

Merchant & Gould, P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903

Appeal No:	2020-003706
Appellant:	Pratibha S. Pilgaonkar et al.
Application No:	14/379,613
Hearing Docket:	Biotech
Hearing Date:	Thursday, January 7, 2021
Hearing Time:	9:00 AM CT
Location:	**Telephonic**

APPELLANT RESPONSE TO NOTICE OF HEARING

Appellant responds to the NOTICE OF HEARING in the above-identified appeal.

Hearing Attendance Options (please select one)

(X) I elect a TELEPHONIC hearing.

( ) I WAIVE the hearing.

( ) I am requesting to RESCHEDULE the hearing. **A separate paper must be filed.**

Conflicts

To aid the judges assigned to the appeal in determining whether any conflicts exist that may require a recusal, please list the names of any additional person(s) who will be participating in the oral hearing and their affiliation with Appellant.

Special Requests

If Appellant has any specials requests related to appearing at telephonic oral hearing, please list those requests. Special requests may include accommodations for hearing impairments. For any special request, please indicate any ways that the PTAB may accommodate the special request.

Representatives of the Applicant, who are located in Spain, would like to attend the Hearing telephonically. Please provide a conference number for domestic and international attendance, if possible.

For any questions regarding Appellant's response to the NOTICE OF HEARING, Appellant may be reached via the contact information provided below.

ERICH JOSEPH GESS	28,510
Typed or Printed Name of Attorney/Agent/Appellant	Registration No.
jgess@merchantgould.com	703-684-2511
E-Mail address	Phone number
[signature]	12/8/20
Signature of Attorney/Agent/Appellant	Date

Electronic Acknowledgement Receipt

EFS ID:	41337057
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	09-DEC-2020
Filing Date:	19-AUG-2014
Time Stamp:	14:24:58
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Confirmation of Hearing by Appellant	16326-18FPWO-Confirmation_of_Hearing.PDF	155703 b5da7794fa12884c02fdc202aec2272b2ba3e0e0	no	2

Warnings:

Information:	
Total Files Size (in bytes):	155703

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 11/20/2020

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
11/20/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

The United States Patent and Trademark Office
PATENT TRIAL AND APPEAL BOARD

Merchant & Gould, P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903

Appeal No:	2020-003706
Appellant:	Pratibha S. Pilgaonkar et al.
Application No:	14/379,613
Hearing Docket:	Biotech
Hearing Date:	Thursday, January 7, 2021
Hearing Time:	9:00 AM CT
Location:	**Telephonic Hearing**

NOTICE OF HEARING
RESPONSE REQUIRED WITHIN 21 DAYS

The Patent Trial and Appeal Board (PTAB) will hear the above-identified appeal on the date indicated. The hearing will commence at the time set, and as soon as the argument in one appeal concludes, the succeeding appeal will be taken up. The time allowed for argument is 20 minutes, unless additional time is requested and approved before the argument commences. If the application involved in this appeal has been published, the hearing will be open to the public.

Hearing Attendance Confirmation or Waiver

Appellant is required to confirm attendance at the hearing or waive the hearing within 21 days of the mailing date of this notice. Appellant may confirm or waive attendance by completing the "APPELLANT RESPONSE TO NOTICE OF HEARING" and returning it to the PTAB.

Options for Hearing Attendance

If Appellant opts to attend the hearing, then Appellant may appear by telephone.

If Appellant is no longer interested in having a hearing, then Appellant must file a waiver of the hearing with the PTAB. This allows the panel of Administrative Patent Judges assigned to the appeal to act promptly on the appeal without waiting for the hearing date.

If Appellant fails to respond to this NOTICE OF HEARING, the PTAB will issue a decision on the briefs based on the written record.

Telephonic Hearing Attendance

Appellant may participate in a hearing by telephone. Appellant will receive an Order detailing the telephonic hearing instructions.

Members of the public may request to listen in on this oral hearing. If resources are available, the Board generally expects to grant such requests. If Appellant objects to the Board granting such requests, for example, because confidential information may be discussed, the party must notify the Board by contacting PTABHearings@uspto.gov at least five business days prior to the oral hearing date.

Special Requests

If Appellant has any special requests related to appearing at a telephonic hearing, Appellant should inform the PTAB. Special requests may include accommodations for hearing impairments. Additionally, Appellant may assist the PTAB by indicating ways to accommodate the special requests. The PTAB will make every effort to accommodate the special requests in the manner suggested by Appellant.

Submission of Appellant's Demonstratives

If Appellant has any Power Point slides or other demonstratives, they must be provided to the PTAB five (5) days before the hearing date by sending them to PTABHearings@uspto.gov.

Submission of Appellant's Response to the Notice of Hearing*

To return a completed APPELLANT RESPONSE TO NOTICE OF HEARING, Appellant may use the following transmittal methods:

1. By the USPTO Electronic Filing System (EFS), available at https://www.uspto.gov/patents-application-process/file-online/

2. By facsimile transmission to:
   - The USPTO Central fax number (official copy): **(571) 273-8300; and**
   - The PTAB Hearing fax number (courtesy copy): **(571) 273-9797.**

In all communications relating to this appeal, please identify the appeal number along with the underlying application number.

Questions

For further information about hearings, see 37 CFR § 41.47 and the Hearings section of the PTAB webpage: http://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/hearings. Also, for questions, please contact the PTAB Hearings Clerk at 571-272-9797.

The United States Patent and Trademark Office
PATENT TRIAL AND APPEAL BOARD

Merchant & Gould, P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903

Appeal No:	2020-003706
Appellant:	Pratibha S. Pilgaonkar et al.
Application No:	14/379,613
Hearing Docket:	Biotech
Hearing Date:	Thursday, January 7, 2021
Hearing Time:	9:00 AM CT
Location:	**Telephonic**

APPELLANT RESPONSE TO NOTICE OF HEARING

Appellant responds to the NOTICE OF HEARING in the above-identified appeal.

Hearing Attendance Options (please select one)

( ) I elect a TELEPHONIC hearing.

( ) I WAIVE the hearing.

( ) I am requesting to RESCHEDULE the hearing. **A separate paper must be filed.**

Conflicts

To aid the judges assigned to the appeal in determining whether any conflicts exist that may require a recusal, please list the names of any additional person(s) who will be participating in the oral hearing and their affiliation with Appellant.

_____

_____

Special Requests

If Appellant has any specials requests related to appearing at telephonic oral hearing, please list those requests. Special requests may include accommodations for hearing impairments. For any special request, please indicate any ways that the PTAB may accommodate the special request.

_____

_____

For any questions regarding Appellant's response to the NOTICE OF HEARING, Appellant may be reached via the contact information provided below.

Typed or Printed Name of Attorney/Agent/Appellant	Registration No.
E-Mail address	Phone number
Signature of Attorney/Agent/Appellant	Date

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/379,613	08/19/2014	1613	1480	16326.0018FPWO	19	1

CONFIRMATION NO. 6655

CORRECTED FILING RECEIPT

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

OC000000119273956

Date Mailed: 08/18/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Pratibha S. Pilgaonkar, Mumbai, INDIA;
Maharukh T. Rustomjee, Mumbai, INDIA;
Anilkumar S. Gandhi, Mumbai, INDIA;

Applicant(s)

DOSE Innova, S.L., Barcelona, SPAIN;

Power of Attorney:
Erich Gess--28510
Melissa Hayworth--45774
Daniel Evans--55868

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2013/053426 02/21/2013

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
INDIA 461/MUM/2012 02/21/2012

Permission to Access Application via Priority Document Exchange: No

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/16/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/379,613**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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IPR2025-01107
MSN Exhibit 1002
Page 132 of 680

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 04/21/2020

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
BECKHARDT, LYNDSEY MARIE	

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
04/21/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PRATIBHA S. PILGAONKAR ET AL.

Appeal 2020-003706
Application 14/379,613
Technology Center 1600

APPEAL DOCKETING NOTICE

The Patent Trial and Appeal Board received the appeal in the above-identified application from the Technology Center on April 17, 2020, and has assigned it the appeal number indicated above.

The recipient of this notice is reminded of its ongoing duty, within 20 days of any change during the proceeding, to update its mandatory notices to identify the real party-in-interest and each judicial or administrative proceeding that could affect, or be affected by, the Board proceeding. 37 C.F.R. § 41.8. For example, another docketed appeal in a related application may have the potential to affect, or be affected by, the Board proceeding.

In all future communications regarding this appeal, please include both the application number and the appeal number. Telephone inquiries can be made by calling 571-272-9797 and referencing the appeal number listed above. The mailing address for the Board is:

PATENT TRIAL and APPEAL BOARD
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VIRGINIA 22313-1450

PTO/SB/32 (07-09)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR ORAL HEARING
BEFORE
THE PATENT TRIAL AND APPEAL BOARD

Docket Number (Optional)
16326.0018FPWO

I hereby certify that this correspondence is being facsimile transmitted to the USPTO, EFS-Web transmitted to the USPTO, or deposited with the United States Postal Service as first class mail with sufficient postage in an envelope addressed to "Commissioner for Patents, P. O. Box 1450, Alexandria VA 22313-1450" [37 CFR 1.8(a)] on _____.

Signature _____

Typed or printed name _____

In re Application of: Pratibha S. Pilgaonkar

Application Number	Filed
14379613	August 19, 2014

For: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Art Unit	Examiner
1613	Lyndsey Marie Beckhardt

Applicant hereby requests an oral hearing before the Patent Trial and Appeal Board in the appeal of the above-identified application.

The fee for this Request for Oral Hearing is (37 CFR 41.20(b)(3)) $ 1,300.00

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account. I have enclosed a duplicate copy of this sheet.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 132725 .

☒ Payment made via EFS-Web.

☐ A petition for an extension of time under 37 CFR 1.136(b) (PTO/SB/23) is enclosed. For extensions of time in reexamination proceedings, see 37 CFR 1.550.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 28,510 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____

/E. Joseph Gess/
Signature

E. Joseph Gess
Typed or printed name

April 15, 2020
Date

703-684-2511
Telephone number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 41.20(b)(3). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor:	Pratibha S. Pilgaonkar	Examiner:	BECKHARDT, LYNDSEY
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.	23552	Confirmation No.	6655

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

REPLY BRIEF

Mail Stop Reply Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commissioner for Patents

In response to the Examiner's Answer dated February 19, 2020, Appellant submits this Reply Brief pursuant to 37 C.F.R. § 41.41.

The Examiner's rebuttal is based on the '779 publication teaching the need for spatial separation of the organic acid and the active substance. The Examiner then applies the '891 publication to show that the use of separate particles in a pharmaceutical formulation is known. The Examiner thereby concludes that one of ordinary skill in the art would have had motivation and a reasonable expectation of success in formulating an oral dosage form in separate particles, with the active agent in one particle and an excipient in another. The Examiner concludes that when the particles are separated into one containing the acid and the other containing the active agent, the necessary components are in "sufficient close proximity" to each other, as required by the '779 publication.

However, how the Examiner reaches this conclusion after a reading of the '779 publication and the inventor's explanatory Declaration is difficult to understand. Both the '779 patent publication and the inventor's own explanatory Declaration require that a single particle must be used to satisfy the necessary proximity and thereby achieve the results of the '779 publication.

It is clear that the Examiner is ignoring the full teachings of the '779 publication, and is giving no weight to the explanatory Declaration of the inventor, which underscores and confirms those teachings.

The full teachings of the '779 publication must be considered. And those teachings require one particle. The Examiner tenuously and merely concludes that two particles would provide spatial separation, while also providing the necessary proximity to ensure immediate diffusion. This mere conclusion flies in the face of the teachings of the '779 publication, particularly when the inventor of the '779 publication specifically explains his invention as requiring a single particle to achieve the desired and improved results. The Brauns Declaration is extrinsic evidence of how a skilled artisan would reasonably understand the disclosure of the '779 publication (the prior art). And that disclosure specifies the use of a single particle to achieve the desired results. In Appellant's opinion, there simply is no basis for the Examiner's conclusion.

The Examiner asserts that it would have been *prima facie* obvious to one of ordinary skill in the art to formulate the single particle taught by the '779 publication as two distinct particles. That one of ordinary skill in the art would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation. As such, why did not the inventor of the '779 patent publication simply use or disclose two particles for spatial separation? Because it is **not** just any spatial separation that is taught and needed in the '779 publication, as explained in the Brauns Declaration. As explained in the Declaration by Brauns, paragraph 19, once the formulation enters the stomach, the acid core layer provides the low pH microenvironment and then diffuses to the active substance layer immediately. The insulating layer just acts as a protective layer between the acid core and active substance layer on storage, but once in the stomach it permits the diffusion of the acid to the active substance layer immediately. This immediate diffusion and combination **requires** a single particle – as taught by the '779 publication. One of ordinary skill in the art would **never** be motivated to separate the components into two particles because that would destroy the teachings of the '779 publication. Separation into two particles would not, and could not, guarantee the important immediate diffusion of the acid to the active substance achieved by a single particle as taught by the '779

publication. Therefore, the improved bioavailability could not be reasonably expected without the use of a single particle. Thus, upon a full understanding of the teachings of the '779 publication, there can be **no *prima facie* case of obviousness**. There is certainly no motivation to use two particles, and there can be no reasonable expectation of success in using two particles to achieve improved bioavailability. The Brauns Declaration explains this completely.

Nevertheless, the Examiner repeatedly maintains and merely concludes that it would be obvious that two particles would give the spatial separation, while also providing the necessary proximity to ensure immediate diffusion. However, there is no mention of necessary proximity in the secondary reference, the '891 publication, to guarantee immediate diffusion of the acid to the active substance and thereby achieve increased bioavailability. As taught in the '779 publication and as explained in the Brauns Declaration, this immediate diffusion can only be achieved by a layered single particle. The Examiner's position totally ignores – and destroys – the teachings of the '779 publication.

Based on the prior art – the '779 publication – a single particle must be used. This is explained in the Brauns Declaration.

The Examiner might have a "hope" that separation into two distinct particles can still achieve the increased bioavailability of the '779 publication, but based upon a reading of the '779 publication, particularly as explained in the Brauns Declaration, there certainly can be no reasonable expectation of success. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). Simply being capable of modifying is not enough. *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990).

There simply is no teaching, or even a suggestion, in U.S. '779 to make the necessary modification in order to use the present claimed composition. There is no reasonable expectation of success based upon U.S. '779. In contrast, Appellant has found quite surprisingly, that the present compositions are stable, easy to prepare and provide effective in-vitro release of the active.

Accordingly, based upon the disclosure of the '779 publication and the inventor's explanation of that disclosure in the Brauns Declaration, there can be no reasonable expectation

of success by one of ordinary skill in the art to achieve the results of the '779 publication when separating the substances of the single particle into two particles. Yet, the Appellant has shown that this is the case, which is a surprising result.

It certainly would be surprising to the inventor of the prior art '779 patent!

For the foregoing reasons, and the reasons set forth in the Appeal Brief filed November 9, 2018, Appellant respectfully requests the Patent Trial and Appeal Board to reverse the obviousness rejection of claims 1-16.

Submitted herewith is a Request for Oral Hearing, the fee under 37 C.F.R. § 41.20(b)(3) for Oral Hearing, and the fee under 37 C.F.R. § 41.20(b)(4) for forwarding the Appeal Brief to the Board of Appeals.

The Director is authorized to charge any deficiency, or credit any overpayment to, Deposit Account No. 13-2725 (Attorney Docket No. 16326.0018FPWO).

Respectfully submitted,

Date: April 15, 2020

/E. Joseph Gess/
E. Joseph Gess
Registration No.: 28,510

MERCHANT & GOULD P.C.
P.O Box 2903
Minneapolis, MN 55402
Telephone No. 703.684. 2511
Facsimile No. 612.332.9081

23552

IPR2025-01107
MSN Exhibit 1002
Page 140 of 680

Electronic Patent Application Fee Transmittal

Application Number:	14379613
Filing Date:	19-Aug-2014
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Filer:	Erich Gess/Lisa Amos
Attorney Docket Number:	16326.0018FPWO

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
REQUEST FOR ORAL HEARING	1403	1	1300	1300
APPEAL FORWARDING FEE	1413	1	2240	2240

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**3540**

Electronic Acknowledgement Receipt	
EFS ID:	39168551
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Erich Gess/Lisa Amos
Filer Authorized By:	Erich Gess
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	15-APR-2020
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.19 (Document supply fees) 37 CFR 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Oral Hearing	2020-04-15_16326-0018FPWO_Request_Oral_Hearing-sb0032.PDF	113304 beb9ab350a62e51d25c3b92e311be2767e21d7c8	no	2
Warnings:					
Information:					
2	Reply Brief Filed	2020-04-15_16326-0018FPWO_Reply_Brief.PDF	130818 b411435ac48a1444cf59433b5ab8f13b31ccbb86	no	4
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32318 5d303469a3b781807287826a8e025fea24beec9b	no	2
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 02/19/2020

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EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Application Number: 14/379,613
Filing Date: 19 Aug 2014
Appellant(s): Pilgaonkar et al.

E. Joseph Gess
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/06/2019.

(1) Grounds of Rejection to be Reviewed on Appeal

Every ground of rejection set forth in the Office action dated 05/30/2019 from which the appeal is taken is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

The following ground(s) of rejection are applicable to the appealed claims.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter

of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Appellant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21, 23, 26, 30, 32 and 40-48 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US 2006/0183779 (previously applied) in view of US 2008/0069891 (previously applied) as evidenced by PubChem (previously applied).

Regarding claim 21, the limitation of a composition comprising a) particles that comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salts; and b) particles that comprise at least one pharmaceutically acceptable organic acid is met by active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-mthyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmaceutically acceptable salts thereof (abstract), wherein PubChem evidences the structure of the '779 publication [0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1), thus teaching the acid contained in the core and the drug in a separate layer distinct from the acid.

The limitation of wherein at least one type of particles is coated with a protective coating layer is met by the ‘779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]).

The limitation of the second type of particles is coated with a protective coating layer is met by the ‘779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]), thus indicating a coating to be applied over the inner particle layer which contains the acid, wherein the second particle contains the acid.

The limitation of wherein the first type of particles is free from acids is met by the ‘779 publication teaching spatial separation of the organic acid and the active substance, wherein the organic acid and the active agent are taught to be in a particle ([0010], [0011]).

Regarding claim 23, the limitation of further comprising at least one pharmaceutically acceptable excipient is met by the ‘779 publication teaching polymer selected from gum Arabic included in the particles [0012]. The ‘779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient.

Regarding claim 26, the limitation of comprising from 0.01 wt% to 90% of dabigatran etexilate (expressed as dabigatran etexilate mesylate) is met by the '779 publication teaching dabigatran etexilate (abstract, [003]) wherein the active agent is taught to be present at 5-60% [0014].

Regarding claims 30, the limitation of 2-95% of the at least one pharmaceutically acceptable organic acid is met by the '779 publication teaching 30-100% of the organic acid in the core [0012].

Regarding claim 32, the limitation of wherein the composition comprises from 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

Regarding claim 40, the limitation of wherein the at least one pharmaceutically acceptable excipient is selected form the group consisting of binder, disintegrants, diluents, surfactants, glidant, lubricants and combinations thereof is met by the '779 publication teaching the '779 publication teaches embodiments wherein talc is present (Table 1, [0014]), wherein the instant specification teaches lubricants include talc [0053], the elected excipient. The '779 publication additionally teaches the use of a binder [0012].

Regarding claims 41 and 46, the limitation of a composition consisting of a mixture of at least one pharmaceutically acceptable excipient, wherein a) the first type comprising dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymer thereof, wherein the first type of particle is free from organic or inorganic acids and a second type comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free form dabigatran etexilate is met by the '779 publication teaching structure [0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The '779 publication teaches dabigatran etexilate and organic acids

provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1). The '779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]). The '779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient. the '779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]), thus indicating a coating to be applied over the inner particle layer which contains the acid, wherein the second particle contains the acid. The '779 publication teaches the active agent, an organic acid with a protective coating and an excipient.

It is noted that the use of 'at least one excipient' allows for additional ingredients in the formulation beyond the listed two particles, and additionally the 'comprising' language regarding the first and second particles allows for additional ingredients in the particles.

Regarding claim 42, the limitation of comprising from 0.01 to 90 wt% of dabigatran etexilate, as dabigatran etexilate mesylate is met by the '779 publication teaching the 5 to 60 wt% of the pharmaceutical composition [0014].

Regarding claims 43 and 48, the limitation of wherein the first type of particles comprise at least one pharmaceutically acceptable excipient is met by the '779 publication teaching the use of binders or talc ([0014], Table 1).

Regarding claim 44, the limitation of wherein the at least one pharmaceutically acceptable recipient is selected from a group including binders, disintegrants, diluents,

lubricants and combos thereof is met by the '779 publication teaching the use of binders or talc ([0014], Table 1).

Regarding claims 45 and 47, the limitation of wherein the composition comprises from 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

The '779 publication does not specifically teach components a) and b) in two distinct types of particles (claim 21, 41).

The '891 publication teaches a pharmaceutical composition may include granulate including at least one active pharmaceutical ingredient. The composition may include a coating on the granulate. The composition further comprises a second particle comprising a fat/wax. The granulate are formed into various dosage forms (abstract, [0018]). The invention comprises two particles, the first type containing the pharmaceutical agent and the second comprising fat/wax material [0020].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779 publication as two distinct particles as the '891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches the an

oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication, thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine prior art elements according to known methods to yield a predictable results of separate particles in place of separate layers for the drug and acid formulation and obvious to try based on the '891 publication teaching it was known to use two separate particles.

(2) Response to Argument

Appellant argues the present invention is a mixture of two distinct types of particles wherein the first type is free from organic and inorganic acids and the second type comprise an organic acid. The primary cited reference is the '779 publication wherein Figure 1 demonstrates a preparation including a special organic acid core, and insulating layer separating the core material and an active substance layer. The '779 publication is a single particle with no other configuration taught.

In response, the '779 publication teaches the use of Dabigatran etexilate ([0003], PubChem evidences page 1, right column, page 3 structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007], wherein the form of the pellet containing an organic acid separating

layer followed by a layer containing and active substance ([0010], Figure 1), thus teaching the use of an acid separated from the active agent to improve the formulation was known at the time of the invention. The '891 publication teaches the use of two separate particles in a pharmaceutical composition. Thus the active agent would remain separate from the acid, which would still be present to provide the desired release/absorption. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779 publication as two distinct particles as the '891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication.

Appellant argues the '779 publication teaches the advantages of special separation of the organic acid and the active agent. The '779 publication provides 2

examples of its layered particle with that of a conventional tablet stating the formation containing the layered single particle were improved by a factor of in comparison to the conventional tablet. Thus the layered tablet containing active substance layer separated by an insulating layer provided improved bioavailability and no other construction or configuration are suggested for achieving the improved bioavailability.

In response, Appellant's arguments regarding additional configurations are addressed above regarding the '891 publication teaching of 2 distinct particles. Regarding the improvement factor compared to a conventional tablet, the '779 publication teaches the separation of the acid from the active agent to lead to improved bioavailability through the inclusion of the acid [0028]. In using the separated particles in the same composition the acid would still be present, and thus lead to increased bioavailability.

Appellant argues the '779 publication demonstrates the formation that contain layered single particles having an organic acid core and an active substance separated by an insulating layer are needed to achieve the improved bioavailability.

In response, the '779 publication (examples 1 and 2) demonstrate the need for an acid to be present, however formations wherein the acid is present in other configurations was not tested. Therefore the '779 publication does not demonstrate that the single particle form is a requirement for the increased bioavailability, rather that the acid is required.

Appellant argues the declaration provided in the '779 publication is by the inventor, Dr. Ulrich Brauns. The declaration states that an acid is needed to create an acidic micro-environment to dissolve the prodrug, maintain stability for storage purposes

and work well for the entire patient population. The declaration states that the acid core layer, an insulating layer and an active substance layer are necessary components of this invention. According to the Brauns in his declaration the active substance, insulating layer and acid must be in a single particle as necessary components. Wherein the insulating layer is protective and permit the diffusion of the active substance into the stomach immediately. This configuration was the only way that Braun and the '779 publication contemplated to control the immediacy.

In response, as Appellant notes the Braun declaration is directed to the need for the acid for bioavailability while also remaining separate from the activity agent during storage. In the '779 publication this is accomplished by the use of a layered microparticles. When the particles are separated into one containing an acid with a coating and an additional particle comprising the active agent the acid particles containing the coating and the separated active substance would still be present, thus the necessary components are still present and in close proximity to each other. Braun did not discuss such an embodiment, therefore does not teach away from such an embodiment. The '779 publication teaches the use of Dabigatran etexilate ([0003], PubChem evidences page 1, right column, page 3 structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007], wherein the form of the pellet containing an organic acid separating layer followed by a layer containing and active substance ([0010], Figure 1), thus teaching the use of an acid separated from the active agent to improve the formulation was known at the time of the invention. The '891 publication teaches the use of two separate particles in a pharmaceutical composition. Thus the active agent would

remain separate from the acid, which would still be present to provide the desired release/absorption. Appellant has not provided evidence to the contrary.

Appellant argues the three component layered single particle solve the necessity of spatial separation as well as creating the necessity spatial arrangement for achieving diffusion. According it cannot be obvious to eon skill in the art to separate the particle and still achieve the diffusion needed to provide good dissolution characteristics and consistent bioavailability.

In response, the '779 publication teaches the use of Dabigatran etexilate ([0003], PubChem evidences page 1, right column, page 3 structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007], wherein the form of the pellet containing an organic acid separating layer followed by a layer containing and active substance ([0010], Figure 1), thus teaching the use of an acid separated from the active agent to improve the formulation was known at the time of the invention. The '891 publication teaches the use of two separate particles in a pharmaceutical composition. Thus the active agent would remain separate from the acid, which would still be present to provide the desired release/absorption. Appellant has not provided evidence to the contrary.

Appellant argues two distinct types of particle would destroy the invention of the '779 publication because the acid core layer, the insulating layer and the active substance layer in a single particle are necessary components. The first named inventor's interpretation and explanation of his own patent document definably should indicate how one of skill in the art reading the '779 publication would interpret its disclosure and scope and cannot be ignored.

In response, the '779 publication and the enclosed declaration teach the need for an acid to be present in close proximity and the need to separate the acid from the active agent for storage. The use of two separated particles intimately mixed in the same oral dosage form would still have the active agent, the acid, the coating layer and the close proximity desired, and thus would not destroy the invention. Rather the use of the separated 2 particles is a design choice of how to provide each element. The '779 publication teaches the use of the active agent layer which is coated, the layer of acid core with a coating and the desire for it to be in a single oral dosage form that is stability stored. The '891 publication additionally teaches an oral dosage form which includes the active agent in a particle and additional ingredients in particle form wherein the composition is stably stored (abstract, [0008]). Thus it would have been obvious to one of ordinary skilled in the art at the time the invention was made to that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication in order to obtain a stable oral dosage form.

Appellant argues the prior art's teaching undermine the very reason being proffered as to why a person of ordinary skill would have combined the known element. The '779 publication does not provide one of ordinary skill in the art with a reason or motivation to modify the specific pharmaceutical predation described therein to make the claimed composition with a reasonable expectation of success. There is no reasonable expectation of success yet Appellant has found quite surprisingly that the present composition are stable, easy to prepare and provide effective in vitro release of the active.

In response, the ‘779 publication teaches the use of the active agent layer which is coated, the layer of acid core with a coating and the desire for it to be in a single oral dosage form that is stability stored. The ‘891 publication additionally teaches an oral dosage form which includes the active agent in a particle and additional ingredients in particle form wherein the composition is stably stored (abstract, [0008]). Thus it would have been obvious to one of ordinary skilled in the art at the time the invention was made to that the separation of the organic acid and the active agent described by the ‘779 publication could be via the layers taught by the ‘779 publication or through the use of separate particles as taught by the ‘891 publication in order to obtain a stable oral dosage form.

Appellant argues the ‘891 publication teaches spatial separation however is not related at all to or concerned with the necessity of close proximity between an acid and active ingredient to obtain a desired result, an acid environment that allows for diffusion.

In response, the ‘891 publication is directed to one active ingredient particle which is coated and one further particle included in various oral dosage forms (abstract). The ‘891 publication is taught as improving storage of dosage forms [0008] wherein the formulation contains two particles, a first containing the active ingredient which is coated and a second particle of fat/wax material to inhibit administration abuse [0020]. Thus the ‘891 publication teaches formations containing the active agent and a second ingredient which is controlling the release of the active agent being in two separate particles and the ‘779 publication teaches the separation of the active agent and an acid, which is used for bioavailability. Thus it was known to separate the active

agent from a secondary formulation ingredient having an effect on the active via 2 particles or layering in a single particle in an oral dosage form.

Appellant argues the '891 publication is not concerned with the need for an acid for bioavailability, the need for separation and diffusion.

In response the '779 publication teaches the use of the acid, a diffusion layer and an active ingredient which are separated. The '891 publication teaches an additional method wherein active agents are used in formulations separated form additional ingredients via a coating and the use of particles. It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication.

Appellant argues one of ordinary skilled in the art would not reasonable predict that the single layered particle could be separated from a composition of different configuration and retain the diffusion needed to accomplish bioavailability in the entire patient population. The application of hindsight is inappropriate where the prior art does not suggest that the prepared modification would reasonable be expected to manifest properties and advantages achieved.

As for the assertion that the rejection is based on hindsight, as noted in MPEP 2145, any obviousness rejection is in a sense necessarily a reconstruction based on hindsight reasoning and is not improper if it takes into account only knowledge within the level of ordinary skill in the art at the time the claimed invention was made. Appellants have provided no evidence that the rejection is not based on

knowledge available to those of ordinary skill in the art. In the instant case the '779 publication teaches the need for an acid in the formulation, a coating layer to separate such form the active agent for storage and release properties. The use of separated particles as taught by the '891 publication would still result in particles separated by coating layers in close proximity, and thus would have a reasonable expectation of success.

Appellant argues one of skill in the art generally views modifying chemical pharmaceutical formations as unpredictable due to the unpredictable nature of chemical arts. This is particularly true when a particular configuration of the formation is described in such a way that it is necessary.

In response, the '779 publication teaches the necessity of the acid being present and yet separated from the active agent. The use of separate particles which still contain the active agent, the acid and the coating layers taught by the '779 publication would maintain all the configurations the '779 publication teaches as necessary, while utilizing a different mechanism of separation as known in the art ('891 publication) separate particles vs separated layers.

Appellant argues the '779 publication in view of the '891 publication cannot disclose or suggest a composition consisting of a mixture of these 2 distinct types or particles as the '779 publication disclose or suggest consisting of these 2 types of particles.

In response, Appellant uses consisting of language in claims 41 and 47, however allows for at least one excipient, therefore allowing for additional ingredients in the

composition. Appellant's arguments regarding the teaching of the use of two distinct particles in place of a layered one taught by the '779 publication is addressed above.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/LYNDSEY M BECKHARDT/
Examiner, Art Unit 1613

Conferees:

/BRIAN-YONG S KWON/
Supervisory Patent Examiner, Art Unit 1613

/DAVID J BLANCHARD/
Supervisory Patent Examiner, Art Unit 1619

Requirement to pay appeal forwarding fee. In order to avoid dismissal of the instant appeal in any application or ex parte reexamination proceeding, 37 CFR 41.45 requires payment of an appeal forwarding fee within the time permitted by 37 CFR 41.45(a), unless appellant had timely paid the fee for filing a brief required by 37 CFR 41.20(b) in effect on March 18, 2013.

Adapted from PTO/AIA/14 (03-13)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~ESTEVE 6 PCT US~~ 16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Inventor Information:

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Postal Code	400 078		Country	INDIA

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Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
☐ An Address is being provided for the correspondence Information of this application.	
Customer Number	~~25,666~~ 23552
Email Address	

Application Information:

Title of the Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
Attorney Docket Number	~~ESTEVE 6 PCT US~~ 16326.0018FPWO	Small Entity	No
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if		Suggested Figure for Publication (if any)	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One	☑ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	~~25,666~~ 23552		

Adapted from PTO/AIA/14 (08-13)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~ESTEVE 6 PCT US~~ 16326.0018FPWO
	Application Number	14/379,613
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Application Number	Continuity Type	Prior Application Number	Filing Date (DD-MMMM-YYYY)
This Application is a	a 371 of international	PCT/EP2013/053426	21 February 2013

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

ApplicationNumber	Country	Filing Date (DD-MMMM-YYYY)	Priority Claimed
461/MUM/2012	INDIA	21 February 2012	☑ Yes ☐ No

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization to Permit Access:

☑ Authorization to Permit Access to the Instant Application by the Participating Offices.

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Adapted from PTO/AIA/14 (03-13)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	~~ESTEVE 6 PCT US~~ 16326.0018FPWO
	Application Number	14/379,613

Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

☑	Assignee	☐	Legal Representative under 35 U.S.C. 117
☐	Person to whom the inventor is obligated to assign	☐	Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

☐	Deceased	☐	Legally incapacitated

Name of the Deceased or Legally Incapacitated Inventor	
If the Assignee is an Organization check here	☑
Organization	~~LABORATORIOS DEL DR. ESTEVE S.A.~~ DOSE Innova, S.L.

Mailing Address Information

Address	~~Avda. Mare de Déu de Montserrat, 221~~ Carrer de Sant Mari, 75-97		
City	Barcelona	State/Province	
Country	SPAIN	Postal Code	~~E-08041~~ 08107
Phone Number		Fax Number	
Email Address			

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Melissa M. Hayworth/			Date (DD-MMMM-YYYY)	2020-01-07
First Name	Melissa M.	Last Name	Hayworth	Registration Number	45774

Electronic Acknowledgement Receipt

EFS ID:	38230746
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	07-JAN-2020
Filing Date:	19-AUG-2014
Time Stamp:	18:52:46
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	16326-0018FPWO_Communication-Name.PDF	77853 7902511f75e3af117b24010b14bb6477030c76de	no	2
Warnings:					

Information:					
2	Req to correct/update/change appl name until pay issue fee	16326-0018FPWO_Dose_Applicant_Name_Change_aia0041.PDF	220106 4d114f7d26f80d398bd7eb9f829efa79a9503f58	no	2
Warnings:					
Information:					
3	Application Data Sheet	16326-0018FPWO-SADS.PDF	5545210 7950274d807a20454a172ed02bd96ba05871da50	no	4
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
		Total Files Size (in bytes):	5843169		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: R46C.REQ
Document Description: Request under 37 CFR 1.46(c) to correct, update or change the applicant.

PTO/AIA/41 (04-15)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST TO CORRECT OR UPDATE THE NAME OF THE APPLICANT UNDER 37 CFR 1.46(c)(1), OR CHANGE THE APPLICANT UNDER 37 CFR 1.46(c)(2)

(FOR USE ONLY IN APPLICATIONS FILED ON OR AFTER SEPTEMBER 16, 2012)

Application Number	14/379613
Filing Date	August 19, 2014
First Named Inventor	Pilgaonkar
Art Unit	1613
Examiner Name	Lyndsey Marie Beckhardt
Practitioner Docket Number	16326.0018FPWO

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant hereby **requests that the name of the applicant be corrected or updated under 37 CFR 1.46(c)(1), or that the applicant be changed under 37 CFR 1.46(c)(2),** in the above-identified application. **Requests under 37 CFR 1.46(c)(1) or (c)(2) cannot be submitted after payment of the issue fee or if the application has been patented.**

Please check the applicable box(es) below.

☒ 1. This request is to **correct or update the name of the applicant** (**under 37 CFR 1.46(c)(1)**) and includes:

☒ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). A Corrected Web-based ADS may be used.

Note: Requests under 37 CFR 1.46(c)(1) may be filed to correct typographical errors in the name of the § 1.46 applicant, or for updating the name of the § 1.46 applicant (*i.e.*, where there is no change in the applicant itself but just in the applicant's name). See the Manual of Patent Examining Procedure (MPEP) section 605.01.

☐ 2. This request is to **change the applicant** (**under 37 CFR 1.46(c)(2)**) and includes:

☐ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) that identifies the changes with proper markings (underlining for insertions and strikethrough for deletions). A Corrected Web-based ADS may be used.

☐ A Statement Under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent). See MPEP 325.

I am the

☐ applicant* ☒ attorney or agent of record Registration number 45774 ☐ attorney or agent acting under 37 CFR 1.34 Registration number _____

Signature /Melissa M. Hayworth/
Typed or printed name Melissa M. Hayworth
Date January 7, 2020

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

☐ ** Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.36. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.	23552	Confirmation No.	6655

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

COMMUNICATION REGARDING NAME OF APPLICANT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Applicant respectfully requests that the Applicant name of the subject application be updated to reflect the current name. To clarify the record, Applicant's representative provides the following summary.

At the time the application was filed, the name of the Applicant/Assignee was Laboratorios Del Dr. Esteve S.A, and the original ADS reflects this named Applicant/Assignee.

On December 17, 2018, a Change of Name document was recorded with the Assignment Branch, changing the name of the Applicant/Assignee from Laboratorios Del Dr. Esteve S.A. to Esteve Pharmaceuticals, S.A. However, the name of the Applicant was not updated on the ADS.

Applicant has now changed the Applicant/Assignee name from Esteve Pharmaceuticals, S.A. to Dose Innova, S.L. A change of name document has been filed with the Assignment Branch. To change the name of Applicant in accordance with this change of name, submitted herewith are a Supplemental Application Data Sheet and a Request to Correct or Update the Name of the Applicant under 37 CFR 1.46(c)(1) form.

If there are any questions relating to this filing, Applicant requests the undersigned attorney be contacted.

Respectfully submitted,

Date: January 7, 2020

/Melissa M. Hayworth/
Melissa M. Hayworth
Registration No. 45774

Merchant & Gould PC
PO Box 2903
Minneapolis, MN 55402-0903
Telephone No.: 703.684.2522
Facsimile No.: 612.332.9081

23552
PATENT TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pratibha S. Pilgaonkar	Examiner:	BECKHARDT, LYNDSEY
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.	23552	Confirmation No.	6655

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

APPEAL BRIEF

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commissioner for Patents

This Appeal Brief is filed further to a Request for Pre-Appeal Request for Review and a Notice of Appeal. The appeal is from the final rejection of claims 21, 23, 26, 30, 32, and 40-48 of the above-identified application, as set forth in the Office Action dated May 30, 2019. Claims 33-37 and 39 have been withdrawn.

I. REAL PARTY IN INTEREST

The real party in interest is ESTEVE PHARMACEUTICALS, S.A.

II. RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any other appeals, interferences or other proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

IPR2025-01107
MSN Exhibit 1002
Page 173 of 680

III. SUMMARY OF THE CLAIMED SUBJECT MATTER

Claim 21 recites a composition comprising a mixture of at least two distinct types of particles.[1] The first type of particles comprise dabigatram etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof.[2] These first type of particles are free from organic acids and inorganic acids.[3] The second type of particles comprise at least one pharmaceutically acceptable organic acid.[4] The second type of particles is coated with a protective coating layer and is free from dabigatram etexilate.[5]

Claim 41 recites a composition consisting of a mixture of the two distinct type of particles and at least one pharmaceutically acceptable excipient.[6] Claim 46 recites a capsule containing a pharmaceutical composition consisting of a mixture of the two distinct type of particles and at least one pharmaceutically acceptable excipient.[7]

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[1] *See* specification, page 4, line 11.

[2] *See* specification, page 4, lines 12-14.

[3] *See* specification, page 6, lines 4-5.

[4] *See* specification, page 4, lines 23-24.

[5] *See* specification, page 4, lines 24-25 and page 6, lines 32-34.

[6] *See* specification, page 4, lines 11-14, 23-25 and page 6, lines 4-5 and lines 32-34.

[7] *See* specification, page 4, line 12 and Examples.

IPR2025-01107
MSN Exhibit 1002
Page 174 of 680

IV. ARGUMENT

A. Claims 21, 23, 26, 30, 32, and 40-48 Are Not Obvious Over U.S. 2006/0183779, U.S. 2008/0069891 and Pub. Chem. 9578572

Claims 21, 23, 26, 30, 32, and 40-48 are rejected under 35 U.S.C. § 103 as allegedly obvious over U.S. 2006/0183779 (U.S. '779) in view of U.S. 2008/0069891 (U.S. '891) as evidenced by PubChem 9578572 ("PubChem"). Appellant respectfully disagrees with the outstanding rejection.

The presently claimed invention relates to a composition comprising: a mixture of at least ***two distinct types of particles***. The first type of particles comprises dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is ***free from organic and inorganic acids***; and the second type of particles comprises at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is ***free from dabigatran etexilate***. (claims 21, 23, 26, 30, 32, and 40). The present compositions are stable, easy to prepare and provide effective in-vitro release of the active.

The presently claimed invention also relates to a composition **consisting of** a mixture of ***two distinct types of particles*** and at least one pharmaceutically acceptable excipient, wherein the claimed two distinct types of particles (i.e., the first and second type of particles) are as defined above (claims 41-48).

The primary cited reference is U.S. '779, which names Brauns as an inventor. U.S. '779 states that the aim of the invention is to provide an improved formulation for oral use of the compound of formula I (i.e., dabigatran etexilate mesylate). As such, U.S. '779 relates to a

specific pharmaceutical preparation of dabigatran etexilate mesylate with reference to Figure 1. Figure 1 indicates that it is a schematic structure of **the** pharmaceutical composition disclosed therein. (Figure 1 and paragraph [0004], emphasis added). This particular preparation includes a spherical organic acid core, an insulating layer separating the core material and active substance layer, an active substance layer, and optionally a coating layer.

U.S. '779, as illustrated in Figure 1, is directed to **a single particle** comprising an organic acid and active substance. There is no disclosure or suggestion of any configuration other than a single particle in U.S. '779 for achieving the improved goal of an improved formulation. And there is no suggestion of success using any configuration other than a single particle. One of skill in the art would understand that one must use the single particle comprising the organic acid and active substance to achieve the improved formulation in light of the teachings of U.S. '779. As such, one of ordinary skill in the art reading and considering U.S. '779 would be led to the conclusion that a single particle containing the organic acid core and active substance dabigatran etexilate mesylate is necessary to achieve the advantages described in U.S. '779.

These advantages are discussed and demonstrated in U.S. '779. As disclosed in U.S. '779, "[o]ne advantage of the formulation thus constructed is the **spatial separation** of the organic acid and active substance **by the insulating layer**. A further advantage of the construction of the pellets as described above is the fact that the organic acid does not go into solution until after the preparation has been taken and then produces an acid microclimate in which the active substance can dissolve." (paragraph [0011], emphasis added).

U.S. '779 describes the individual layered particles as pellets and provides a description of how to make the pellets as disclosed therein beginning at paragraph [0016]. As described in

the paragraphs subsequent to paragraph [0016], the insulating layer is applied to the acid-containing core material; then the active substance is applied from a dispersion containing binder and optionally separating agent, and finally the system may be coated with a coating of a pharmaceutically conventional film forming agent, plasticiser and optionally pigment – thus achieving the layered single particle as described in U.S. '779 and illustrated in Figure 1. (paragraphs [0016] – [0020]).

U.S. '779 provides two example formulations of its single layered particle and tests them for bioavailability in comparison to a convention tablet, with and without pretreatment with pantoprazole. (paragraph [0025]). As stated in paragraph [0029] of U.S. '779, the relative bioavailability for the Example 1 formulation containing the layered single particles was improved by a factor of 5 in comparison to the conventional tablet. As stated in paragraph [0034] of U.S. '779, the relative bioavailability for the Example 2 formulation containing the layered single particles was improved by a factor of 4 in comparison to the conventional tablet. As noted above, in each case the formulation was that of a single particle comprising an organic acid core and an active substance layer.

As such, U.S. '779 relates to improved formulations of dabigatran etexilate mesylate and specifically, formulations that contain layered single particles having an organic acid core and an active substance layer separated by an insulating layer. This construction provided the improved bioavailability. U.S. '779 demonstrates that these **layered single particles** are needed to achieve the improved bioavailability. U.S. '779 does not disclose or suggest any other construction or configuration for achieving the improved bioavailability.

The importance of using a single layered particle was further explained during the prosecution of U.S. '779 in a Declaration by the inventor, Dr. Ulrich Brauns.

A Declaration under 37 C.F.R. § 1.132 by Dr. Ulrich Brauns was ***submitted during prosecution of U.S. '779*** (hereinafter "the Declaration"). A copy of this Declaration was submitted and made of record as evidence in the present case with the amendment accompanying the RCE filing on April 16, 2018. A copy of the Declaration also is attached hereto. Brauns is the first named inventor of U.S. '779, and from the inventor's perspective further emphasizes the importance of using a single particle in the Declaration. The reasons that single layered particles are critical to the invention of U.S. '779 are discussed in detail in the Declaration.

As explained by Brauns, the inventor of U.S. '779, in paragraph 13 of the Declaration:

> 13. It was hypothesized that some patient stomachs were more basic because of normal variability, by disease, or co-medication with drugs that increase gastric pH. That is, if the gastric environment of the patient is not sufficiently acidic, the prodrug (dabigatran etexilate mesylate) does not dissolve sufficiently to ensure adequate bioavailability. This was not expected but only detected during formulation development. To solve this problem, the formulation itself was re-design to a) **act as an acidic microenvironment** while in the stomach in order to quickly dissolve the majority of the prodrug prior to entering the small intestine; b) be stable before entering GI (Gastro Intestinal) tract for **storage purposes**; and c) **work well for the entire patient population**, meaning that bioavailability would be consistent and high for the entire patient population. This solution to the problem was not easy given the unique structure of dabigatran etexilate salt and the resulting solution to the problem, that is providing the particular form of pharmaceutical preparation as claimed, which forms the subject matter of this invention.

(Brauns declaration at paragraph 13, emphasis added).

As further explained by Brauns, in paragraph 19 of the Declaration:

> 19. The present formulation was designed to accommodate the specific and unique properties of the prodrug, dabigatran etexilate. An

> ***acid core layer***, an ***insulating layer*** and an ***active substance layer*** **are necessary components** of this invention. For example, the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. The insulating layer first acts as a protective layer between the acid core and active substance layer on storage but then permits the diffusion of acid to the active substance layer **immediately** in passage through the stomach. The active substance layer provides the correct dosage of prodrug….

(Brauns declaration at paragraph 19, emphasis added).

Accordingly, Brauns in his declaration, in discussing ***his invention*** as set forth in his patent application (U.S. '779), teaches that an acid core, an insulating layer separating the insulating layer and active substance layer, and an active substance layer ***within a single particle*** are ***necessary components***. In the declaration, Brauns explains that the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. As explained in the declaration, this acidic microenvironment is needed to dissolve the prodrug (dabigatran etexilate mesylate) to ensure adequate bioavailability for the entire patient population. And the Brauns Declaration explains how the acid core and layers interact ***within the single particle***. In the Brauns Declaration, it is stated that the insulating layer has two functions: firstly as a protective layer between the acid core and active substance on storage and secondly it permits the diffusion of acid to the acid substance layer immediately in passage through the stomach.

As such, Brauns explains that the single particle spatial distance is there for storage, but the single particle is necessary for upon administration the acid layer must "immediately" diffuse into the active substance layer. To achieve this immediate diffusion, the active substance layer and the acid layer has to be in the same particle, as stated by inventor Brauns. Brauns identified this configuration within a single particle as ***necessary*** (*i.e.*, this configuration was the only way that Brauns and U.S. '779 contemplated to control the immediacy).

The inventor Brauns teaches that the designed formulation of U.S. '779 - wherein the three components are necessary components which must be in a single particle - solves the necessity of spatial separation, as well as creating the necessary spatial arrangement for achieving diffusion, which ultimately results in the creation of an acidic microenvironment to provide consistent bioavailability for the entire patient population. This is entirely consistent with the disclosure of U.S. '779 and its sole disclosure of a single particle containing an organic acid core and an active substance layer. It is only with the single particle that the advantages are achieved, based on U.S. '779, and as explained by Brauns in this Declaration. ***Accordingly, it cannot be obvious to one of ordinary skill in the art to separate the particles and still achieve the diffusion needed to provide the good dissolution characteristics and consistent bioavailability.***

In view of the disclosure in U.S. '779 and as described by the inventor of that disclosure, modifying the invention of U.S. '779 with two distinct types of particles ***would destroy*** the "invention" of U.S. '779, because the acid core layer, the insulating layer, and the active substance layer in a single particle are ***necessary components*** and provide the needed acidic microenvironment for diffusion. The first named inventor's interpretation and explanation of his own patent document definitively should indicate how one of skill in the art reading U.S. '779 would interpret its disclosure and scope. The declaration by Brauns, discussing his invention as set forth in U.S. '779, cannot be ignored.

Obviousness requires motivation, rationale for change and reasonable expectation of success. Here, the prior art's teachings undermine the very reason being proffered as to why a

person of ordinary skill would have combined the known elements. *DePuy Spine Inc. v. Medtronic Sofamor Danek Inc.*, 567 F.3d 1314 (Fed. Cir. 2009).

As such, U.S. '779 does not provide one of ordinary skill in the art with a reason or motivation to modify the specific pharmaceutical preparation described therein to make the claimed composition with a reasonable expectation of success. In view of the disclosure in U.S. '779, a skilled artisan would not have considered modifying its particular form of a formulation and then expected the presently claimed composition as an identifiable, predictable solution. U.S. '779 only suggests a single particle, as confirmed by Brauns in his Declaration.

"The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). Simply being capable of modifying is not enough. *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990). There simply is no suggestion in U.S. '779 to make the necessary modification in order to use the present claimed composition. There is no reasonable expectation of success based upon U.S. '779, yet, Appellant has found quite surprisingly, that the present compositions are stable, easy to prepare and provide effective in-vitro release of the active.

U.S. '891 as evidenced by PubChem does not cure this deficiency of a reason or motivation to modify U.S. '779 with a reasonable expectation of success. US '891 teaches a spatial separation; however, U.S. '891 is not related at all to, or concerned with, the necessity of a close proximity between an acid and active ingredient to obtain a desired result, *i.e.*, an acidic environment that allows for diffusion. The PubChem document simply confirms the active substance chemical structure, and adds nothing else. What the Office Action's analysis does not

consider is that ***the diffusion in U.S. '779 is needed to accomplish bioavailability in the entire patient population***. This concern, particular to U.S. '779, is due to some patient stomachs being more basic because of normal variability, by disease, or by co-medication with drugs that increase gastric pH and the prodrug dabigatran etexilate mesylate needs an acidic environment to dissolve sufficiently for adequate bioavailability. This concern is not at all a consideration or requirement of US '891. Accordingly, the spatial separation of U.S. '891 does not extrapolate to the need for ***separation and diffusion*** in U.S. '779.

One of skill in the art could not reasonably predict that the single layered particles of U.S. '779 could be separated to form a composition of a different configuration and retain the diffusion needed to accomplish bioavailability in the entire patient population. Having all three components in a single particle was necessary for the invention as disclosed in U.S. '779, and using two distinct particles as presently claimed would destroy the invention as disclosed in U.S. '779. The application of hindsight is inappropriate where the prior art does not suggest that the prepared modification could reasonably be expected to manifest the properties and advantages achieved. *See In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995). Moreover, it is improper to use the claims "as a frame," and take the "naked parts of separate prior art references [ ] as a mosaic to recreate a facsimile of the claimed invention" without a finding of why ordinary artisans would have found that mosaic obvious, improperly employs hindsight bias. See W.L. Gore & Assocs., Inc. v. Garlock, Inc. 721 F.2d 1540, 1552-53 (Fed. Cir. 1983).

It is further noted that one of skill in the art generally views modifying chemical pharmaceutical formulations as unpredictable. Due to this general unpredictable nature of chemical arts, potential solutions are less likely to be genuinely predictable. *Eisai Co., Ltd. V.*

Dr. Reddy's Labs, Ltd. 533 F.3d 1353, 1359 (Fed. Cir. 2008); *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1088, 1090 (Fed. Cir. 2008). This is true especially when a particular configuration of the formulation is described in such a way that it is necessary. And different active pharmaceutical ingredients have unique structures and properties. As acknowledged by inventor Brauns, the disclosure of U.S. '779 indicated that the single particle configuration was necessary for the unique structure and characteristics of dabigatran etexilate mesylate. The inventor's explanation confirms how one of skill in the art would and should interpret the disclosure of U.S. '779.

Accordingly, U.S. '779 in view of U.S. '891 as evidenced by PubChem 9578572 do not disclose or suggest the composition of claim 1, or claims 23, 26, 30, and 32 dependent therefrom, comprising the specifically recited ***mixture of at least two distinct types of particles***.

With regard to claims 41-48, these claims include the closed transition of "consisting of." As such, claim 41 recites a composition **consisting of** a mixture of ***two distinct types of particles*** and at least one pharmaceutically acceptable excipient, and claim 47 recites a capsule containing a pharmaceutical composition **consisting of** a mixture of ***two distinct types of particles*** and at least one pharmaceutically acceptable excipient. The first type of particles comprises dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is ***free from organic and inorganic acids***; and the second type of particles comprises at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is ***free from dabigatran etexilate***.

U.S. '779 in view of U.S. '891 as evidenced by PubChem **cannot** disclose or suggest a composition **consisting of** a mixture of ***these two distinct types of particles*** as specifically claimed and at least one pharmaceutically acceptable excipient. U.S. '779 in view of U.S. '891 as evidenced by PubChem do not disclose or suggest the specifically claimed ***first type of particles*** and/or the specifically claimed ***second type of particles***. As such, U.S. '779 in view of U.S. '891 as evidenced by PubChem cannot disclose or suggest compositions **consisting of** these two types of particles and at least one pharmaceutically acceptable excipient. In no way can U.S. '779 in view of U.S. '891 as evidenced by PubChem disclose or suggest claims 41-48 reciting "consisting of" language.

Accordingly, for at least these reasons, there is no *prima facie* case of obviousness. Appellant submits respectfully that U.S. '779 in view of U.S. '891 as evidenced by PubChem 9578572 do not disclose or suggest the composition of claims 21, 23, 26, 30, 32, and 40-48.

V. CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections of Appellant's claims 21, 23, 26, 30, 32, and 40-48 under 35 U.S.C. § 103(a) are improper, and therefore, it is respectfully requested the rejections be reversed.

Respectfully submitted,

Date: December 6, 2019

/E. Joseph Gess/

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CLAIMS APPENDIX

Claims on Appeal

21. A composition comprising: a mixture of at least two distinct types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic acids and inorganic acids; and
b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

23. The composition according to claim 21, further comprising at least one pharmaceutically acceptable excipient.

26. The composition according to claim 21, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.

30. The composition according to claim 21, comprising from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

32. A unit dosage form prepared from the composition according to claim 21, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

40. The composition according to claim 23, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

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41. A composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein
a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and
b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

42. The composition according to claim 41, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.

43. The composition according to claim 41, wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.

44. The composition according to claim 41, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

45. A capsule unit dosage form prepared from the composition according to claim 44, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

46. A capsule containing a pharmaceutical composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein
a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

47. The capsule according to claim 46 containing from 50 mg to 200 mg of dabigatran etexilate mesylate.

48. The capsule according to claim 46, wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.

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EVIDENCE APPENDIX

Declaration Under 37 C.F.R. § 1.132, Dr. Ulrich Brauns

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of	: Ulrich Brauns	) Art Unit	: 1616
Serial No.	: 11/381,890	) Examiner	: Sabiha Naim Qazi
Confirmation No.	: 5127		
Filed	: May 5, 2006		
Title	: ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF		
Docket No.	: 01-1306-1-C1		

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Ulrich Brauns, being duly warned, declare that:

1. I am a citizen of Germany, residing in Biberach an der Riss, Germany.

2. I have studied Pharmacy at the University of Kiel, Germany and became licensed to practice as a pharmacist in 1982. I continued my studies at the University of Kiel and received a Dr. rer. nat. in Pharmaceutics in 1986. My thesis was entitled "Properties of solubilizing Cyclodextrin Derviatives."

3. From 1986 to 1993, I served as Laboratory Head and then Head of Department of Pharmaceutical Development at Chemische Fabrik Promonta GmbH (ALTANA Group) in Hamburg, Germany. I have been employed by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany since 1993. Between 1993 and 2002, I served as Laboratory Group Leader, Pharmaceutical R&D, Boehringer Ingelheim Pharma GmbH & Co. KG (formerly Dr. Karl Thomae GmbH) in Biberach, Germany. In 1998, Boehringer Ingelheim KG and Dr. Karl Thomae GmbH merged into Boehringer Ingelheim Pharma KG. On February 18, 2003, Boehringer Ingelheim Pharma KG changed its name to Boehringer Ingelheim Pharma GmbH & Co. KG.

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From 2002 to 2006, I was Senior Project Leader, Project Management R&D and from 2006 to 2013 I have been a Director of Project Management R&D. Since 2013, I serve as Vice President and Head of Global CMC Project Management in Boehringer Ingelheim Biopharmaceuticals GmbH. My responsibilities include leading a global department with approximately 30 project leaders in the USA, Austria and Germany.

4. I am the sole inventor of the claims of the above-identified application and am knowledgeable about the subject matter of this invention.

5. I am familiar with the grounds for rejection made against the application and have been asked to discuss the inventiveness of the pharmaceutical composition shown in Figure 1 and bioavailability data presented in Figure 2 of the specification.

6. Dabigatran etexilate is a unique acid labile double-prodrug (hereinafter referred to as "prodrug"). Upon exposure to enzymes after absorption, the prodrug is cleaved to form dabigatran, the active metabolite (see compound of formula I in the specification on page 2).

7. Bioavailability requires both solubility and permeability through the GI membranes. Dabigatran, the active moiety, forms a zwitterion at physiological pH but is too polar to pass through the lipophilic membranes in the GI tract via diffusion. Thus, the double prodrug of dabigatran was prepared so that the ester and carbamate ends would increase lipophilicity of the drug so that it may be absorbed in the GI membranes. Although these modifications decreased aqueous solubility, they increased permeability. After absorption through the GI walls, the prodrug is cleaved to the active moiety dabigatran.

8. The prodrug retains some basic properties and can be protonated. However, the prodrug is a weak base so protonation only occurs at rather low pH. A balance between un-protonated species (which is absorbed) and protonated species (which is relevant for aqueous solubility) is decisive for oral bioavailability.

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9. The formation of a dabigatran etexilate salt served two purposes: (1) increase aqueous solubility and thus, oral bioavailability and (2) exhibit stability and low hygroscopicity during storage. As pointed out in the parent U.S. application no. 10/383,198 (and proven by comparative data in Declaration form), it was surprising that methanesulfonic acid ("mesylate") formed a stable dabigatran etexilate salt. One of skill in the art would have expected the opposite to be true, that is, a strong acid, such as methanesulfonic acid, would cleave the double-prodrug and make it less stable during storage. Thus, the methanesulfonic acid salt form of dabigatran etexilate itself is nonobvious due to these unexpected properties. This application's current claims require the specific methanesulfonic acid salt form of dabigatran etexilate. Therefore, the claims are nonobvious at least on this basis, i.e., for all of the same reasons and evidence provided in the parent U.S. application no. 10/383,198. Additional reasons support the nonobviousness of the particular formulation claims of this application.

10. It was discovered during development that the formation of the prodrug salt alone was not sufficient for providing adequate bioavailability in the entire patient population. An additional acidic environment was preferred to enhance dissolution of the prodrug due to its weakly basic properties to allow for subsequent prodrug absorption.

11. In early clinical trials, dabigatran etexilate mesylate was administered as a conventional tablet. This tablet was prepared according to composition of Table I, page 9, in the specification. It was thought that the gastric juices in the stomach (~ pH 1-2) would be sufficient solubilize the prodrug in the conventional tablet so that it would be absorbed immediately upon entering the small intestine. In other words, availability for absorption would be very high at the beginning of the small intestine. This was an important criterion because the pH of the small intestine is too high to dissolve the prodrug. Page 8, lines 1-3, of the specification discusses solubility of dabigatran etexilate (pH level > 5 results in an insoluble prodrug).

12. The preliminary tests using conventional tablet technology resulted in highly variable plasma levels of dabigatran in healthy volunteers and in some cases, malabsorption. Some volunteers had little to no absorption and thus, little to no bioavailability. However, when the prodrug was administered as an acidic oral solution, the variability of plasma levels of dabigatran decreased significantly. Dabigatran etexilate was shown to dissolve relatively well in water at low pH levels. See bottom of page 7 and top of page 8 of the specification. Thus, a conventional dosage form of dabigatran etexilate mesylate did not give the most desired results for all patient populations.

13. It was hypothesized that some patient stomachs were more basic because of normal variability, by disease, or co-medication with drugs that increase gastric pH. That is, if the gastric environment of the patient is not sufficiently acidic, the prodrug does not dissolve sufficiently to ensure adequate bioavailability. This was not expected but only detected during formulation development. To solve this problem, the formulation itself was re-designed to (a) act as an acidic microenvironment while in the stomach in order to quickly dissolve the majority of the prodrug prior to entering the small intestine; (b) be stable before entering GI tract for storage purposes; and (c) work well for the entire patient population, meaning that bioavailability would be consistent and high for the entire patient population. This solution to the problem was not easy given the unique structure of dabigatran etexilate salt and the resulting solution to the problem, that is providing the particular form of pharmaceutical preparation as claimed, which forms the subject matter of this invention.

14. The current application's claims are thus distinguished from the cited references not only because they are directed to the specific mesylate salt of the prodrug but further because they are directed to a specific pharmaceutical preparation of dabigatran etexilate mesylate (see Figure 1). Figure 1 illustrates a spherical organic acid core, an insulating layer, an active substance layer and optionally, a coating layer of the present invention.

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15. In order to test the new oral formulation in high-pH stomach conditions, two sets of 15 volunteers were treated. In the first set, 15 volunteers were given the formulation of Example 1 (in the specification) by mouth on an empty stomach. Bioavailability was measured. The same 15 volunteers were then treated with 40 mg of pantoprazole, a compound that increases the pH of the stomach, twice daily for three days prior to administering formulation of Example 1. Pantoprazole was also continued during administration of formulation of Example 1. The degree of the absorption was determined by measuring the quantity of active metabolite excreted in the urine. The relative bioavailability after pre-treatment with pantoprazole was 94% on average compared with administration without any pre-treatment.

16. In the second set, 15 volunteers were given the formulation of Example 2 (in the specification) by mouth on an empty stomach. Bioavailability was measured. The same 15 volunteers were then treated with 40 mg of pantoprazole twice daily for three days prior to administering formulation of Example 2. Pantoprazole was also continued during administration of formulation of Example 2. The degree of the absorption was determined by measuring the quantity of active metabolite excreted in the urine. The relative bioavailability after pre-treatment with pantoprazole was 76% on average compared with administration without any pre-treatment.

17. The conventional tablet formulation of the prodrug used in the early clinical trials was also tested under comparable conditions to Examples 1 and 2 above. For example, a tablet containing 50 mg of dabigatran etexilate mesylate was prepared according to Table 1, page 9, in the specification. The bioavailability of the conventional tablet after pre-treatment with pantoprazole was 18%.

18. The comparative results are shown in Figure 2 of the specification. Here, the bioavailability (based on the area under the plasma concentration/time curve) of the active metabolite in volunteers treated with and without pantoprazole is shown. The new formulations of Example 1 and 2 provide an improved bioavailability (about a factor of 4 or 5) over that of the tablet formulation in a model simulating a patient population with non-acidic stomachs. This new formulation is advantageous for the

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entire patient population and more suitable for administration specifically to a patient population with non-acidic stomachs.

19. The present formulation was designed to accommodate the specific and unique properties of the prodrug, dabigatran etexilate. An acid core layer, an insulating layer and an active substance layer are necessary components of this invention. For example, the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. The insulating layer first acts as a protective layer between the acid core and active substance layer on storage but then permits the diffusion of acid to the active substance layer immediately in passage through the stomach. The active substance layer provides the correct dosage of prodrug. This could not have been obvious in view of the prior art of record in this case because the lack of bioavailability of dabigatran in clinical trial volunteers with elevated gastric pH was not anticipated by those directly involved in the early development of the prodrug.

20. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: March 11, 2014

Ulrich Brauns

Dr. Ulrich Brauns

PTO/AIA/22 (03-13)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 16326.0018FPWO
Application Number 14/379,613	Filed August 19, 2014
For ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN	
Art Unit 1613	Examiner BECKHARDT, LYNDSEY MARIE

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☑	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$ 200
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☐	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 132725.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 28510.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/E. Joseph Gess/ — Signature

2019-12-06 — Date

E. Joseph Gess — Typed or printed name

703.684.2511 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Electronic Patent Application Fee Transmittal

Application Number:	14379613
Filing Date:	19-Aug-2014
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Filer:	Erich Gess/Lisa Amos
Attorney Docket Number:	16326.0018FPWO

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
		Total in USD ($)		**200**

Electronic Acknowledgement Receipt	
EFS ID:	37948805
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Erich Gess/Lisa Amos
Filer Authorized By:	Erich Gess
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	06-DEC-2019
Filing Date:	19-AUG-2014
Time Stamp:	08:58:06
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$200
RAM confirmation Number	E2019B6000061896
Deposit Account	132725
Authorized User	Lisa Amos
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.19 (Document supply fees) 37 CFR 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Appeal Brief Filed	2019-12-06_16326-0018FPWO_Appeal-Brief.PDF	934335 272bcfc4228d39ef8c15f0a5a4213bd47b3cd878	no	22
Warnings:					
Information:					
2	Extension of Time	2019-12-06_16326-0018FPWO_EOT.PDF	125433 3321362dbf12be92b07466a4a4581bb6ae77dbc3	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	31318 036642e060eece3a2070f2938c73f8b53ace28bd	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1091086		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 10/08/2019

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
10/08/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

Notice of Panel Decision from Pre-Appeal Brief Review

Application No.	Applicant(s)		
14/379,613	Pilgaonkar et al.		
Examiner	**Art Unit**	**AIA (FITF) Status**	
YONG S KWON	1613	No	

This is in response to the Pre-Appeal Brief Request for Review filed 29 August 2019 .

1. ☐ **Improper Request** - The Request is improper and a conference will not be held for the following reason(s):

☐ The Notice of Appeal has not been filed concurrent with the Pre-Appeal Brief Request.
☐ The request does not include reasons why a review is appropriate.
☐ A proposed amendment is included with the Pre-Appeal Brief request.
☐ Other: _____ .

The time period for filing a response continues to run from the receipt date of the Notice of Appeal or from the mail date of the last Office communication, if no Notice of Appeal has been received.

2. ☑ **Proceed to Board of Patent Appeals and Interferences** - A Pre-Appeal Brief conference has been held. The application remains under appeal because there is at least one actual issue for appeal. Applicant is required to submit an appeal brief in accordance with 37 CFR 41.37. The time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. Further, the time period for filing of the appeal brief is extendible under 37 CFR 1.136 based upon the mail date of this decision or the receipt date of the notice of appeal, as applicable.

☑ The panel has determined the status of the claim(s) is as follows:
Claim(s) allowed: _____ .
Claim(s) objected to: _____ .
Claim(s) rejected: 21, 23, 26, 30, 32 and 40-48 .
Claim(s) withdrawn from consideration: 33-37 and 39 .

3. ☐ **Allowable application** - A conference has been held. The rejection is withdrawn and a Notice of Allowance will be mailed. Prosecution on the merits remains closed. No further action is required by applicant at this time.

4. ☐ **Reopen Prosecution** - A conference has been held. The rejection is withdrawn and a new Office action will be mailed. No further action is required by applicant at this time.

All participants:

(1) YONG S KWON .	(3) Lyndsey Beckhardt .
(2) Bennet Celsa .	(4) _____ .

/BRIAN-YONG S KWON/ Supervisory Patent Examiner, Art Unit 1613		

PTO/AIA/31 (03-14)
Approved for use through 07/31/2016. OMB 0651-0031
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

NOTICE OF APPEAL FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD

Docket Number (Optional): 16326.0018FPWO

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on _____.

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Typed or printed name _____

In re Application of: Pratibha S. Pilgaonkar et al.

Application Number	Filed
14/379,613	August 19, 2014

For: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Art Unit	Examiner
1614	Lyndsey Beckhardt

Applicant hereby **appeals** to the Patent Trial and Appeal Board from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 800

☐ Applicant asserts small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by 50%, and the resulting fee is: $ _____

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Therefore, the fee shown above is reduced by 75%, and the resulting fee is: $ _____
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 132725.

☑ Payment made via EFS-Web.

☐ A petition for an extension of time under 37 CFR 1.136(a) (PTO/AIA/22 or equivalent) is enclosed.
For extensions of time in reexamination proceedings, see 37 CFR 1.550.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant

☑ attorney or agent of record
Registration number 45774

☐ attorney or agent acting under 37 CFR 1.34
Registration number _____

Signature /Melissa M. Hayworth/

Typed or printed name Melissa M. Hayworth

Telephone Number 703.684.2522

Date August 29, 2019

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
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Electronic Patent Application Fee Transmittal

Application Number:	14379613
Filing Date:	19-Aug-2014
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Filer:	Melissa M. Hayworth/Lisa Kenney
Attorney Docket Number:	16326.0018FPWO

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
NOTICE OF APPEAL	1401	1	800	800
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**800**

Electronic Acknowledgement Receipt	
EFS ID:	37025287
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	29-AUG-2019
Filing Date:	19-AUG-2014
Time Stamp:	19:42:31
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$800
RAM confirmation Number	E20198SJ46499224
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Pre-Brief Conference request	16326-0018FPWO_Pre-Appeal-Request.PDF	223161 09624eda73732c7e2e2bdb0525e86f6fd4dad986	no	2
Warnings:					
Information:					
2	Pre-Brief Conference request	16326-0018FPWO-Pre-Appeal_Brief.PDF	144564 be39947fa9324f830eacb4e41616e9454a02afda	no	5
Warnings:					
Information:					
3	Notice of Appeal Filed	16326-0018FPWO_Notice_of_Appeal.PDF	239152 83191a6a81a69c79524337219e4923006f1cbf4f	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30812 2ced86d25f83f534f6c15a8308a0705c1fb388cb	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	637689		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: AP.PRE.REQ

PTO/AIA/33 (03-13)
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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
16326.0018FPWO

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Signature _____

Typed or printed name _____

Application Number	Filed
14/379,613	2014-08-19

First Named Inventor: Pratibha S. Pilgaonkar

Art Unit	Examiner
1613	BECKHARDT, LYNDSEY

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 45774.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Melissa M. Hayworth/
Signature

Melissa M. Hayworth
Typed or printed name

703.684.2522
Telephone number

August 29, 2019
Date

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☐ *Total of _____ forms are submitted.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pratibha S. Pilgaonkar	Examiner:	BECKHARDT, LYNDSEY
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.	23552	Confirmation No.	6655

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commissioner for Patents

The present pre-appeal brief request for review is being made as Applicant respectfully believes the Examiner has failed to show proper motivation for making the modification and expectation of success in the obviousness rejection. Thus, no *prima facie* case of obviousness has been established.

The sole rejection of record of all claims under consideration is under 35 U.S.C. § 103. The rejection is over US2006/0183779 (US '779) in view of US 2008/0069891 (US '891) as evidenced by PubChem 9578572 (PubChem).

The presently claimed invention relates to a composition comprising: a mixture of at least ***two distinct types of particles***. The first type of particles comprises dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is ***free from organic and inorganic acids***; and the second type of particles comprises at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is ***free from dabigatran etexilate***. (claims 21, 23, 26, 30, 32, and 40). The presently claimed invention also relates to a composition **consisting of** a mixture of ***two distinct types of particles*** and at least one pharmaceutically acceptable excipient, wherein the claimed two distinct types of particles (*i.e.*, the first and second type of particles) are as defined above (claims 41-48).

IPR2025-01107
MSN Exhibit 1002
Page 211 of 680

The primary reference is US '779, which names Brauns as an inventor. US '779 relates to a specific pharmaceutical preparation of dabigatran etexilate mesylate with reference to Figure 1. This particular preparation includes a spherical organic acid core, an insulating layer separating the core material and active substance layer, an active substance layer, and optionally a coating layer. A Declaration under 37 C.F.R. § 1.132 by Dr. Ulrich Brauns was ***submitted during prosecution of US '779***. A copy of this Declaration was submitted and made of record as evidence in the present case with the amendment accompanying the RCE filing on April 16, 2018.

As explained by Brauns, the inventor of US '779, in paragraph 13 of the Declaration:

> 13. It was hypothesized that some patient stomachs were more basic because of normal variability, by disease, or co-medication with drugs that increase gastric pH. That is, if the gastric environment of the patient is not sufficiently acidic, the prodrug (dabigatran etexilate mesylate) does not dissolve sufficiently to ensure adequate bioavailability. This was not expected but only detected during formulation development. To solve this problem, the formulation itself was re-design to a) **act as an acidic microenvironment** while in the stomach in order to quickly dissolve the majority of the prodrug prior to entering the small intestine; b) be stable before entering GI (Gastro Intestinal) tract for **storage purposes**; and c) **work well for the entire patient population**, meaning that bioavailability would be consistent and high for the entire patient population. This solution to the problem was not easy given the unique structure of dabigatran etexilate salt and the resulting solution to the problem, that is providing the particular form of pharmaceutical preparation as claimed, which forms the subject matter of this invention.

(Brauns declaration at paragraph 13, emphasis added).

As further explained by Brauns, in paragraph 19 of the Declaration:

> 19. The present formulation was designed to accommodate the specific and unique properties of the prodrug, dabigatran etexilate. An ***acid core layer***, an ***insulating layer*** and an ***active substance layer*** **are necessary components** of this invention. For example, the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. The insulating layer first acts as a protective layer between the acid core

> and active substance layer on storage but then permits the diffusion of acid to the active substance layer immediately in passage through the stomach. The active substance layer provides the correct dosage of prodrug….

(Brauns declaration at paragraph 19, emphasis added).

Accordingly, Brauns in his declaration, in discussing ***his invention*** as set forth in his patent application (US '779) teaches that an acid core, an active substance layer, and an insulating layer separating the acid core and active substance layer, within a single particle, are ***necessary components*** of US '779. In the declaration, Brauns explains that the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. As explained in the declaration, this acidic microenvironment is needed to dissolve the prodrug (dabigatran etexilate mesylate) to ensure adequate bioavailability for the entire patient population. And the Brauns Declaration explains how the acid core and layers interact within the single particle. In the Declaration, it is stated that the insulating layer has two functions: firstly as a protective layer between the acid core and active substance on storage and secondly it permits the diffusion of acid to the acid substance layer immediately in passage through the stomach.

As such, Brauns explains that the single particle spatial distance is there for storage and the single particle is necessary for upon administration, the acid layer must "immediately" diffuse into the active substance layer. To achieve this immediate diffusion, the active substance layer and the acid layer has to be in the same particle, as stated by inventor Brauns. Brauns identified this configuration within a single particle as ***necessary*** (*i.e.*, this configuration was the only way that Brauns and US '779 contemplated to control the immediacy).

The inventor Brauns teaches that the designed formulation of US '779 - wherein the three components are necessary components and they must be in a single particle - solves the necessity of spatial separation, as well as creating the necessary spatial arrangement for achieving diffusion, which ultimately results in the creation of an acidic microenvironment to provide consistent bioavailability for the entire patient population. ***Accordingly, it was not obvious to separate the particles and still achieve the diffusion needed to provide the good dissolution characteristics and consistent bioavailability.***

In view of the disclosure in US '779 and as described by the inventor of that disclosure, modifying the invention of US '779 with two distinct types of particles ***would destroy*** the "invention" of US '779, because the acid core layer, the insulating layer, and the active substance layer in a single particle are ***necessary components*** and provide the needed acidic microenvironment for diffusion. The first named inventor's interpretation and explanation of his own patent document definitively should indicate how one of skill in the art reading US '779 would interpret its disclosure and scope. This declaration by Brauns, discussing his invention as set forth in US '779, cannot be ignored.

Obviousness requires motivation, rationale for change and reasonable expectation of success. Here, the prior art's teachings as stated and confirmed by Brauns in his Declaration, undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements. As such, US '779 does not provide one of ordinary skill in the art with a reason or motivation to modify the specific pharmaceutical preparation described therein to make the claimed composition with a reasonable expectation of success. In view of the disclosure in US '779, a skilled artisan would not have considered modifying its particular form of a formulation and then expected the presently claimed composition as an identifiable, predictable solution. To the contrary, the Brauns Declaration makes it clear that the teachings of US '779 require a single particle or otherwise success would not be achieved.

US '891 as evidenced by PubChem does not cure this deficiency of a reason for motivation to modify US '779 with a reasonable expectation of success. US '891 teaches a spatial separation; however, US '891 is not related at all to or concerned with the necessity of a close proximity between acid and active ingredient to obtain a desired result, *i.e.*, an acidic environment that allows for diffusion. PubChem merely discloses that dabigatran etexilate is a thrombin inhibitor.

What the Office Action's analysis does not consider is that ***the diffusion in US '779 is needed to accomplish bioavailability in the entire patient population***. This concern, particular to US '779, is due to some patient stomachs being more basic because of normal variability, by disease, or by co-medication with drugs that increase gastric pH, and the prodrug dabigatran etexilate mesylate needs an acidic environment to dissolve sufficiently for adequate

bioavailability. This is not at all a consideration or requirement of US '891. Accordingly, the spatial separation of US '891 does not extrapolate to the need for ***separation and diffusion*** in US '779.

One of skill in the art could not reasonably predict that the single layered particles of US '779 could be separated to form a composition of a different configuration and retain the diffusion needed to accomplish bioavailability in the entire patient population. Having all three components in a single particle was necessary for the invention as disclosed in US '779, and using two distinct particles as presently claimed would destroy the invention as disclosed in US '779.

It is further noted that one of skill in the art generally views modifying pharmaceutical formulations as unpredictable, especially when a particular configuration of the formulation is described in such a way that it is necessary. And different active pharmaceutical ingredients have unique structures and properties. As acknowledged by inventor Brauns, the disclosure of US '779 indicated that the single particle configuration was necessary for the unique structure and characteristics of dabigatran etexilate mesylate.

In conclusion, it is respectfully submitted by Applicant that US '779 in view of US '891 as evidenced by PubChem do not disclose or suggest the composition of claim 21 comprising the specifically recited ***mixture of at least two distinct types of particles***. Reversal of the Examiner's rejection of claims 21, 23, 26, 30, 32, and 40-48 under 35 U.S.C. § 103(a) is therefore believed appropriate, and is respectfully requested.

Please charge any additional fees to Deposit Account No. 132725 (16326-0018FPWO).

Respectfully submitted,

Date: August 29, 2019

/Melissa M. Hayworth/
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23552

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 05/30/2019

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EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
05/30/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

Office Action Summary	**Application No.** 14/379,613	**Applicant(s)** Pilgaonkar et al.	
	Examiner LYNDSEY M BECKHARDT	**Art Unit** 1613	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 02/28/2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 21,23,26,30,32-37 and 39-48 is/are pending in the application.

5a) Of the above claim(s) 33-37 and 39 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 21,23,26,30,32 and 40-48 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Claims 21, 23, 26, 30, 32-37 and 39-48 are currently pending. Claims 21, 23, 26, 30, 32, 40-48 are currently under examination.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Interview Request

Applicant has submitted an interview request on 02/28/2019, accompanying Applicant's response to the non-final office action. This interview request is denied as Examiner and Applicant had an interview on 01/30/2019 initiated by Applicant, thus all issues pertaining to the previous office action have already been discussed.

Examiner's Note

Unless otherwise indicated, previous objection/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the 02/28/2019 response will be addressed to the extent they apply to current rejection(s).

Maintained Rejections:

The following rejections are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21, 23, 26, 30, 32 and 40-48 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US 2006/0183779 (previously applied) in view of US 2008/0069891 (previously applied) as evidenced by PubChem (previously applied).

Regarding claim 21, the limitation of a composition comprising a) particles that comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salts; and b) particles that comprise at least one

pharmaceutically acceptable organic acid is met by active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-mthyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmaceutically acceptable salts thereof (abstract), wherein PubChem evidences the structure of the '779 publication [0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1), thus teaching the acid contained in the core and the drug in a separate layer distinct from the acid.

The limitation of wherein at least one type of particles is coated with a protective coating layer is met by the '779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]).

The limitation of the second type of particles is coated with a protective coating layer is met by the '779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]), thus indicating a coating to be applied over the inner particle layer which contains the acid, wherein the second particle contains the acid.

The limitation of wherein the first type of particles is free from acids is met by the '779 publication teaching spatial separation of the organic acid and the active substance, wherein the organic acid and the active agent are taught to be in a particle ([0010], [0011]).

Regarding claim 23, the limitation of further comprising at least one pharmaceutically acceptable excipient is met by the '779 publication teaching polymer selected from gum Arabic included in the particles [0012]. The '779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient.

Regarding claim 26, the limitation of comprising from 0.01 wt% to 90% of dabigatran etexilate (expressed as dabigatran etexilate mesylate) is met by the '779 publication teaching dabigatran etexilate (abstract, [003]) wherein the active agent is taught to be present at 5-60% [0014].

Regarding claims 30, the limitation of 2-95% of the at least one pharmaceutically acceptable organic acid is met by the '779 publication teaching 30-100% of the organic acid in the core [0012].

Regarding claim 32, the limitation of wherein the composition comprises from 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

Regarding claim 40, the limitation of wherein the at least one pharmaceutically acceptable excipient is selected form the group consisting of binder, disintegrants, diluents, surfactants, glidant, lubricants and combinations thereof is met by the '779 publication teaching the '779 publication teaches embodiments wherein talc is present (Table 1, [0014]), wherein the instant specification teaches lubricants include talc [0053], the elected excipient. The '779 publication additionally teaches the use of a binder [0012].

Regarding claims 41 and 46, the limitation of a composition consisting of a mixture of at least one pharmaceutically acceptable excipient, wherein a) the first type comprising dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymer thereof, wherein the first type of particle is free from organic or inorganic acids and a second type comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free form dabigatran etexilate is met by the '779 publication teaching structure [0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1). The '779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]). The '779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient. the '779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]), thus indicating a coating to be applied over the inner particle layer which contains the acid, wherein the second particle contains the acid. The '779 publication teaches the active agent, an organic acid with a protective coating and an excipient.

It is noted that the use of 'at least one excipient' allows for additional ingredients in the formulation beyond the listed two particles, and additionally the 'comprising'

language regarding the first and second particles allows for additional ingredients in the particles.

Regarding claim 42, the limitation of comprising from 0.01 to 90 wt% of dabigatran etexilate, as dabigatran etexilate mesylate is met by the '779 publication teaching the 5 to 60 wt% of the pharmaceutical composition [0014].

Regarding claims 43 and 48, the limitation of wherein the first type of particles comprise at least one pharmaceutically acceptable excipient is met by the '779 publication teaching the use of binders or talc ([0014], Table 1).

Regarding claim 44, the limitation of wherein the at least one pharmaceutically acceptable recipient is selected from a group including binders, disintegrants, diluents, lubricants and combos thereof is met by the '779 publication teaching the use of binders or talc ([0014], Table 1).

Regarding claims 45 and 47, the limitation of wherein the composition comprises from 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

The '779 publication does not specifically teach components a) and b) in two distinct types of particles (claim 21, 41).

The '891 publication teaches a pharmaceutical composition may include granulate including at least one active pharmaceutical ingredient. The composition may include a coating on the granulate. The composition further comprises a second particle comprising a fat/wax. The granulate are formed into various dosage forms

(abstract, [0018]). The invention comprises two particles, the first type containing the pharmaceutical agent and the second comprising fat/wax material [0020].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779 publication as two distinct particles as the '891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication, thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine prior art elements according to known methods to yield a predictable results of separate particles in place of separate layers for the drug and acid formulation and obvious to try based on the '891 publication teaching it was known to use two separate particles.

Response to Arguments:

Applicant's arguments have been fully considered and are not deemed to be persuasive.

Applicant argues Brauns is the first named invention of the '779 publication and provides an interpretation of the disclosure of the '779 publication from the perspective of the inventor. The inventors interpretation should guide how one of skill in the art would interpret the disclosure of the '779 publication.

In response, Applicant has reviewed the provided Braun declaration, submitted as non-patent literature as it is not a declaration for the instant case. In reviewing the declaration it is noted that Brauns teaches the use of the layered particles and the desire for separation of the acid and drug, however does not consider the use of two separate particles, and therefore does not teach away from such a concept or teach that such a method would not work.

Applicant argues the present claims are directed to a mixture of two distinct particles. The presently claimed invention also related to a composition consisting of a mixture of two distinct particles.

In response, Applicant claims a composition consisting of two distinct types of particles and at least one excipient, and therefore opens up the claim to many different components that would be considered excipients and is not limited to the 2 types of particles.

Applicant argues as explained by the inventor Brauns, the '779 relates to a specific pharmaceutical preparation of dabigatran etexilate mesylate with reference to Figure 1. This particular preparation includes a spherical organic acid core, an insulating layer and an active substance layer, optionally a coating layer. The

declaration submitted during the prosecution of the '779 publication teaches the need for an acid so the drug will work well for the entire parathion population.

In response, the instant claims, using two separate particles and the '779 publication are both directed to the use of an acid which is separated from the active agent.

Applicant argues the layering present in the '779 publication are necessary components of the invention to provide a low pH microenvironment once the formation enters the stomach and the insulating layer acts as a protective layer between the acid core and the active substance layer. Braun explains that the acid core layer provides low pH microenvironment to ensure adequate bioavailability for the entire population. The insulating layer is taught to have 2 functions to protect between the acid core and active substance and permit diffusion of the acid immediately in the passage through the stomach. Braun identified the layered configuration as necessary (i.e. this confiscation was the only way the Brauns and the '779 publication contemplated to control the immediacy).

In response, as Applicant notes the Braun declaration is directed to the need for the acid for bioavailability while also remaining separate from the activity agent during storage. In the '779 publication this is accomplished by the use of a layered microparticles. When the particles are separated into one containing an acid with a coating and an additional particle comprising the active agent the acid particles containing the coating and the separated active substance would still be present, thus the necessary components are still present and in close proximity to each other. Braun did not discuss such an embodiment, therefore does not teach away from such an

embodiment. The '779 publication teaches the use of Dabigatran etexilate ([0003], PubChem evidences page 1, right column, page 3 structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007], wherein the form of the pellet containing an organic acid separating layer followed by a layer containing and active substance ([0010], Figure 1), thus teaching the use of an acid separated from the active agent to improve the formulation was known at the time of the invention. The '891 publication teaches the use of two separate particles in a pharmaceutical composition. Thus the active agent would remain separate from the acid, which would still be present to provide the desired release/absorption. Applicant has not provided evidence to the contrary.

Applicant argues it was not obvious to separate the particles and still achieve the diffusion needed to provide the good dissolution characteristics and consistent bioavailability.

In response, the '779 publication teaches the use of Dabigatran etexilate ([0003], PubChem evidences page 1, right column, page 3 structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007], wherein the form of the pellet containing an organic acid separating layer followed by a layer containing and active substance ([0010], Figure 1), thus teaching the use of an acid separated from the active agent to improve the formulation was known at the time of the invention. The '891 publication teaches the use of two separate particles in a pharmaceutical composition. Thus the active agent would remain separate from the acid, which would still be present to provide the desired release/absorption. Applicant has not provided evidence to the contrary. It would have

been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779 publication as two distinct particles as the '891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication.

Applicant submits that the inventors interpretation should guide how one of skill I the art would interpret the disclosure of the '779 publication.

In response, Examiner's interpretation of the '779 publication is in line with the Braun declaration provided (NPL) regarding the interpretation of the invention. The '779 publication is directed to a particle which includes and acid separated from the active agent during storage, wherein the acid is required for bioavailability. The '779 publication does not negate the use of two separate particles which would accomplish

the same results, the delivery of an acid and active agent at the same time, wherein the acid and the drug are separated during storage via an insulating layer on the particles. The instant rejection is not an anticipation rejection, therefore the teachings must not only be found in the '779 publication, but what we would be obvious from such a references. As noted above the '891 publication teaches that it was known to use an active agent particle and an excipient particle in the same oral formulation, thus it would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication.

Applicant argues obviousness requires motivation, rationale for change and reasonable expectation of success. The prior art's teaching undermine the very reason being proffered as to why a person of ordinary skill would have combined known elements.

In response, the '779 publication does not undermine the use of two separate particles. As stated above the '779 publication is directed to the use of an acid to help with the bioavailability of the active agent and the need for separation of the acid and drug during storage before use. The '779 publication uses layering of a particle to accomplish such, however does not negate or teach away from the use of two separate particles to accomplish the same goal. It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891

publication, thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine prior art elements according to known methods to yield a predictable results of separate particles in place of separate layers for the drug and acid formulation and obvious to try based on the ‘891 publication teaching it was known to use two separate particles.

Applicant argues the ‘891 publication is not related at all to or concerned with the necessity of a close proximity between acid and active ingredient ot obtain a desired results. The ‘779 publication teaches the acid is needed for the diffusion to accomplish bioavailability in the entire population.

In response, as noted the ‘779 publication (prior art in use in the instant rejection) teaches the need and desire for the acid to be near the active agent during the release for bioavailability, therefor such a need was known in the prior art. The ‘891 publication teaches a single pharmaceutical composition that includes both the excipient granulate and the active agent granule, thus the two granule would be in close proximity via being in the same composition such as a capsule [0039].

Applicant argues modifying pharmaceutical formulations are unpredicatable, especially when a particular configuration of the formulation is described in such a way that it is necessary. Different active pharmaceutical ingredient shave unique structure and properties. The ‘779 publication indicated that a single particle configuration was necessary for the unique structure and characteristic of dabigatran etexilate mesylate.

In response, one of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the ‘779 publication teaches an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the ‘891

publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). The '779 publication teaches the need for the components, an active agent, a protective layer and an acid core. Thus the components are all still present and spatially separated as required by the '779 publication.

Applicant argues claim 41 and 47 recites the composition consisting of a mixture of two distinct types of particles and at least one excipient. The '779 publication cannot disclosure or suggest a composition consisting of a mixture of these two distinct types of particles.

In response, Applicant uses consisting of language in claims 41 and 47, however allows for at least one excipient, therefore allowing for additional ingredients in the composition. Applicant's arguments regarding the teaching of the use of two distinct particles in place of a layered one taught by the '779 publication is addressed above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY MARIE BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached on Monday, Tuesday and Thursday 7:30 to 3pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information

system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LMB/
Examiner, Art Unit 1613

/DENNIS J PARAD/
Primary Examiner, Art Unit 1612

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
	No Classified Search		

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
East (keyword and Inventor) see attached	9/24/2015	LMB
Google (keyword) see attached East search terms	9/24/2015	LMB
East (keyword and Inventor) see attached	3/7/2016	LMB
Google (keyword) see attached East search terms	3/7/2016	LMB
East (keyword and Inventor) see attached	7/25/2017	LMB
East (keyword and Inventor) see attached	01/08/2018	LMB
East (keyword and Inventor) see attached	11/08/2018	LMB
Google (keyword) see attached East search terms	11/08/2018	LMB
East (keyword and Inventor) see attached	05/20/2019	LMB

/LMB/	

IPR2025-01107
MSN Exhibit 1002
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/LMB/	

IPR2025-01107
MSN Exhibit 1002
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	12	L2 or L3 or L4	USPAT	OR	OFF	2019/05/20 12:32
L6	51	L2 or L3 or L4	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L8	29	L6 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L10	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2019/05/20 12:32
L11	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L17	2199080	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L18	49629	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L19	8	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L21	9405	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L23	2340	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L24	2340	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L26	45726	(drug or active or pharmaceutical) same (particle or microsphere) same (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L27	6849	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L28	2315638	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32

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		or blend) same organic acid				
L32	49	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L33	38	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L34	45	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L35	51	L32 or L33 or L34	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L38	0	("20060183779").PN.	USPAT; USOCR	OR	OFF	2019/05/20 12:32
L39	0	("200600183779").PN.	USPAT; USOCR	OR	OFF	2019/05/20 12:32
L40	0	("200600183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L42	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L47	12	L44 or L45 or L46	USPAT	OR	OFF	2019/05/20 12:32
L48	51	L44 or L45 or L46	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L50	29	L48 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L52	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2019/05/20 12:32
L53	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L59	2199080	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L60	49629	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L61	8	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L63	9405	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L65	2340	((tartaric or organic acid) near5 particle) same((drug or active agent or	US-PGPUB;	OR	OFF	2019/05/20 12:32

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		pharmaceutical or dabigatran) near3 particle)	USPAT			
L66	2340	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L68	45726	(drug or active or pharmaceutical) same (particle or microsphere) same (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L69	6849	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L73	49	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L74	38	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L75	45	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:32
L76	51	L73 or L74 or L75	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L79	0	("20060183779").PN.	USPAT; USOCR	OR	OFF	2019/05/20 12:32
L80	0	("200600183779").PN.	USPAT; USOCR	OR	OFF	2019/05/20 12:32
L81	0	("200600183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L83	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L85	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L90	12	L87 or L88 or L89	USPAT	OR	OFF	2019/05/20 12:32
L91	51	L87 or L88 or L89	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:32
L93	29	L91 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2019/05/20 12:33
L95	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2019/05/20 12:33
L96	0	("2005038077").PN.	US-PGPUB; USPAT;	OR	OFF	2019/05/20 12:33

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			USOCR			
L102	49629	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:33
L103	8	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:33
L105	9405	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:33
L107	2340	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2019/05/20 12:33

EAST Search History (Interference)

< This search history is empty>

5/20/2019 12:41:20 PM
C:\Users\lshaak\Documents\EAST\Workspaces\14379613.wsp

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.	23552	Confirmation No.	6655

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

REQUEST FOR INTERVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

The Applicant's representative respectfully requests a formal Interview with the Examiner to help advance prosecution of the subject application.

Respectfully submitted,

Date: February 28, 2019

/Melissa M. Hayworth/
Melissa M. Hayworth
Registration No. 45774

Merchant & Gould PC
PO Box 2903
Minneapolis, MN 55402-0903
Telephone No.: 703.684.2522
Facsimile No.: 612.332.9081

23552
PATENT TRADEMARK OFFICE

Electronic Acknowledgement Receipt

EFS ID:	35292226
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	28-FEB-2019
Filing Date:	19-AUG-2014
Time Stamp:	18:30:17
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	2019-02-28_16326_0018FPWO_Response.PDF	164611 db8f8b0a73008d45a3e4428f59b3a87e4087a624b	no	13

Warnings:

Information:					
2	Letter Requesting Interview with Examiner	2019-02-28_16326-0018FPWO_Request_Interview.PDF	76705 71d6a97cccb40097c76623185723ebb25a043f84	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	241316	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.	23552	Confirmation No.	6655

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

RESPONSE UNDER 37 C.F.R. §1.111

U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commissioner for Patents

In complete response to the Office Action dated 30 November 2018, Applicant submits herewith the following response and the attached Request for Interview.

Listing of the Claims is provided beginning on page 2.

Remarks begin on page 7.

Listing of Claims:

1 – 20. (Cancelled)

21. (Previously Presented) A composition comprising: a mixture of at least two distinct types of particles wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic acids and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

22. (Cancelled)

23. (Previously Presented) The composition according to claim 21, further comprising at least one pharmaceutically acceptable excipient.

24. (Cancelled)

25. (Cancelled)

26. (Previously Presented) The composition according to claim 21, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.

27. - 29. (Cancelled)

30. (Previously Presented) The composition according to claim 21, comprising from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

31. (Cancelled)

32. (Previously Presented) A unit dosage form prepared from the composition according to claim 21, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

33. (Withdrawn) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a composition according to claim 21.

34. (Withdrawn) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a unit dose according to claim 32.

35. (Withdrawn) A process for the preparation of the composition according to claim 23, comprising the step of mixing the first type of particles and the second type of particles with the at least one at least one pharmaceutically acceptable excipient.

36. (Withdrawn) The process of claim 35, wherein the first type of particles are prepared by granulation.

37. (Withdrawn) The process according to claim 36, comprising the steps of:
i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient;
ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;
iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

v) coating the organic acid granules with a protective coating layer;

vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

38. (Cancelled)

39. (Withdrawn) The process according to claim 36, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

v) coating the organic acid pellets of step (iv) with a protective coating layer;

vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

40. (Previously Presented) The composition according to claim 23, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

41. (Previously Presented) A composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

42. (Previously Presented) The composition according to claim 41, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.

43. (Previously Presented) The composition according to claim 41, wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.

44. (Previously Presented) The composition according to claim 41, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

45. (Previously Presented) A capsule unit dosage form prepared from the composition according to claim 44, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

46. (Previously Presented) A capsule containing a pharmaceutical composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

47. (Previously Presented) The capsule according to claim 46 containing from 50 mg to 200 mg of dabigatran etexilate mesylate.

48. (Previously Presented) The capsule according to claim 46, wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.

REMARKS

Claims 21, 23, 26, 30, 32-37, and 39-48 are pending, with claims 21, 41, and 46 being independent. Claims 33-37 and 39 are withdrawn from consideration. In the present response, no claim amendments are presented. The Listing of Claims is provided for the Examiner's reference.

Applicant respectfully requests the Examiner to reconsider and withdraw the outstanding rejections in view of the following remarks. If the present response is not deemed persuasive, Applicant's representative requests an opportunity to discuss any outstanding rejections with the Examiner and submit herewith a Request for Interview.

Statement of Substance of Interview

Applicant's representative thanks Examiner Beckhardt for the interview conducted on 22 January 2019. During the interview, Applicant's representative discussed claims 1, 41, and 46 and US 2006/0183779 (US '779 naming Brauns as an inventor). Applicant's representative also discussed the Declaration under 37 C.F.R. § 1.132 by Dr. Ulrich Brauns ("the Brauns declaration") submitted ***during prosecution of the '779 application***.

As discussed during the interview, Dr. Brauns is the first named inventor of US '779, and thus, the Brauns declaration is from the perspective of the inventor of US '779. As explained during the interview, the Brauns declaration demonstrates that modifying the invention of US '779 with a second distinct particle would destroy the invention. The Brauns declaration discusses the need for the acid to be close together with the active agent without intermixing to allow for separation and diffusion, which could only be accomplished with the use of layers. As discussed during the interview, the Braun declaration discussed the requirement for layering.

Applicant appreciates that the Examiner stated that she will reconsider the declaration based on it being provided in the prosecution history of US '779.

Rejections under 35 U.S.C. § 103

Claims 21, 23, 26, 30, 32, and 40-48 are rejected under 35 U.S.C. § 103 as allegedly obvious over US 2006/0183779 (US '779) in view of US 2008/0069891 (US '891) as evidenced by PubChem. In view of the present claims, Applicant respectfully disagrees with the outstanding

rejection. As stated above, Brauns is the first named inventor of US '779 and provides the interpretation of the disclosure of US '779 from the perspective of the inventor. The inventor's interpretation should guide how one of skill in the art would interpret the disclosure of US '779.

The presently claimed invention relates to a composition comprising: a mixture of at least ***two distinct types of particles***. The first type of particles comprises dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is ***free from organic and inorganic acids***; and the second type of particles comprises at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is ***free from dabigatran etexilate***.

The presently claimed invention also relates to a composition **consisting of** a mixture of ***two distinct types of particles*** and at least one pharmaceutically acceptable excipient, wherein the claimed two distinct types of particles (*i.e.*, the first and second type of particles) are as defined above. The presently claimed invention further relates to a ***capsule*** containing a pharmaceutical composition **consisting of** a mixture of ***two distinct types of particles*** and at least one pharmaceutically acceptable excipient, wherein the claimed two distinct types of particles are as defined above. It is noted that the first type of particle also may comprise at least one pharmaceutically acceptable excipient.

In contrast, as explained by the inventor Brauns, US '779 relates to a specific pharmaceutical preparation of dabigatran etexilate mesylate with reference to Figure 1. This particular preparation includes a spherical organic acid core, an insulating layer, an active substance layer, and optionally a coating layer. Submitted previously was a copy of the Declaration under 37 C.F.R. § 1.132 by Dr. Ulrich Brauns. This declaration was ***submitted during prosecution of US '779***. As explained by Brauns, the inventor of US '779,

> 13. It was hypothesized that some patient stomachs were more basic because of normal variability, by disease, or co-medication with drugs that increase gastric pH. That is, if the gastric environment of the patient is not sufficiently acidic, the prodrug (dabigatran etexilate mesylate) does not dissolve sufficiently to ensure adequate bioavailability. This was not expected but only detected during formulation development. To solve this problem, the formulation itself was re-design to a) **act as an acidic microenvironment** while in the stomach in order to quickly dissolve the majority of the prodrug prior to entering the small intestine; b) be stable before entering GI (Gastro Intestinal) tract for **storage purposes**; and c) **work well for the entire patient population**, meaning that bioavailability

> would be consistent and high for the entire patient population. This solution to the problem was not easy given the unique structure of dabigatran etexilate salt and the resulting solution to the problem, that is providing the particular form of pharmaceutical preparation as claimed, which forms the subject matter of this invention.

(Brauns declaration at paragraph 13, emphasis added).

As further explained by Brauns,

> 19. The present formulation was designed to accommodate the specific and unique properties of the prodrug, dabigatran etexilate. An ***acid core layer***, an ***insulating layer*** and an ***active substance layer*** **are necessary components** of this invention. For example, the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. The insulating layer first acts as a protective layer between the acid core and active substance layer on storage but then permits the diffusion of acid to the active substance layer immediately in passage through the stomach. The active substance layer provides the correct dosage of prodrug….

(Brauns declaration at paragraph 19, emphasis added).

Accordingly, Brauns in his declaration teaches that an acid core, an insulating layer, and an active substance layer within a single particle are ***necessary components*** of US '779. In the declaration, Brauns explains that the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. As explained in the declaration, this acidic microenvironment is needed to dissolve the prodrug (dabigatran etexilate mesylate) to ensure adequate bioavailability for the entire patient population. And the Brauns Declaration explains how the acid core and layers interact within the single particle. In the Declaration, it is stated that the insulating layer has two functions: firstly as a protective layer between the acid core and active substance on storage and secondly it permits the diffusion of acid to the acid substance layer immediately in passage through the stomach.

As such, Brauns explains that the single particle spatial distance is there for storage and for upon administration, the acid layer must "immediately" diffuse into the active substance layer. To achieve this immediate diffusion, the active substance layer and the acid layer had to be in the same particle, as stated by inventor Brauns. Brauns identified this configuration within a single particle as ***necessary*** (*i.e.*, this configuration was the only way that Brauns and US '779 contemplated to control the immediacy).

The inventor Brauns teaches that the designed formulation of US '779 - wherein the three components are necessary components and they must be in a single particle - solves the necessity of spatial separation, as well as creating the necessary spatial arrangement for achieving diffusion, which ultimately results in the creation of an acidic microenvironment to provide consistent bioavailability for the entire patient poplation. ***It was not obvious to separate the particles and still achieve the diffusion needed to provide the good dissolution characteristics and consistent bioavailability.***

In view of the disclosure in US '779 and as described by the inventor of that disclosure, modifying the invention of US '779 with two distinct types of particles ***would destroy*** the "invention" of US '779, because the acid core layer, the insulating layer, and the active substance layer in a single particle are ***necessary components*** and provide the needed acidic microenvironment for diffusion.

Applicant respectfully submits that the inventor's interpretation should guide how one of skill in the art would interpret the disclosure of US '779. The first named inventor's interpretation and explanation of his own patent document definitively should indicate how one of skill in the art reading US '779 would interpret its disclosure and scope.

Obviousness requires motivation, rationale for change and reasonable expectation of success. Here, the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements. DePuy Spine Inc. v. Medtronic Sofamor Danek Inc. 567 F.3d 1314 (Fed. Cir. 2009).

As such, US '779 does not provide one of ordinary skill in the art with a reason or motivation to modify the specific pharmaceutical preparation described therein to make the claimed composition with a reasonable expectation of success. In view of the disclosure in US '779, a skilled artisan would not have considered modifying its particular form of a formulation and then expected the presently claimed composition as an identifiable, predictable solution.

"The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Gordon, 733 F.2d 900 (Fed. Cir. 1984). Simply being capable of modifying is not enough. In re Mills, 916 F.2d 680, 682 (Fed. Cir. 1990).

US '891 as evidenced by PubChem does not cure this deficiency of a reason or motivation to modify US '779 with a reasonable expectation of success. US '891 teaches a spatial separation; however, US '891 is not related at all to or concerned with the necessity of a close proximity between acid and active ingredient to obtain a desired result, *i.e.*, an acidic environment that allows for diffusion. What the Office Action's analysis does not consider is that ***the diffusion in US '779 is needed to accomplish bioavailability in the entire patient population***. This concern, particular to US '779, is due to some patient stomachs being more basic because of normal variability, by disease, or by co-medication with drugs that increase gastric pH and the prodrug dabigatran etexilate mesylate needs an acidic environment to dissolve sufficiently for adequate bioavailability. This is not at all a consideration or requirement of US '891. Accordingly, the spatial separation of US '891 does not extrapolate to the need for ***separation and diffusion*** in US '779.

One of skill in the art could not reasonably predict that the single layered particles of US '779 could be separated to form a composition of a different configuration and retain the diffusion needed to accomplish bioavailability in the entire patient population. Having all three components in a single particle was necessary for the invention as disclosed in US '779, and using two distinct particles as presently claimed would destroy the invention as disclosed in US '779.

It is further noted that one of skill in the art generally views modifying pharmaceutical formulations as unpredictable, especially when a particular configuration of the formulation is described in such a way that it is necessary. And different active pharmaceutical ingredients have unique structures and properties. As acknowledged by inventor Brauns, the disclosure of US '779 indicated that the single particle configuration was necessary for the unique structure and characteristics of dabigatran etexilate mesylate. The inventor's interpretation should guide how one of skill in the art would interpret the disclosure of US '779.

Accordingly, US '779 in view of US '891 as evidenced by PubChem do not disclose or suggest the composition of claim 1 comprising the specifically recited ***mixture of at least two distinct types of particles***.

With regard to claims 41-48, these claims include the closed transition of "consisting of". As such, claim 41 recites a composition **consisting of** a mixture of ***two distinct types of particles*** and at least one pharmaceutically acceptable excipient, and claim 47 recites a capsule containing a pharmaceutical composition **consisting of** a mixture of ***two distinct types of particles*** and at least

one pharmaceutically acceptable excipient. The first type of particles comprises dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is ***free from organic and inorganic acids***; and the second type of particles comprises at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is ***free from dabigatran etexilate***.

US '779 in view of US '891 as evidenced by PubChem **cannot** not disclose or suggest a composition **consisting of** a mixture of ***these two distinct types of particles*** as specifically claimed and at least one pharmaceutically acceptable excipient. US '779 in view of US '891 as evidenced by PubChem do not disclose or suggest the specifically claimed ***first type of particles*** and/or the specifically claimed ***second type of particles***. As such, US '779 in view of US '891 as evidenced by PubChem cannot disclose or suggest compositions **consisting of** these two types of particles and at least one pharmaceutically acceptable excipient. In no way can US '779 in view of US '891 as evidenced by PubChem disclose or suggest claims 41-48 reciting "consisting of" language.

For at least these reasons, there is no prima facie case of obviousness. Accordingly, Applicant respectfully requests that the Examiner withdraw the outstanding rejection under 35 U.S.C. §103(a) over US '779 in view of US '891 as evidenced by PubChem.

Conclusion

For the reasons noted above, the art of record does not disclose or suggest the inventive concept of the present invention as defined by the claims.

In view of the foregoing remarks, reconsideration of the claims and allowance of the subject application are earnestly solicited. If there are any questions relating to this response or the application, Applicant requests that the Examiner telephone the undersigned attorney.

If the foregoing remarks are not deemed persuasive, Applicant's representative requests an opportunity to discuss the presently claimed invention with the Examiner. As such, Applicant includes herewith a formal Request for Interview.

The Examiner is authorized to charge any additional fees or refund any overpayments to Deposit Account No. 13-2725 (Docket No. 16326.0018FPWO).

Respectfully submitted,

Date: 28 February 2019

/Melissa M. Hayworth/
Melissa M. Hayworth
Registration No. 45774

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23522
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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/379,613	Filing Date 08/19/2014	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)			
FOR	NUMBER FILED	NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $420 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	02/28/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/GLORIA J TRAMMELL/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 01/30/2019

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MINNEAPOLIS, MN 55402-0903

EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
01/30/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

Applicant-Initiated Interview Summary	**Application No.** 14/379,613	**Applicant(s)** Pilgaonkar et al.	
	Examiner LYNDSEY M BECKHARDT	**Art Unit** 1613	**AIA Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) Examiner Beckhardt. (3) _____.

(2) Joe Gess. (4) _____.

Date of Interview: 22 January 2019.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1,41 and 46.

Identification of prior art discussed: The '779 publication (Brauns).

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant discussed the '779 publication teaching the components in layers in a single particle, wherein the instant claims require two separate particles. Examiner agreed the '779 publication particles do not meet the limitations of the instant claims by itself. Applicant discussed the previously supplied declaration being from the inventor of the '779 publication (Braun Declaration) which discussed the need for the acid to be close together with the active agent without intermixing to allow for diffusion which could only be accomplished with the use of layers. The Braun declaration discussed the requirement for layering, wherein the drug and acid particles alone not allowing for the mixing, thus teaching away and providing no motivation or expectation of success as the inventor of the '779 publication indicates that the use of separate particles goes against his invention. Examiner stated she will reconsider the declaration based on it being provided in the case history of the prior art ('779 publication). No agreement was reached..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/LMB/	/DENNIS J PARAD/ Primary Examiner, Art Unit 1612

IPR2025-01107
MSN Exhibit 1002
Page 258 of 680

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	16326.0018FPWO	6655

23552 7590 11/30/2018

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EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
11/30/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

Office Action Summary	Application No. 14/379,613	Applicant(s) Pilgaonkar et al.	
	Examiner LYNDSEY M BECKHARDT	Art Unit 1613	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 04/16/2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 21,23,26,30,32-37 and 39-48 is/are pending in the application.

5a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 21,23,26,30,32 and 40-48 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Continuation of Disposition of Claims* 5a) Of the above claim(s) is/are withdrawn from consideration: 33-37 and 39

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Claims 21, 23, 26, 30, 32-37 and 39-48 are currently under examination. Claims 21, 23, 26, 30, 32 and 40-48 are currently under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/16/2018 has been entered.

Information Disclosure Statement

Applicant's Informational Disclosure Statement, filed on 04/16/2018 has been considered. Please refer to Applicant's copy of the 1449 submitted herein.

Examiner's Note

Unless otherwise indicated, previous objection/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the 04/16/2018 response will be addressed to the extent they apply to current rejection(s).

Modified Rejection:

The following rejections are modified based on Applicant's claim amendments and newly added claims.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21, 23, 26, 30, 32 and 40-48 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US 2006/0183779 (previously applied) in view of US 2008/0069891 (previously applied) as evidenced by PubChem (previously applied).

Regarding claim 21, the limitation of a composition comprising a) particles that comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salts; and b) particles that comprise at least one pharmaceutically acceptable organic acid is met by active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-mthyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmaceutically acceptable salts thereof (abstract), wherein PubChem evidences the structure of the '779 publication [0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1), thus teaching the acid contained in the core and the drug in a separate layer distinct from the acid.

The limitation of wherein at least one type of particles is coated with a protective coating layer is met by the '779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]).

The limitation of the second type of particles is coated with a protective coating layer is met by the '779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011],

[0013], [0015]), thus indicating a coating to be applied over the inner particle layer which contains the acid, wherein the second particle contains the acid.

The limitation of wherein the first type of particles is free from acids is met by the '779 publication teaching spatial separation of the organic acid and the active substance, wherein the organic acid and the active agent are taught to be in a particle ([0010], [0011]).

Regarding claim 23, the limitation of further comprising at least one pharmaceutically acceptable excipient is met by the '779 publication teaching polymer selected from gum Arabic included in the particles [0012]. The '779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient.

Regarding claim 26, the limitation of comprising from 0.01 wt% to 90% of dabigatran etexilate (expressed as dabigatran etexilate mesylate) is met by the '779 publication teaching dabigatran etexilate (abstract, [003]) wherein the active agent is taught to be present at 5-60% [0014].

Regarding claims 30, the limitation of 2-95% of the at least one pharmaceutically acceptable organic acid is met by the '779 publication teaching 30-100% of the organic acid in the core [0012].

Regarding claim 32, the limitation of wherein the composition comprises from 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

Regarding claim 40, the limitation of wherein the at least one pharmaceutically acceptable excipient is selected form the group consisting of binder, disintegrants, diluents, surfactants, glidant, lubricants and combinations thereof is met by the '779 publication teaching the '779 publication teaches embodiments wherein talc is present (Table 1, [0014]), wherein the instant specification teaches lubricants include talc [0053], the elected excipient. The '779 publication additionally teaches the use of a binder [0012].

Regarding claims 41 and 46, the limitation of a composition consisting of a mixture of at least one pharmaceutically acceptable excipient, wherein a) the first type comprising dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymer thereof, wherein the first type of particle is free from organic or inorganic acids and a second type comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free form dabigatran etexilate is met by the '779 publication teaching structure [0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1). The '779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]). The '779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient. the '779 publication teaching the core layer containing an insulating layer and

the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]), thus indicating a coating to be applied over the inner particle layer which contains the acid, wherein the second particle contains the acid. The '779 publication teaches the active agent, an organic acid with a protective coating and an excipient.

It is noted that the use of 'at least one excipient' allows for additional ingredients in the formulation beyond the listed two particles, and additionally the 'comprising' language regarding the first and second particles allows for additional ingredients in the particles.

Regarding claim 42, the limitation of comprising from 0.01 to 90 wt% of dabigatran etexilate, as dabigatran etexilate mesylate is met by the '779 publication teaching the 5 to 60 wt% of the pharmaceutical composition [0014].

Regarding claims 43 and 48, the limitation of wherein the first type of particles comprise at least one pharmaceutically acceptable excipient is met by the '779 publication teaching the use of binders or talc ([0014], Table 1).

Regarding claim 44, the limitation of wherein the at least one pharmaceutically acceptable recipient is selected from a group including binders, disintegrants, diluents, lubricants and combos thereof is met by the '779 publication teaching the use of binders or talc ([0014], Table 1).

Regarding claims 45 and 47, the limitation of wherein the composition comprises from 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

The ‘779 publication does not specifically teach components a) and b) in two distinct types of particles (claim 21, 41).

The ‘891 publication teaches a pharmaceutical composition may include granulate including at least one active pharmaceutical ingredient. The composition may include a coating on the granulate. The composition further comprises a second particle comprising a fat/wax. The granulate are formed into various dosage forms (abstract, [0018]). The invention comprises two particles, the first type containing the pharmaceutical agent and the second comprising fat/wax material [0020].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the ‘779 publication as two distinct particles as the ‘891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the ‘779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the ‘779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the ‘891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the ‘779 publication

could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication, thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine prior art elements according to known methods to yield a predictable results of separate particles in place of separate layers for the drug and acid formulation and obvious to try based on the '891 publication teaching it was known to use two separate particles.

Response to Arguments:

Applicant's arguments have been fully considered and are not deemed to be persuasive.

Applicant provides the Brauns declaration demonstrates that modifying the invention of the '779 with a second distinct particle would destroy the invention. The declaration (provided as NPL reference) discusses Dabigatran's need for a prodrug as dabigatran etexilate salt. The prodrug salt alone was not sufficient for providing adequate bioavailability to the entire patient. It was administered as a tablet and thought that gastric juices in the stomach would be sufficient to solubilize the prodrug. The degree of absorption was determined to be a function of the pH of the stomach of a patient. An acid core layer of an active substance was necessary component of the invention to provide a low pH microenviroment once the formulation enters the stomach.

In response, the '779 publication teaches the use of an Dabigatran etexilate ([0003], PubChem evidences page 1, right column, page 3 structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007], wherein the form of the pellet containing an organic acid

separating layer followed by a layer containing and active substance ([0010], Figure 1), thus teaching the use of an acid separated from the active agent to improve the formulation was known at the time of the invention. The '891 publication teaches the use of two separate particles in a pharmaceutical composition. Thus the active agent would remain separate from the acid, which would still be present to provide the desired release/absorption. Applicant has not provided evidence to the contrary.

Applicant argues the new claim language is directed to a composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient. The new claims additional require a capsule.

In response, Applicant's newly added claims are addressed above. It is noted that the use of 'at least one excipient' allows for additional ingredients in the formulation beyond the listed two particles, and additionally the 'comprising' language regarding the first and second particles allows for additional ingredients in the particles. Regarding claims 41 and 46, the limitation of a composition consisting of a mixture of at least one pharmaceutically acceptable excipient, wherein a) the first type comprising dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymer thereof, wherein the first type of particle is free from organic or inorganic acids and a second type comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate is met by the '779 publication teaching structure [0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a

separating layer followed by a layer containing the active substance ([0010], Figure 1). The ‘779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]). The ‘779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient. the ‘779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]), thus indicating a coating to be applied over the inner particle layer which contains the acid, wherein the second particle contains the acid. The ‘779 publication teaches the active agent, an organic acid with a protective coating and an excipient.

Applicant argues as explained in the ‘779 publication the dabigatran etexilate mesylate separation include aspherical organic acid core, an insulating layer, an active substance layer and optionally a coating layer. An acid core layer, an insulating layer and an active substance layer are necessary component of this invention. The acid core provides a low pH microenvironment once the formulation enters the stomach, the insulating layer acts as a protective layer between the acid core and active substance layer on storage but permits diffusion and the active substance layer provides correct dosage of the prodrug. As such the acid core layer, the insulating layer and the active substance layer in a single particle are necessary components. Two distinct types of particles would destroy the invention.

In response, when the particles are separated into one containing an acid with a coating and an additional particle comprising the active agent the acid particles

containing the coating and the separated active substance would still be present, thus the necessary components are still present.

Applicant argues the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements. As discussed during the interview the Braun declaration demonstrates that all three components must be in a single particle. Braun's explains how the acid core and layers interact, the resulting layer first act as a protective layer and then permit diffusion. Braun explains that the spatial distance is there for storage, and upon administration the acid layer must immediately diffuse into the active substance layer. Braun identified this configuration within a single particle as necessary.

In response, the '779 publication teaches the use of Dabigatran etexilate ([0003], PubChem evidences page 1, right column, page 3 structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007], wherein the form of the pellet containing an organic acid separating layer followed by a layer containing and active substance ([0010], Figure 1), thus teaching the use of an acid separated from the active agent to improve the formulation was known at the time of the invention. The '891 publication teaches the use of two separate particles in a pharmaceutical composition. Thus the active agent would remain separate from the acid, which would still be present to provide the desired release/absorption. Applicant has not provided evidence to the contrary.

Applicant argues the '779 publication does not provide one of ordinary skill in the rate with a reason or motivation to modify the specific pharmaceutical preparation described therein to make the claimed composition with a reasonable expectation of

success. One of skill in the art would not have considered modifying the prior art and expected presently claimed composition as an identifiable predictable solution. The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirable of the modification.

In response, the '891 publication teaches a pharmaceutical composition may include granulate including at least one active ingredient, a coating and a second particle (abstract, [0018]). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779 publication as two distinct particles as the '891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication.

Applicant argues one of skill in the art generally view modifying pharmaceutical formulations as unpredictable, especially when a particular configuration of the formulation is identified as necessary.

In response, one of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). The '779 publication teaches the need for the components, an active agent, a protective layer and an acid core. Thus the components are all still present and spatially separated as required by the '779 publication.

Applicant argues one of skill would not have been motivated to separate the particles of the '779 publication. Having all three components in a single particle was necessary for the invention of the '779 publication and using two distinct particles as presently claimed would destroy the invention of the '779 publication.

In response, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779 publication as two distinct particles as the '891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. It would have been obvious to one of ordinary skill in the art at the

time the invention was made that the separation of the organic acid and the active agent described by the ‘779 publication could be via the layers taught by the ‘779 publication or through the use of separate particles as taught by the ‘891 publication.

Applicant argues the ‘891 does not cure the deficiencies of a reason or motivation to modify the ‘779 publication with a reasonable expectation of success.

In response, Applicant’s arguments regarding the ‘779 publication are addressed above.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY MARIE BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached on Monday, Tuesday and Thursday 7:30 to 3pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Brian-Yong Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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/LMB/
Examiner, Art Unit 1613

/DENNIS J PARAD/
Primary Examiner, Art Unit 1612

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
	No Classified Search		

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Search Notes		
Search Notes	Date	Examiner
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East (keyword and Inventor) see attached	3/7/2016	LMB
Google (keyword) see attached East search terms	3/7/2016	LMB
East (keyword and Inventor) see attached	7/25/2017	LMB
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Google (keyword) see attached East search terms	11/08/2018	LMB

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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(Not for submission under 37 CFR 1.99)

Application Number	14379613
Filing Date	2014-08-19
First Named Inventor	Pilgaonkar
Art Unit	1613
Examiner Name	Lyndsey Marie Beckhardt
Attorney Docket Number	16326.0018FPWO

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14379613
	Filing Date	2014-08-19
	First Named Inventor	Pilgaonkar
	Art Unit	1613
	Examiner Name	Lyndsey Marie Beckhardt
	Attorney Docket Number	16326.0018FPWO

	1	Declaration under 37 C.F.R. 1.132 of Dr. Ulrich Brauns filed in U.S. Application No. 11/381890 dated 11 March 2014.	

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Examiner Signature	/LYNDSEY M BECKHARDT/	Date Considered	11/08/2018

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	11	L1 or L2 or L3	USPAT	OR	OFF	2018/11/08 15:36
L5	48	L1 or L2 or L3	US-PGPUB; USPAT; USOCR	OR	OFF	2018/11/08 15:36
L7	26	L5 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2018/11/08 15:36
L9	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2018/11/08 15:36
L10	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/11/08 15:36
L16	2127319	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L17	47813	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L18	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L20	9028	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L22	2234	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L23	2234	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L25	43879	(drug or active or pharmaceutical) same (particle or microsphere) same (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L26	6578	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L27	2253254	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend) same organic acid	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L31	46	((Pratibha) near2 (Pilgaonkar)).INV.	US-	OR	OFF	2018/11/08

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			PGPUB; USPAT			15:36
L32	37	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L33	42	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L34	48	L31 or L32 or L33	US-PGPUB; USPAT; USOCR	OR	OFF	2018/11/08 15:36
L37	0	("20060183779").PN.	USPAT; USOCR	OR	OFF	2018/11/08 15:36
L38	0	("200600183779").PN.	USPAT; USOCR	OR	OFF	2018/11/08 15:36
L39	0	("200600183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/11/08 15:36
L41	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/11/08 15:36
L46	11	L43 or L44 or L45	USPAT	OR	OFF	2018/11/08 15:36
L47	48	L43 or L44 or L45	US-PGPUB; USPAT; USOCR	OR	OFF	2018/11/08 15:36
L49	26	L47 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2018/11/08 15:36
L51	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2018/11/08 15:36
L52	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/11/08 15:36
L58	2127319	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L59	47813	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L60	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L62	9028	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36
L64	2234	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36

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L65	2234	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/11/08 15:36

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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	14379613	Filing Date	2014-08-19	Docket Number (if applicable)	16326.0018FPWO	Art Unit	1613
First Named Inventor	Pilgaonkar			Examiner Name	Lyndsey Marie Beckhardt		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 132725

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

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Signature of Registered U.S. Patent Practitioner			
Signature	/Melissa M. Hayworth/	Date (YYYY-MM-DD)	2018-04-16
Name	Melissa M. Hayworth	Registration Number	45774

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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Electronic Patent Application Fee Transmittal

Application Number:	14379613
Filing Date:	19-Aug-2014
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Filer:	Melissa M. Hayworth/Lisa Kenney
Attorney Docket Number:	16326.0018FPWO

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 1ST REQUEST	1801	1	1300	1300
		Total in USD ($)		**1300**

Electronic Acknowledgement Receipt	
EFS ID:	32348140
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	23552
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	16326.0018FPWO
Receipt Date:	16-APR-2018
Filing Date:	19-AUG-2014
Time Stamp:	14:40:11
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1300
RAM confirmation Number	041718INTEFSW14413000
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment Submitted/Entered with Filing of CPA/RCE	0018FPWO_RCE_Amendment.PDF	126903 c714680f0176f9463bfa9a1e2fcb4f4e038c17e9	no	11
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	0018FPWO_IDS.PDF	1034961 64d8c7dffe80244ef3596f995610c2a70449ab44	no	4
Warnings:					
Information:					
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3	Non Patent Literature	Brauns_Declaration.PDF	324861 b8d11c63b6279a09b593725193cd1935ef6f503f	no	6
Warnings:					
Information:					
4	Request for Continued Examination (RCE)	0018FPWO_RCE_Transmittal.PDF	1349941 22cbb60b55ddb39fe80954af292948f15afa09bd	no	3
Warnings:					
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5	Fee Worksheet (SB06)	fee-info.pdf	30742 be8074976ff2bf20fe5244a575e2a690240c05f1	no	2
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	14/379,613	Group Art Unit:	1613
Filed:	August 19, 2014	Docket No.:	16326.0018FPWO
Customer No.	23552	Confirmation No.	6655

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

RESPONSE UNDER 37 C.F.R. §1.114

U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commissioner for Patents

In response to the Final Office Action dated 16 January 2018, Applicant submits herewith a Request for Continued Examiner, a Request for Interview, and the following response.

Amendments to the Claims are reflected in the Listing of the Claims beginning on page 2.

Remarks begin on page 7.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-20. (canceled)

21. (Currently Amended) A composition comprising: a mixture of at least two distinct types of particles wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic acids and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

22. (Cancelled)

23. (Previously Presented) The composition according to claim 21, further comprising at least one pharmaceutically acceptable excipient.

24. (Cancelled)

25. (Cancelled)

26. (Currently Amended) The composition according to claim 21, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, ~~expressed~~ as dabigatran etexilate mesylate.

27. - 29. (Cancelled)

30. (Previously Presented) The composition according to claim 21, comprising from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

31. (Cancelled)

32. (Previously Presented) A unit dosage form prepared from the composition according to claim 21, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

33. (Withdrawn) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a composition according to claim 21.

34. (Withdrawn) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a unit dose according to claim 32.

35. (Withdrawn) A process for the preparation of the composition according to claim 23, comprising the step of mixing the first type of particles and the second type of particles with the at least one at least one pharmaceutically acceptable excipient.

36. (Withdrawn) The process of claim 35, wherein the first type of particles are prepared by granulation.

37. (Withdrawn) The process according to claim 36, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

v) coating the organic acid granules with a protective coating layer;

vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

38. (Cancelled)

39. (Withdrawn) The process according to claim 36, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

v) coating the organic acid pellets of step (iv) with a protective coating layer;

vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

40. (New) The composition according to claim 23, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

41. (New) A composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

42. (New) The composition according to claim 41, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.

43. (New) The composition according to claim 41, wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.

44. (New) The composition according to claim 41, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

45. (New) A capsule unit dosage form prepared from the composition according to claim 44, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

46. (New) A capsule containing a pharmaceutical composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

47. (New) The capsule according to claim 46 containing from 50 mg to 200 mg of dabigatran etexilate mesylate.

48. (New) The capsule according to claim 46, wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.

REMARKS

Claims 21, 23, 26, 30, 32, and new claims 40-47 are pending, with claims 21, 41, and 46 being independent. Claims 33-37 and 39 are withdrawn from consideration. In the present amendment, claim 21 has been amended to more clearly recite particularly the present invention and claims 24, 25, and 27 have been cancelled without prejudice to or disclaimer of the subject contained therein. New claims 40-48 have been added. Support for the amendments and new claims can be found throughout the application, including in the original claims. Therefore, no new matter has been added.

Applicant respectfully requests the Examiner to reconsider and withdraw the outstanding rejections in view of the foregoing amendments and the following remarks. If the present response is not deemed persuasive, Applicant's representative requests an opportunity to discuss any outstanding rejections with the Examiner.

Statement of Substance of Interview

Applicant's representative thanks Examiner Parad for the interview conducted on 29 March 2017. During the interview, Applicant's representative discussed claim amendments as presented herein. Applicant's representative also discussed the Declaration under 37 C.F.R. § 1.132 by Dr. Ulrich Brauns ("the Brauns declaration") submitted during prosecution of US '779. Dr. Brauns is the first named inventor of US '779. As explained during the interview, the Brauns declaration demonstrates that modifying the invention of US '779 with a second distinct particle would destroy the invention, as explained by the inventor Dr. Brauns US '779. A copy of the Brauns declaration is submitted herewith for the Examiner's consideration. The Brauns declaration is cited in an Information Disclosure Statement on a form SB08 so that the Examiner may indicate consideration thereof.

As discussed during the interview, Applicant submits the present response, including the claim amendments and a copy of the Brauns declaration for further consideration, with a Request for Continued Examination.

Rejections under 35 U.S.C. § 103

Claims 21, 23-27, 30 and 32 are rejected under 35 U.S.C. § 103 as allegedly obvious over US 2006/0183779 (US '779) in view of US 2008/0069891 (US '891) as evidenced by PubChem. Herein, US '779 also is identified interchangeably as "Brauns". In view of the claims as presented herein, Applicant respectfully disagrees.

The presently claimed invention relates to a composition comprising: ***a mixture of at least two distinct types of particles***. The first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is ***free from organic and inorganic acids***; and the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is ***free from dabigatran etexilate***.

The presently claimed invention also relates to a composition consisting of ***a mixture of two distinct types of particles*** and ***at least one pharmaceutically acceptable excipient***, wherein the claimed two distinct types of particles are as defined above. The presently claimed invention further relates to a ***capsule*** containing a pharmaceutical composition consisting of ***a mixture of two distinct types of particles*** and ***at least one pharmaceutically acceptable excipient***, wherein the claimed two distinct types of particles are as defined above. It is noted that the first type of particle may also comprise at least one pharmaceutically acceptable excipient.

In contrast, as explained by the inventor Brauns of US '779, US '779 relates to a specific pharmaceutical preparation of dabigatran etexilate mesylate with reference to Figure 1. This particular preparation includes a spherical organic acid core, an insulating layer, an active substance layer, and optionally a coating layer. Included herewith is a copy of the Brauns declaration submitted during prosecution of US '779. As explained by the inventor,

> The present formulation was designed to accommodate the specific and unique properties of the prodrug, dabigatran etexilate. An ***acid core layer***, an ***insulating layer*** and an ***active substance layer*** **are necessary components** of this invention. For example, the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. The insulating layer first acts as a protective layer between the acid core and active substance layer on storage but then permits the diffusion of acid to the active substance layer immediately in passage through the stomach. The active substance layer provides the correct dosage of prodrug.

(Brauns declaration at paragraph 19, emphasis added). As such, the acid core layer, the insulating layer, and the active substance layer in a single particle are ***necessary components*** of US '779 (as admitted by the inventor Brauns). In view of the disclosure in US '779 and as described by the inventor, modifying the invention of US '779 with two distinct types of particles ***would destroy*** the "invention" of US '779, because the acid core layer, the insulating layer, and the active substance layer in a single particle are ***necessary components***.

Obviousness requires motivation, rationale for change and reasonable expectation of success. Here, the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements. DePuy Spine Inc. v. Medtronic Sofamor Danek Inc. 567 F.3d 1314 (Fed. Cir. 2009).

As discussed during the interview, the Brauns declaration demonstrates that US '779 (Brauns) contemplated that all three components ***must be in a single particle***. Brauns explains how the acid core and layers interact: "The insulating layer first acts as a protective layer between the acid core and active substance layer on storage but then permits the diffusion of acid to the active substance layer immediately in passage through the stomach." As such, Brauns explains that the spatial distance is there for storage, and upon administration, the acid layer must "immediately" diffuse into the active substance layer. To achieve this immediate diffusion, the active substance layer and the acid layer had to be in the same particle, as stated by inventor Brauns. Brauns identified this configuration within a single particle as ***necessary*** (i.e., this configuration was the only way that Brauns contemplated to control the immediacy).

As such, Brauns does <u>not</u> provide one of ordinary skill in the art with a reason or motivation to modify the specific pharmaceutical preparation described therein to make the claimed composition with a reasonable expectation of success. In view of this disclosure, a skilled artisan would <u>not</u> have considered modifying the prior art and expected the presently claimed composition as an identifiable, predictable solution.

"The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Gordon, 733 F.2d 900 (Fed. Cir. 1984). Simply being capable of modifying is not enough. In re Mills, 916 F.2d 680, 682 (Fed. Cir. 1990).

It is further noted that one of skill in the art generally views modifying pharmaceutical formulations as unpredictable, especially when a particular configuration of the formulation is identified as necessary.

Accordingly, one of skill in the art would not have been motivated to separate the particles of Brauns. Moreover, one of skill in the art could not reasonably predict that the single layered particles of Brauns could be separated to form a composition of a different configuration. Having all three components in a single particle was necessary for the invention of Brauns, and using two distinct particles as presently claimed would destroy the invention of Brauns.

US '891 as evidenced by PubChem does not cure this deficiency of a reason or motivation to modify US '779 with a reasonable expectation of success. Accordingly, US '779 in view of US '891 as evidenced by PubChem do not disclose or suggest a composition comprising: ***a mixture of at least two distinct types of particles***. US '779 in view of US '891 as evidenced by PubChem do not disclose or suggest the presently claimed ***first type of particles comprising dabigatran etexilate*** in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, ***wherein the first type of particles is free from organic and inorganic acids***. US '779 in view of US '891 as evidenced by PubChem do not disclose or suggest the presently claimed ***second type of particles comprising at least one pharmaceutically acceptable organic acid***, wherein the second type of particles is coated with a protective coating layer and ***is free from dabigatran etexilate***.

Moreover, US '779 in view of US '891 as evidenced by PubChem do not disclose or suggest a composition consisting of ***a mixture of two distinct types of particles*** and ***at least one pharmaceutically acceptable excipient***. US '779 in view of US '891 as evidenced by PubChem do not disclose or suggest the presently claimed ***first type of particles*** and the presently claimed ***second type of particles***. Furthermore, US '779 in view of US '891 as evidenced by PubChem do not disclose or suggest the presently claimed composition consisting of ***first type of particles comprising dabigatran etexilate*** in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, ***wherein the first type of particles is free from organic and inorganic acids*** and also comprises at least one pharmaceutically acceptable excipient.

For at least these reasons, there is no prima facie case of obviousness. Accordingly, Applicant respectfully requests that the Examiner withdraw the outstanding rejection under 35 U.S.C. §103(a) over US '779 in view of US '891 as evidenced by PubChem.

Conclusion

For the reasons noted above, the art of record does not disclose or suggest the inventive concept of the present invention as defined by the claims.

In view of the foregoing amendments and remarks, reconsideration of the claims and allowance of the subject application are earnestly solicited. If there are any questions relating to this response or the application, Applicant requests that the Examiner telephone the undersigned attorney.

If the foregoing amendments and remarks are not deemed persuasive, Applicant's representative requests an opportunity to discuss the presently claimed invention with the Examiner and the Examiner's supervisor, with whom Applicant's representative has previously discussed the present application. As such, Applicant includes herewith a formal Request for Interview.

The Examiner is authorized to charge any additional fees or refund any overpayments to Deposit Account No. 13-2725 (Docket No. 16326.0018FPWO).

Respectfully submitted,

Date: 16 April 2018

/Melissa M. Hayworth/
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23522
PATENT TRADEMARK OFFICE

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Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14379613
Filing Date	2014-08-19
First Named Inventor	Pilgaonkar
Art Unit	1613
Examiner Name	Lyndsey Marie Beckhardt
Attorney Docket Number	16326.0018FPWO

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14379613
	Filing Date	2014-08-19
	First Named Inventor	Pilgaonkar
	Art Unit	1613
	Examiner Name	Lyndsey Marie Beckhardt
	Attorney Docket Number	16326.0018FPWO

	1	Declaration under 37 C.F.R. 1.132 of Dr. Ulrich Brauns filed in U.S. Application No. 11/381890 dated 11 March 2014.	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14379613
	Filing Date	2014-08-19
	First Named Inventor	Pilgaonkar
	Art Unit	1613
	Examiner Name	Lyndsey Marie Beckhardt
	Attorney Docket Number	16326.0018FPWO

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Melissa M. Hayworth/	Date (YYYY-MM-DD)	2018-04-16
Name/Print	Melissa M. Hayworth	Registration Number	45774

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/379,613	Filing Date 08/19/2014	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 04/16/2018	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $100 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $460 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**0**

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
VICTOR BARLOW

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Merchant & Gould

An Intellectual Property Law Firm

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Suite 600
Alexandria, VA 22314

TEL 703.684.2511
FAX 612.332.9081
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Fax Transmission | March 27, 2018

To:	Examiner Parad	From:	Joe Gess
Company:	USPTO	Our Ref.:	ESTEVE 6 PCT US
Your Ref:	14/379,613	Fax No.:	612.332.9081
Fax No.:	571.270.4817	Phone No.:	703.684.2511
Phone No.:		Total Pages:	2
State/Country:		E-Mail:	
Confirmation Via Mail:	☐ Yes ☒ No	Return Fax To:	

Document Transmitted: Proposed Interview Agenda

Message: Please see attached agenda from Joe Gess.

This transmission contains information that is confidential and/or legally privileged. It is intended for use only by the person to whom it is directed. If you have received this telecopy in error, please notify us by telephone immediately so that we can arrange for the return of the original documents to us.

If you did NOT receive all of the pages, please call us in the U.S.A. at 703.684.2511 or fax us at 612.332.9081.

S/N 14/379,613 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Applicant:	Pratibha S. PHADNKAR	Confirmation No. :	6655
Application No.	14/379,613	Examiner:	Lyndsey BECKHARDT
Filed:	August 19, 2014	Group Art Unit:	1613
Customer No.	23552	Docket No.:	ESTEVE 6 PCT US

Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

PROPOSED INTERVIEW AGENDA

Below is a proposed agenda for the interview scheduled on Thursday, March 29 at 10:30 a.m. with Primary Examiner Dennis Parad. Examiner Parad is thanked for the opportunity to interview the case at this time.

1. The primary reference, Brauns, requires a **single** particle with an organic acid core, an insulating layer, and an active substance layer. The three-layered components on a single particle are considered **necessary** components of the invention of Brauns.

2. The secondary reference, Habid, cannot be combined with Brauns without destroying the invention of Brauns.

3. Thus, there is no *prima facie* case of obviousness established.

4. Amendments will be proposed which more clearly establishes the presently claimed invention as a physical mixture of at least two particles with one being free of an organic acid and the other free of dabigatran etexilate.

5. An appropriate power of attorney has been filed.

Respectfully submitted,

Date: March 27, 2018

/E. Joseph Gess/

E. Joseph Gess
Registration No. 28,510

Merchant & Gould PC
PO Box 2903
Minneapolis, MN 55402-0903
Telephone No.: 703.684.2511
Facsimile No.: 703.684.2501

23552
PATENT TRADEMARK OFFICE

IPR2025-01107
MSN Exhibit 1002
Page 310 of 680

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US	6655

23552 7590 04/03/2018

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MINNESOTA 55402-0903
UNITED STATES OF AMERICA

EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
04/03/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO23552@merchantgould.com

Applicant-Initiated Interview Summary	**Application No.** 14/379,613	**Applicant(s)** Pilgaonkar et al.	
	Examiner DENNIS J PARAD	**Art Unit** 1612	**AIA Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) DENNIS J. PARAD. (3) _____.

(2) E. Joseph Gess. (4) _____.

Date of Interview: 29 March 2018.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 21,23-27,30 and 32.

Identification of prior art discussed: US 2006/0183779 and US 2008/0069891.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant's representative proposed claim amendments by further defining the contents of each of the distinct particles claimed that is further limiting than the limitations recited in claims 24 and 25 (see attached agenda). Applicant's representative also proposed introducing evidence from the prosecution history of the '779 reference that Applicant alleges demonstrates that modifying the invention of '779 with a second distinct particle destroys the invention of '779. Further search and/or consideration would be required to determine if the weight of the evidence submitted is sufficient to overcome the prior art rejection. No agreement was reached..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☑ Attachment

/DENNIS J PARAD/ Primary Examiner, Art Unit 1612	

IPR2025-01107
MSN Exhibit 1002
Page 312 of 680

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US

CONFIRMATION NO. 6655

POA ACCEPTANCE LETTER

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

OC000000098300308

Date Mailed: 03/27/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/21/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/cvorachack/

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US

CONFIRMATION NO. 6655

25666
THE FIRM OF HUESCHEN AND SAGE
SEVENTH FLOOR, KALAMAZOO BUILDING
107 WEST MICHIGAN AVENUE
KALAMAZOO, MI 49007

POWER OF ATTORNEY NOTICE

OC000000098300146

Date Mailed: 03/27/2018

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/21/2018.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/cvorachack/

ESTA. 1307 /wo/US

Doc Code: PA..
Document Description: Power of Attorney

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
14/379,613	August 19, 2014

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☐ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

OR

☒ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☐ The address associated with the above-mentioned Customer Number

OR

☒ The address associated with Customer Number: 23552

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

LABORATORIOS DEL DR. ESTEVE S.A.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	19th March 2018
Name	Nicolas-Vincent, RUIZ		
Title	Legal Representative		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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POWER OF ATTORNEY BY APPLICANT

No more than ten (10) patent practitioners total may be appointed as set forth below by name and registration number. This page need not be submitted if appointing the Patent Practitioner(s) associated with a Customer Number (see form PTO/AIA/82B):

Name	Registration Number
E. Joseph Gess	28510
Melissa M. Hayworth	45774
Daniel R. Evans	55608

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Laboratorios Del Dr. Esteve S.A.

Application No./Patent No.: 14/379613 Filed/Issue Date: August 19, 2014

Titled: Oral Pharmaceutical Compositions of Dabigatran Etexilate

Laboratorios Del Dr. Esteve S.A., a Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 035424, Frame 0104, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Melissa M. Hayworth/	21 March 2018
Signature	Date
Melissa M. Hayworth	45774
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	32117608
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	25666
Filer:	Melissa M. Hayworth/Lisa Kenney
Filer Authorized By:	Melissa M. Hayworth
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	21-MAR-2018
Filing Date:	19-AUG-2014
Time Stamp:	14:47:58
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	16326-0018FPWO_Power_of_Attorney-ESTA-1307-WO-US.PDF	293851 f002e714ad572f8eb2879deb80b40b4c0ea7b842	no	2

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

2	Assignee showing of ownership per 37 CFR 3.73	2018-03-21_373c_16326-0018F PWO.PDF	118198 7ab6a34af2735f3a86a942f102f95a9db65d6684	no	3

Warnings:

Information:

Total Files Size (in bytes):	412049

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08b (07-09)
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Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	1613
Examiner Name	LYNDSEY MARIE BECKHARDT, Esq.
Attorney Docket Number	ESTEVE 6 PCT US

NON PATENT LITERATURE DOCUMENTS

Examiner Initial *	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T [2]
	1	Australian Public Assessment Report for Dabigatran Etexilate Mesylate, May 2011.	

Examiner Signature	/LYNDSEY M BECKHARDT/	Date Considered	01/09/2018

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1. Applicants unique citation designation number. (optional) 2. Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450 Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.
SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LMB/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US	6655

25666 7590 01/16/2018

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EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

MAIL DATE	DELIVERY MODE
01/16/2018	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/379,613	Applicant(s) Pilgaonkar et al.	
	Examiner LYNDSEY M BECKHARDT	Art Unit 1613	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 11/09/2017 .

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

2a)☑ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 21,23-27,30,32-37 and 39 is/are pending in the application.

5a) Of the above claim(s) 33-37 and 39 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 21,23-27,30 and 32 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 11/09/2017.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

IPR2025-01107
MSN Exhibit 1002
Page 325 of 680

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Claims 21, 23-27, 30, 32-37 and 39 are currently pending. Claims 21, 23-27, 30 and 32 are currently under examination.

Information Disclosure Statement

Applicant's Informational Disclosure Statement, filed on 11/09/2017 has been considered. Please refer to Applicant's copy of the 1449 submitted herein.

Examiner's Note

Unless otherwise indicated, previous objection/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the 11/09/2017 response will be addressed to the extent they apply to current rejection(s).

Modified Rejections:

The following rejections will be modified based on Applicant's claim amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21, 23-27, 30 and 32 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US 2006/0183779 (previously applied) in view of US 2008/0069891 (previously applied) as evidenced by PubChem (previously applied).

Regarding claim 21, the limitation of a composition comprising a) particles that comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salts; and b) particles that comprise at least one

pharmaceutically acceptable organic acid is met by active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-mthyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmaceutically acceptable salts thereof (abstract), wherein PubChem evidences the structure of the '779 publication [0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1).

The limitation of wherein at least one type of particles is coated with a protective coating layer is met by the '779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]).

The limitation of the second type of particles is coated with a protective coating layer is met by the '779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]), thus indicating a coating to be applied over the inner particle layer which contains the acid, wherein the second particle contains the acid.

Regarding claim 23, the limitation of further comprising at least one pharmaceutically acceptable excipient is met by the '779 publication teaching polymer selected from gum Arabic included in the particles [0012]. The '779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient.

Regarding claims 24-25, the limitation of wherein the first type of particles is free from acids is met by the '779 publication teaching spatial separation of the organic acid

and the active substance, wherein the organic acid and the active agent are taught to be in a particle ([0010], [0011]).

Regarding claim 26, the limitation of comprising from 0.01 wt% to 90% of dabigatran etexilate (expressed as dabigatran etexilate mesylate) is met by the '779 publication teaching dabigatran etexilate (abstract, [003]) wherein the active agent is taught to be present at 5-60% [0014].

Regarding claims 27 and 30, the limitation of wherein at least 90% by weight of the organic acid present in the composition is contained in the second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients and 2-95% of the at least one pharmaceutically acceptable organic acid is met by the '779 publication teaching 30-100% of the organic acid in the core [0012].

Regarding claim 29, the limitation of wherein the first type of particles is coated with a protective coating layer and the second type of particle is coated with a protective coating layer is met by the '779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]).

Regarding claim 32, the limitation of wherein the composition comprises from 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

The '779 publication does not specifically teach components a) and b) in two distinct types of particles (claim 21).

The ‘891 publication teaches a pharmaceutical composition may include granulate including at least one active pharmaceutical ingredient. The composition may include a coating on the granulate. The composition further comprises a second particle comprising a fat/wax. The granulate are formed into various dosage forms (abstract, [0018]). The invention comprises two particles, the first type containing the pharmaceutical agent and the second comprising fat/wax material [0020].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the ‘779 publication as two distinct particles as the ‘891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the ‘779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the ‘779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the ‘891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the ‘779 publication could be via the layers taught by the ‘779 publication or through the use of separate particles as taught by the ‘891 publication.

Response to Arguments:

Applicant's arguments have been fully considered and are not deemed to be persuasive.

Applicant argues that one skilled in the art would not have been motivated to modify the single pellet compositions disclosed in the '779 publication which compositions are designed to provide improved dissolution and absorption based on the generic disclosure in the '891 publication that a composition may comprise an API in the first particle and a fat/wax in the second particle with a reasonable expectation of success.

In response, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779 publication as two distinct particles as the '891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010].

Applicant argues they provided a declaration by Ziauddin TYEBJI demonstrating that superior dissolution characteristics associated with the instant claimed composition would not have been expected based on the references of record in the instant application.

In response, Applicant's arguments are addressed below regarding the declaration.

Applicant argues the '779 publication provides characteristics/dissolution mechanism provided by this structure as well as detailed analysis of the structure and dissolution mechanism of the formulation of the present invention. The Australian Public Assessment Report for Dabigatran Etexilate Mesylate demonstrates the dissolution. The Declaration demonstrates that the formulation in the '779 publication require an acidic microclimate to achieve the disclosed dissolution characteristics not achievable with the instantly claimed compositions. The '891 publication discloses formulations designed to inhibit administration of abuse of an API wherein the formulations comprise a fat/wax and that it was known in the art at the time the present application as filed that bioavailable of one formulation of dabigatran etexilate was not predictive of the bioavailability of alternative formulations of dabigatran etexilate.

In response, the instant claims do not contain limitations directed to the release rate of the drug particles. Additionally Applicant has demonstrated that release is different between different particle formulations, however this is not considered an unexpected or superior results, as some differences are expected between different formulations.

Applicant askes the Declaration of TYEBJI of record be reconsidered based on the claim amendments.

In response, the declaration states that Formulation A has two types of particles/pellets (one comprising dabigatran etexilate mesylate and the other comprising a coated organic acid) and Formulation B is described in Example 1 of the '779 publication, which is the same as that disclosed in WO 2003/074056. Formulation B has only one type of particles/pellets having both dabigatran etexilate mesylate and organic

acid. Formulation A is taught to have dabigatran etexilate mesylate particles and tartaric acid pellets which are seal coated with a lubricated seal coat. The formulation of the present invention having two types of particles/pellets can provide faster dissolution particularly at earlier time points as compared to formulation having one type of particle/pellets.

In response, the Formulation A and B cannot be properly compared to each other, as the ratio and amount of tartaric acid and active substance are not the same in the formulation A and B. Thus the comparison is not strictly between the use of two separate particles or a layered particle, but rather have additional factors differentiating the two formulations. As the formulations can be directly compared, a proper assessment cannot take place regarding the dissolution time of the active ingredient.

The Zhenggue Xu declaration demonstrates a bioequivalence study that was carried out using formulations A and B were administered in two different studies fed and fasting. The data shown above clearly demonstrate that in addition to exhibiting a faster dissolution profile than the composition disclosed in the '056 publication, the compositions of the present invention also exhibit the same bioavailability as the compositions disclosed in the '056 publication.

In response, the Formulation A and B cannot be properly compared to each other, as the ratio and amount of tartaric acid and active substance are not the same in the formulation A and B. Thus the comparison is not strictly between the use of two separate particles or a layered particle, but rather have additional factors differentiating the two formulations. As the formulations can be directly compared, a proper assessment cannot take place regarding the dissolution time of the active ingredient.

37 CFR 1.132 Declaration

The examiner acknowledges receipt of the Declaration under 37 CFR 1.132 by Ziauddin TYEBJI, filed 11/09/2017.

The Declarations under 37 CFR 1.132 filed 11/09/2017 are insufficient to overcome the rejection of claims 21, 23-30 and 32 based upon *obviousness* by the '779 publication and the '891 publication as evidenced by PubChem as set forth in the last Office action because:

The declaration states Australian Public Assessment Report for Dabigatran Etexilate Mesylate demonstrates the oral bioavailability of pellets, powder and capsules comprising dabigatran was analyzed. The results demonstrate that alternative formulation to the prior art capsules, like pellets or powder have different bioavailability. The bioavailability results obtained with one specific formulation cannot be expected to be maintained when a different formulation is used.

In response, as noted above the instant claims are not directed to a drug release rate. Further different forms of formulation are expected to have different release rates and therefore it is not unexpected. Applicant has not presented superior results.

Applicant argues the '779 publication teaches that the specific structure of the dabigatran formulation creates an acidic microclimate. This microclimate is responsible for the dissolution of the drug. The water enters the tartaric acid nucleus and dissolves it. Then the dissolved tartaric acid goes out of the core entering into the dabigatran layer creating an acid microclimate needed for the transportation of dabigatran trough the gastric mucosa. The acid microenvironment increases the drug dissolution and absorption and renders the extent of absorption independent variations in the gastric

pH. The close contact between the acid and the dabigatran which makes the microclimate possible.

In response, the use of acid in a distinct particle mixed with particles which contain the drug would still result in close contact of the drug and acid to create the acid microenvironment after administration.

Applicant argues the '779 publication shows in figure 2 that a conventional tablet formulation herein all the components are blended and tableted by compressions shows a very low bioavailability when administered together with pantoprazole. Dabigatran etexilate is known to dissolve relatively well in water at low pH levels whereas at pH levels above 5 is it virtually insoluble.

In response, the tablet to which the capsules were compared contained the active substance but no water soluble acid [0033], wherein the capsules to which they are compared contain the tartaric acid. Thus the figure demonstrates that need for an acid for release of Dabigatran, this however is not unexpected. Further the layered capsules and that of two separate microparticles one containing drug, one containing the acid both still have the acid present for the release of the active agent.

Applicant argues the present application would not have been expected to result in a good bioavailability because the acidic microclimate needed for the transportation of dabigatran and absorption through the gastric mucosa cannot be formed at all, as evidenced by the picture shown below.

In response, the acid in the microparticles and the drug in the microparticles would be in close contact, thus would result in the same acidic microclimate by the

layered microparticles, absent factual evidence to the contrary. Applicant has not presented evidence to the contrary.

Applicant argues it would not have been expected that the bioavailability and dissolution rate obtained with the particles of the invention could be achieved using a formulation comprising two distinct types of pellets as in the present invention rather than a layered pellet structure as taught by the prior art the '779 publication.

In response, Applicant's arguments cannot take the place of factual evidence to the contrary. Applicant has not presented comparison date between the layered structure and that of the two separate microparticles.

Applicant argues the '891 publication teaches two distinct types of particles has the function of limiting the extent of solvent access to the active particles and thus it may not help to retain the release rate consistent with the initial desired rate of the active ingredient, thereby frustrating does dumping attempts associated with abuse. The aim of using two distinct types of particles in the '891 publication is to inhibit abuse of the API, whereas in the present invention the division of the particles of the '779 publication into two types of particles achieves earlier dissolution of the active substance which would be totally unexpected in view of the '891 publication.

In response, as noted above the instant claims are not directed to a release rate. Further the sustained release of the active agent by the '891 publication is a result of the selected excipient material and coating ingredients ([0013], [0014]) and is not taught as being a result of the use of the separate particles. Thus using the ingredients taught by the '779 publication in two separate granules taught by the '891 publication has not been shown to result in a sustained release.

Applicant argues one skilled in the art would not apply the teachings of the '891 publication, which is directed to formulations of opioids which are aimed to avoid abuse from the patient to the formulations of the '779 publication since dabigatran etexilate is not an active ingredient susceptible to abuse.

In response, the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication.

Applicant argues the '891 publication discloses that the wax and fat material should be included in an amount sufficient to inhibit abuse of the API. No hint on the use of a two particulate formulation proving a desired bioavailability of the drug described in the '891 publication.

In response, as noted above the instant claims are not directed to a release rate. Further the sustained release of the active agent by the '891 publication is a result of the selected excipient material and coating ingredients ([0013], [0014]) and is not taught as being a result of the use of the separate particles. Thus using the ingredients taught

by the '779 publication in two separate granules taught by the '891 publication has not been shown to result in a sustained release.

Applicant argues the '891 publication does not provide suggestion to specifically separate the active substance from the organic acid.

In response, the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010].

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949).

Upon consideration of the facts taught by the prior art and the information submitted by the Affiant, the balance of evidence indicates that the prior art teaches the instantly claimed inventions.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY MARIE BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached on Monday, Tuesday and Thursday 7:30 to 3pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LYNDSEY M BECKHARDT/
Examiner, Art Unit 1613

/DENNIS J PARAD/
Primary Examiner, Art Unit 1612

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/379,613	Pilgaonkar et al.
	Examiner	Art Unit
	LYNDSEY M BECKHARDT	1613

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
	No Classified Search		

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
East (keyword and Inventor) see attached	9/24/2015	LMB
Google (keyword) see attached East search terms	9/24/2015	LMB
East (keyword and Inventor) see attached	3/7/2016	LMB
Google (keyword) see attached East search terms	3/7/2016	LMB
East (keyword and Inventor) see attached	7/25/2017	LMB
East (keyword and Inventor) see attached	01/08/2018	LMB

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

IPR2025-01107
MSN Exhibit 1002
Page 341 of 680

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S86	1	("20060074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/05 07:35
S85	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/05 07:35
S171	1	("20060074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04
S170	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04
S169	1	("20060074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04
S168	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04
S167	1	("20060183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04
S166	0	("200600183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04
S165	0	("200600183779").PN.	USPAT; USOCR	OR	OFF	2018/01/08 14:04
S164	0	("20060183779").PN.	USPAT; USOCR	OR	OFF	2018/01/08 14:04
S163	1	"14379613"	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04
S162	2	S161 and dabigatran	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04
S161	47	S158 or S159 or S160	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04

S160	41	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S159	37	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S158	45	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S157	1	"14379613"	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
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S150	2041	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S149	91	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle) and multiparticulate	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
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S147	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
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S144	2014093	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
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S142	10	((brauns) near2 (ulrich)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
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S131	41	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S130	37	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S129	45	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S128	1	("20060074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04

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MSN Exhibit 1002
Page 344 of 680

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S118	37	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
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S114	10	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend) same organic acid	US-PGPUB; USPAT	ADJ	OFF	2018/01/08 14:04
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S112	6172	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S111	41062	(drug or active or pharmaceutical) same (particle or microsphere) same (mixture	US-PGPUB;	OR	OFF	2018/01/08 14:04

		or combination or dual or types or blend)	USPAT			
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S108	2041	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S107	91	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle) and multiparticulate	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S106	8451	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S105	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S104	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S103	44871	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S102	2014093	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S101	7	((landerer) near2 (sabine)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
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			USOCR			14:04
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S93	26	S91 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2018/01/08 14:04
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S88	37	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04
S87	45	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2018/01/08 14:04

1/9/2018 9:35:55 AM
C:\Users\lshaak\Documents\EAST\Workspaces\14379613.wsp

* * * * *

Applicants : Pratibha S. PILGAONKAR, Maharukh T. RUSTOMJEE, and Anilkumar S. GANDHI

Serial No. : 14/379,613

Filed : 19 August 2014

Title : ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Art Unit : 1613

Examiner : LYNDSEY MARIE BECKHARDT, Esq.

* * * * *

Honorable Commissioner for Patents

PO Box 1450

Alexandria, VA 22313

RESPONSE AND AMENDMENT UNDER 37 CFR §§ 1.111 AND 1.115

PRESENTATION OF A DECLARATION UNDER 37 CFR § 1.132

Sir:

Responsive to the Office Action, dated 11 August 2017, kindly amend as follows.

IN THE CLAIMS: See Listing of Claims. This listing will replace all prior versions of claims in the application.

REMARKS

The Applicants acknowledge the Examiner's comprehensive Office Action with appreciation. Claims 21, 23-30, and 32-39 are pending in the application; however, Claims 33-39 remain withdrawn from consideration as a result of the previously issued Restriction Requirement. The Office acknowledges the Request for Continued Examination (RCE) filed on 1 June 2017. The Office maintains the prior art rejection under 35 USC § 103.

To begin, with the instant Amendment, base Claim 21 has been amended to recite the limitation "wherein the second type of particles is coated with a protective coating layer."

Claims 21, 23-30, and 32 remain rejected for obviousness under 35 USC § 103(a) based on the disclosure of US 2006/0183779 in view of US 2008/0069891, as evidenced by PubChem (PubChem, Dabigatran Etexilate). The PubChem entry is cited to demonstrate that the compound/chemical structure disclosed in the '779 publication is dabigatran etexilate.

The Office reiterates its position that the '779 publication discloses that dabigatran etexilate combined with organic acids provides improved formulation. The Office further reiterates that the '779 publication discloses pellets comprising a core containing an organic acid, a separating layer, and a layer containing the active substance (specifically citing paragraph [0010] and Figure 1 of the '779 publication). The Office goes on to reiterate that the disclosure in the '779 publication related to an optional outermost layer meets the limitation of a "protective coating layer."

The Office goes on to reiterate that the '779 publication meets (or renders obvious) the limitations of the dependent claims as discussed at pages 5-6 of the instant Office Action.

The Office again acknowledges that the '779 publication does not specifically disclose instant components a) and b) in two distinct types of particles; however, it remains the position of the Office that this deficiency is cured by the '891 publication.

The Office reiterates its position that the '891 publication discloses a pharmaceutical composition which may include a granulate comprising at least one pharmaceutical ingredient, which composition may include a coating on the granulate. The Office goes on to reiterate that the disclosed composition may further comprise a second particle comprising a fat/wax and that the composition may be formed into various dosage forms. The Office further reiterates that the invention disclosed in the '891 publication comprises two particles, the first type containing the pharmaceutical agent and the second comprising a fat/wax material.

It remains the position of the Office that it would have been obvious to formulate the oral composition disclosed in the '779 publication as two distinct particles since the '891 publication discloses pharmaceutical compositions comprising two distinct particles, one of which includes a pharmaceutical agent. The Office states that one skilled in the art would have been motivated to do so since the '779 publication discloses the need for spatial separation of the organic acid and the active substance and that there would have been a reasonable expectation of success since the '779 publication discloses an oral pharmaceutical formulation in the form of particles and since the '891 publication discloses that it was known to formulate active agents and excipients for oral dosage forms in separate particles.

With respect to the previously submitted arguments based on the comparative data provided in the instant specification and the previously submitted Declarations, the Office states that the arguments/data are insufficient to overcome the obviousness rejection.

Specifically, the Office states that the comparative data are not truly comparative because there are several differences between the compared formulations (such as the ratio of tartaric acid/active substance and the nature of the excipients).

It is the further position of the Office that the instant claims are not commensurate in scope with the demonstrated results since, in the Examples presented, the acid containing particles are coated but the active agent containing particles are not

coated, whereas the instant claims recite wherein at least one type of particle is coated with a protective coating layer.

As noted above, with the instant Amendment, base Claim 21 has been amended to recite the limitation "wherein the second type of particles is coated with a protective coating layer."

The Applicants respectfully submit that one skilled in the art would not have been motivated to modify the single pellet compositions disclosed in the '779 publication, which compositions are designed to provide improved dissolution and absorption, based on the generic disclosure in the '891 publication that a composition may comprise an API in a first particle (which particle may be coated) and a fat/wax material (to inhibit administration of abuse of the API) in a second particle, to arrive at the instantly claimed compositions, which comprise a particle comprising dabigatran etexilate and a second particle comprising an organic acid wherein the organic acid containing particle is coated, with any reasonable expectation of success.

Moreover, with the instant Response, the Applicants provide a Declaration by Ziauddin TYEBJI, a scientist skilled in this particular art which demonstrates that the superior dissolution characteristics associated with the instantly claimed compositions would not have been expected based on the references of record in the instant application.

Specifically, the Declarant provides a detailed analysis of the structure of the formulations disclosed in the '779 publication (and the characteristics/dissolution mechanism provided by this structure), as well as a detailed analysis of the structure and dissolution mechanism of the formulations of the present invention, in conjunction with an explanation of what was known in the art concerning dabigatran etexilate formulations at the time the instant application was filed, as evidenced by the Australian Public Assessment Report for Dabigatran Etexilate Mesylate (published May 2011, and included on the enclosed Form PTO-SB08).

To summarize, the TYEBJI Declaration demonstrates that the formulations disclosed in the '779 publication require an acidic microclimate to achieve the disclosed dissolution characteristics, which acidic microclimate is not achievable with the instantly claimed compositions; that the '891 publication discloses formulations designed to inhibit administration of abuse of an API, wherein the API is comprised in a particle which may be coated, and wherein the formulations comprise a fat/wax material (to inhibit administration of abuse of the API) in a second particle; and that it was known in the art at the time the present application was filed that the bioavailability of one formulation of dabigatran etexilate was not predictive of the bioavailability of alternative formulations of dabigatran etexilate.

Therefore, in view of what was known in the art at the time of the filing of the present application, the improved dissolution characteristics of the instantly claimed compositions would not have been predicted based on the references of record in the instant application, alone or in combination.

In view of the foregoing, the Applicants respectfully submit that the instant claims, as presently amended, are not rendered obvious by the disclosure of the references of record in the instant application, alone or in combination. Reconsideration and withdrawal of the obviousness rejection under 35 USC § 103(a) is respectfully requested.

Finally, in accordance with MPEP § 821.04, the Applicants request rejoinder of withdrawn Claims 33-39 upon the identification of allowable subject matter.

* * * * *

Accordingly, entry of the present amendment, entry of the present TYEBJI Declaration into the record of the application, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned agent has made an earnest effort to place this application into condition for immediate allowance. If she can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call her at her below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: _____

MICHELE M. CUDAHY, Reg. No. 55,093

Dated: 9 November 2017
Customer No.: 25,666
Seventh Floor, Kalamazoo Building
107 West Michigan Avenue
Kalamazoo, MI 49007
(269) 382-0030

Enclosure(s) : Listing of Claims
TYEBJI Declaration
Form PTO-SB08 and Accompanying Reference

* * * * *

THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.

LISTING OF CLAIMS

1-20 (canceled)

21. (currently amended) A composition comprising a mixture of at least two distinct types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein ~~at least one~~ the second type of particles is coated with a protective coating layer.

22. (canceled)

23. (previously presented) The composition according to claim 21, further comprising at least one pharmaceutically acceptable excipient.

24. (previously presented) The composition according to claim 21, wherein the first type of particles is free from acids.

25. (previously presented) The composition according to claim 21, wherein the second type of particles is free from dabigatran etexilate.

26. (previously presented) The composition according to claim 21, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, expressed as dabigatran etexilate mesylate.

27. (previously presented) The composition according to claim 21, wherein at least 90% by weight of the organic acid present in the composition is contained in the second type of particles and the rest, if any, of the organic acid forms part of the pharmaceutically acceptable excipients.

28. (canceled)

29. (canceled)

30. (previously presented) The composition according to claim 21, comprising from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

31. (canceled)

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32. (previously presented) A unit dosage form prepared from the composition according to claim 21, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

33. (withdrawn) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a composition according to claim 21.

34. (withdrawn) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a unit dose according to claim 32.

35. (withdrawn) A process for the preparation of the composition according to claim 23, comprising the step of mixing the first type of particles and the second type of particles with the at least one at least one pharmaceutically acceptable excipient.

36. (withdrawn) The process of claim 35, wherein the first type of particles are prepared by granulation.

37. (withdrawn) The process according to claim 36, comprising the steps of:
    i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient;
    ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;
    iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;
    iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;
    v) coating the organic acid granules with a protective coating layer;
    vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;
    vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

38. (canceled)

39. (withdrawn) The process according to claim 36, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

v) coating the organic acid pellets of step (iv) with a protective coating layer;

vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

PTO/SB/08b (07-09)
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Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	1613
Examiner Name	LYNDSEY MARIE BECKHARDT, Esq.
Attorney Docket Number	ESTEVE 6 PCT US

NON PATENT LITERATURE DOCUMENTS

Examiner initial *	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T [2]
	1	Australian Public Assessment Report for Dabigatran Etexilate Mesylate, May 2011.	☐
			☐
			☐
			☐
			☐
			☐
			☐
			☐
			☐
			☐

Examiner Signature		Date Considered	

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1. Applicants unique citation designation number (optional) 2. Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450 Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assisstance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT OFFICE

Applicants	: Pratibha S. PILGAONKAR, Maharukh T. RUSTOMJEE, and Anilkumar S. GANDHI
Serial No.	: 14/379,613
Filed	: 19 August 2014
Title	: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
Art Unit	: 1613
Examiner	: LYNDSEY MARIE BECKHARDT, Esq.

HONORABLE COMMISSIONER FOR PATENTS
PO BOX 1450
ALEXANDRIA, VA 22313

DECLARATION UNDER 37 CFR § 1.132

I, Ziauddin TYEBJI, a citizen of India and residing in Spain, declare and say that:

I hold the degree of M. Pharm. (Pharmaceutical Technology).

Since 2009 I have been working as Global Director of Product Development at Laboratorios del Dr. Esteve.

I am familiar with the invention described and claimed in US Application Serial No. 14/379,613 filed 19 August 2014 for "ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE".

I am thoroughly familiar with the above-mentioned patent application and fully support the arguments presented with respect to the unexpected effects of the claimed invention.

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The analysis presented herein demonstrates that the dissolution characteristics provided by the compositions of the present invention would not have been expected based on the known characteristics of dabigatran etexilate.

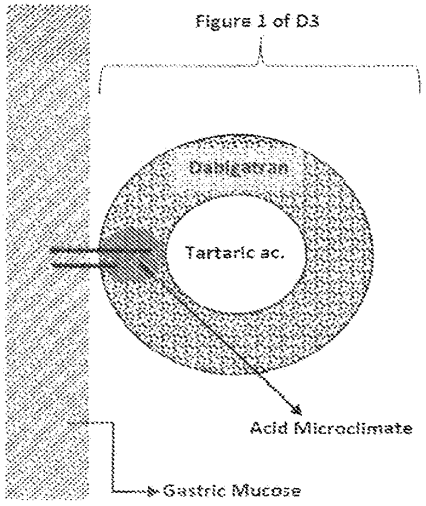
* * * * *

At the time of the filing of the present application, a bioequivalence study in healthy patients was already available, (**Australian Public Assessment Report for Dabigatran Etexilate Mesylate, published in May 2011**). In this study, the oral bioavailability of pellets, powder and capsules comprising dabigatran was analyzed. The results demonstrate that alternative formulations to the prior art capsules, like pellets or powder, have different bioavailability (see pages 21 and 22 and Table 5).

Thus, it was known that the bioavailability results obtained with one specific formulation cannot be expected to be maintained when a different formulation is used.

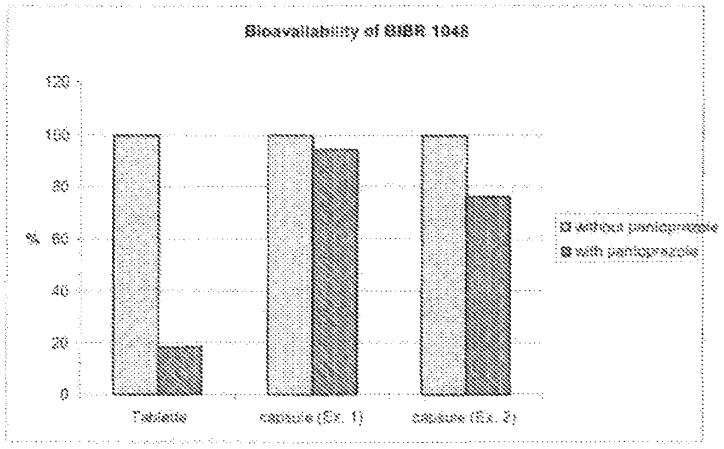
* * * * *

Paragraph [0011] of US 2006/0183779 (US'779) teaches that the specific structure of the dabigatran formulation (like the layers of an onion) creates an acidic microclimate. This microclimate is responsible for the dissolution of the drug (and thus, its absorption in the blood). This mechanism may be depicted as follows:



When water comes into the pellet structure, it enters the tartaric acid nucleus (core material) and dissolves it. Then, the dissolved tartaric acid goes out of the core entering into the dabigatran layer (active substance layer) creating the acid microclimate needed for the transportation of dabigatran trough the gastric mucosa. According to Clin. Pharmacokinet 2008; 47(5):285-295 (which reference is already of record in the present application), this acidic microenvironment increases drug dissolution and absorption and renders the extent of absorption independent of variations in the gastric pH. (see page 288, first paragraph, of Clin. Pharmacokinet 2008). Thus, it is the physical close contact between the acid and the dabigatran which makes this microclimate possible. This physical close contact is achieved with the specific layered-configuration of the particle disclosed in US'779.

The relevance of the layered-pellet structure (as used in US'779) and the relevance of the acidic microclimate for the bioavailability of dabigatran is shown in figure 2 of US'779, which is reproduced below:

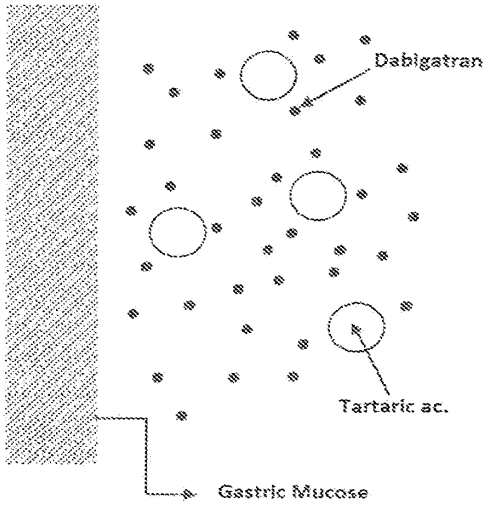


As it is clearly shown in said figure, a conventional tablet formulation wherein all the components are blended and tabletted by compression shows a very low bioavailability when administered together with pantoprazole (*Tablette* in the Figure). Dabigatran etexilate is known to dissolve relatively well in water at low pH levels, whereas at pH levels above 5 it is virtually insoluble in accordance with the definition of the European Pharmacopoeia (as disclosed at paragraph [0024] of US'779).

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Pantoprazole serves to produce an elevated gastric pH (see paragraph [0024] of US'779).

The formulation of the present application would not have been expected to result in a good bioavailability because the acidic microclimate needed for the transportation of dabigatran and absorption through the gastric mucosa cannot be formed at all, as evidenced by the picture shown below representing the formulation of the present invention at the absorption site:



In spite of that, the formulation of the present invention ***unexpectedly shows the desired bioavailability***.

Further, at the time of filing the present application, one skilled in the art would have recognized that the prior art as a whole taught that dabigatran absorption was possible by employing a specific layered-pellet structure composition (US'779) and that other types of formulations were demonstrated to have a different bioavailability (Australian Public Assessment Report for Dabigatran Etexilate Mesylate).

Thus, one skilled in the art would not have expected that the bioavailability and dissolution rate obtained with the particles of the invention could be achieved using a

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formulation comprising two distinct types of pellets as in the present invention rather than a layered-pellet structure as taught in the prior art US'779.

With respect to the combination of US'779 with the teaching of US'891 since the latter teaches a formulation having two types of particles, US'891 relates to a very specific type of formulations comprising a very specific group of drugs, opioids (used to alleviate pain) that have the potential for abuse.

US'891 teaches that a pharmaceutical composition may include granulate including at least one active pharmaceutical ingredient. The composition may include a coating on the granulate comprising the active ingredient. The composition further comprises particles comprising a fat/wax. US'891 discloses two particles, the first type containing the pharmaceutical agent and the second comprising fat/wax material.

The provision of two distinct types of particles in the formulations of US'891 has the function of limiting the extent of solvent access to the active particles and, thus, it may help to retain the release rate consistent with the initial desired rate of active ingredient release, thereby frustrating dose dumping attempts associated with abuse (paragraphs [0110], [0111] and [0117]). Thus, the aim of using of two types of particles in US'891 is to ***inhibit abuse*** of the API, whereas in the present invention the division of the particles of US'779 into two types of particles achieves earlier dissolution of the active substance, which would be totally unexpected in view of US'891.

Dabigatran is not an opioid drug and it is used for the prophylaxis and treatment of thromboembolic disorders. In fact, it is mainly used for the prevention of venous thromboembolism in patients that have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement). Dabigatran has no effect in the central or peripheral nervous system and thus, no use as a recreational drug is possible.

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One skilled in the art would not apply the teachings of US'891, which is directed to formulations of opioids which are aimed to avoid the abuse from the patient, to the formulations of US'779 since dabigatran etexilate is not an active ingredient susceptible to abuse.

Moreover, US'891 discloses (at paragraph [0020]) that the wax and fat material should be included in an amount sufficient to inhibit abuse of the API. No hint on the use of a two-particulate formulation providing a desired bioavailability of the drug is described in US'891.

Also, even if US'891 teaches the separation of an active substance from another component of the formulation, said second component is a fat/wax in US'891, totally unrelated to the organic acid of the particles of US'779 and of the presently claimed formulations. In fact, US'891 mentions tartaric acid (see paragraph [0163]) as a member of an effervescent couple, which would be one additional ingredient or excipient in the formulations of US'891 (paragraph [0146]). Thus, even if one skilled in the art could have considered dividing the particles of US'779 into two types of particles, he would not have found any teaching or suggestion in US'891 to specifically separate the active substance from the organic acid since in US'891 the organic acid is an additional excipient which may be present in the formulations but which is not disclosed in any case as forming part of a differentiated particle, said differentiated particle being fat/wax in US'891.

* * * * *

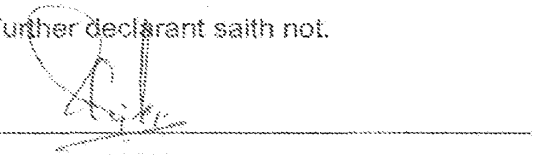
In conclusion, in view of what was known in the art at the time of the filing of the present invention, the improved dissolution characteristics of the instantly claimed compositions would not have been predicted based on the references of record in the instant application, alone or in combination.

* * * * *

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 or the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant saith not.



Ziauddin TYEBJI

Signed at Barcelona on

Date: 04 Nov 2017

Electronic Acknowledgement Receipt

EFS ID:	30898568
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	25666
Filer:	George Patrick Sage/Michele Cudahy
Filer Authorized By:	George Patrick Sage
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	09-NOV-2017
Filing Date:	19-AUG-2014
Time Stamp:	09:37:27
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	RESPONSE_AMENDMENT_9NOV17.pdf	5859139 588224061ba3bf972e5d805ca7f67f79237f1d28	no	6

Warnings:

Information:					
2	Claims	CLAIMS_9NOV17.pdf	2686640 91b7f0becbcb4bd30d9703a68343c91f51516d52	no	3
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	PTO_SB08_9NOV17.pdf	1022258 983d1dd05788145167d393e46168e4357fedff22	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Affidavit-traversing rejectns or objectns rule 132	132_DECLARATION_SCANNED.pdf	6016097 61d0e2a3340518fe49494962814b1654f34c2eb2	no	7
Warnings:					
Information:					
5	Non Patent Literature	REF1_SCANNED.pdf	11706510 697d0b6fcf5866ba45676fdeb08e072a7876fa47	no	136
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		Total Files Size (in bytes):	27290644		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/379,613	Filing Date 08/19/2014	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	11/09/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
SHEILA D. CHAPMAN

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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07/25/2017

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		**Docket No.:**	**ESTEVE 6 PCT US**
Applicant(s):	**LABORATORIOS DEL DR. ESTEVE S.A.**	**Examiner:**	**Beckhardt, Lyndsey Marie**
Application No.:	**14/379,613**	**Art Unit:**	**1613**
U.S. Filing Date:	**August 19, 2014**	**Conf. No.:**	**6655**
Title:	**ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE**	**Customer No.:**	**25,666**

DECLARATION UNDER 37 CFR 1.132 IN U.S. PATENT APPLICATION NO. 14/379,613

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Zhengguo XU, a citizen of China and residing at Spain, do hereby declare

1. THAT I am familiar with the invention described and claimed in the patent application 14/379,613. I am submitting this declaration in support of the patentability of the claims of the application.

2. THAT I received the degree of MSc. of Biopharmacy.

3. THAT I have worked from 2004 in Laboratorios del Dr. Esteve as a pharmacokineticist.

4. THAT under my supervision and/or with my participation, the experiments described below were carried out which illustrate the advantages of the presently claimed compositions.

In-vivo bioequivalence study of formulation of the present invention having two types of particles/pellets (Formulation A) and formulation having one type of particles/pellets (Formulation B)

An in-vivo bioequivalence study (relative bioavailability study) was carried out wherein the two different formulations (Formulations A and B described in paragraph [0119] o the patent application) were administered in two different studies (fed and fasting). The study consists of a randomized, balanced, open label, two treatment, four period, two sequence, single dose, crossover, fully replicate, bioequivalence study of two different formulations of Dabigatran Etexilate Mesylate capsules (Formulation A and B as per the present application) in healthy adult human subjects under fed and fasting conditions.

The geometric least squares mean, ratio of formulation A (A) and formulation B (B) i.e. (A/B) %, Intra Subject CV(%) and 90% confidence intervals for the ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-inf of Free Dabigatran are summarized in the following tables.

Results in fasting study:

Pharmacokinetic parameter	Geometric Least Squares Means (Formulation A)	Geometric Least Squares Means (Formulation B)	Ratio (A/B) (%)	90% Confidence Limits (A vs. B)	Intra Subject CV %
Ln(Cmax)(ng/mL)	192.8271	191.5396	100.45	(87.13 , 115.84)	14.41
Ln(AUC0-t)(ng hr/mL)	1636.1942	1602.5370	102.09	(89.80 , 117.07)	16.07
Ln(AUC0-inf)(ng hr/mL)	1680.8333	1640.7486	102.44	(89.84 , 117.20)	16.48

Results in fed study:

Pharmacokinetic parameter	Geometric Least Squares Means (Formulation A)	Geometric Least Squares Means (Formulation B)	Ratio (A/B) (%)	90% Confidence Limits (A vs. B)	Intra Subject CV %
Ln(Cmax)(ng/mL)	144.7350	139.8758	103.22	(93.53 , 112.04)	22.86
Ln(AUC0-t)(ng hr/mL)	1480.9219	1442.3907	102.47	(93.42 , 109.53)	14.27
Ln(AUC0-inf)(ng hr/mL)	1521.5415	1476.3162	102.92	(93.06 , 109.94)	13.51

The data shown above clearly demonstrate that, in addition to exhibiting a faster dissolution profile than the compositions disclosed in WO 03/074056 (see comparative data in the present application at pages 21-23), the compositions of the present invention also exhibit the same bioavailability as the compositions disclosed in WO 03/074056.

The superior properties associated with the compositions of the present invention would not have been predicted based on the teachings of WO 03/074056 (or its US equivalent, US 2006/0183779).

The undersigned declarant declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this May 5th, 2016



Zhengguo XU

CONSIDERED: /LMB/

07/25/2017

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		**Docket No.:**	**ESTEVE 6 PCT US**
Applicant(s):	**LABORATORIOS DEL DR. ESTEVE S.A.**	**Examiner:**	**Beckhardt, Lyndsey Marie**
Application No.:	**14/379,613**	**Art Unit:**	**1613**
U.S. Filing Date:	**August 19, 2014**	**Conf. No.:**	**6655**
Title:	**ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE**	**Customer No.:**	**25,666**

DECLARATION UNDER 37 CFR 1.132 IN U.S. PATENT APPLICATION NO. 14/379,613

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ziauddin TYEBJI, a citizen of India and residing at Spain, do hereby declare

1. THAT I am familiar with the invention described and claimed in the patent application 14/379,613. I am submitting this declaration in support of the patentability of the claims of the application.

2. THAT I received the degree of M. Pharm. (Pharmaceutical Technology).

3. THAT I have worked from 2009 at Laboratorios del Dr. Esteve as Global Director of Product Development.

4. THAT under my supervision and/or with my participation, the experiments described below were carried out which illustrate the advantages of the presently claimed compositions.

Comparative Evaluation of Two Formulation Approaches for Dabigatran Etexilate Mesylate

The dissolution profiles of two formulations comprising dabigatran etexilate mesylate were evaluated.

Formulation A is a according to the present invention and has two types of particles/pellets (one of them comprising dabigatran etexilate mesylate and the other one comprising a coated organic acid)

Formulation B is the formulation described in example 1 of US 2006/0183779 A1. This formulation is exactly the same one disclosed in example 1 of PCT application WO 2003/074056 which is and equivalent of US'779. This formulation is also the one which has been tested in example 3 of the present invention. In said example it is stated that "*the formulation was prepared according to the teachings of US 2006/074056*". This quote is erroneous and it was meant to say "*the formulation was prepared according to the teachings of WO 2003/074056*". Formulation B has only one type of particles/pellets having both dabigatran etexilate mesylate and organic acid.

Formulation A

Dabigatran etexilate granules	
Ingredient	mg/capsule
Intragranular	
Dabigatran etexilate mesylate equivalent to 150 mg dabigatran etexilate	172.95
Isopropyl alcohol (IPA)	q.s.
Extragranular	
Microcrystalline cellulose	67.05
Croscarmellose sodium	50
Total weight	290
Sodium tartaric acid granules	
Ingredient	mg/capsule
Core	
Tartaric acid (TAP® 600)	196.34
Coating	

Hydroxypropylmethyl cellulose	5.62
Lactose	5.62
Talc	8.42
Isopropyl alcohol/water	q.s.
Total weight	216

Procedure:

(i) Preparation of Dabigatran Etexilate Mesylate Granules Portion

The weighed quantity of dabigatran etexilate mesylate was loaded in the granulator and granulated using isopropyl alcohol. The granules were further dried in a fluidized bed drier. The granules were then sized, sifted and blended with microcrystalline cellulose, croscarmellose sodium in a suitable blender to give dabigatran etexilate mesylate granules portion.

(ii) Preparation of Seal Coated Tartaric Acid Pellets

Hydroxypropyl cellulose was added to the isopropyl alcohol/water mixture under continuous stirring to obtain a clear solution. Lactose was added to this solution and mixed, followed by addition of talc and stirring. The suspension thus formed was filtered through a suitable sieve and sprayed under continuous stirring on tartaric acid pellets using a fluidized bed coater with Wurster column to achieve desired weight gain. The coated tartaric acid pellets were then dried.

The lubricated seal coated tartaric acid pellets and dabigatran etexilate mesylate granules were filled in capsules using the automatic capsule filling machine in HPMC size 0 capsules.

Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A) and formulation having one type of particles/pellets (Formulation B)

Dissolution profiles of the two formulations were determined in 0.01N HCl pH 2 media at 100 rpm USP type I (basket). The results are shown in the table below:

	% Release	
Time (minutes)	Formulation A (two types of pellets)	Formulation B (one type of pellets)
10	65.1	19.2

15	79.2	57
20	86.7	86.1
30	92	97
45	95.5	97.6
60	96.8	98.5

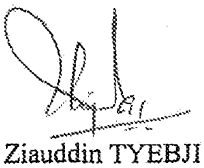
Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A above) and formulation having one type of particles/pellets (Formulation B above) indicates that formulations of the present invention having two types of particles/pellets can provide faster dissolution particularly at earlier time points as compared to formulation having one type of particles/pellets.

The data shown above clearly demonstrate that the compositions disclosed in WO 03/074056 (see comparative data in the present application at pages 21-23), the compositions of the present invention exhibit a faster dissolution profile.

The superior properties associated with the compositions of the present invention would not have been predicted based on the teachings of WO 03/074056 (or its US equivalent, US 2006/0183779).

The undersigned declarant declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this May 5th, 2016



Ziauddin TYEBJI

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	1613
Examiner Name	LYNDSEY MARIE BECKHARDT, Esq.
Attorney Docket Number	ESTEVE 6 PCT US

U.S. PATENT DOCUMENTS

Examiner initial *	Cite No.	Document Number Number - Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US-6,087,380	07-11-2000	Hauel, et al.	
	2	US 2005/0234104	10-20-2005	Schmid, et al.	
	3	US 2011/0129538	06-02-2011	Landerer, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Cite No. 1	Foreign Patent Document Country[3] Code Number[4] Kind Code (if known)[5]	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	4	WO WO 2005/028468	03-31-2005	BOEHRINGER INGELHEIM PH		
	5	WO WO 2012/001156	01-05-2012	KRKA TOVARNA ZDRAVIL		
	6	WO WO 98/37075	08-27-1998	BOEHRINGER INGELHEIM PH		

Examiner Signature	/LYNDSEY M BECKHARDT/	Date Considered	07/25/2017

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Sheet 1 of 4

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

U.S. PATENT DOCUMENTS

Examiner initial *	Cite No	Document Number Number - Kind Code [2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US-2004/0109890	06-10-2004	SUGIMOTO	
	2	US-2005/0123606	06-09-2005	KIDANE	
	3	US-2006/0183779	08-17-2006	BRAUNS	

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Cite No. 1	Foreign Patent Document Country [3] Code Number [4] Kind Code (if known) [5]	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	4	WO 00/12064	03-09-2000	CHEN		
	5	CN 101632668	01-27-2010	BRAUNS		
	6	EP 1366760	02-12-2002	SUGIMOTO		
	7	JP 2001-524131	11-27-2001	CHEN		
	8	JP 2002-316923	10-31-2002	SUGIMOTO		
	9	JP 2002-523443	07-30-2002	CHEN		

Examiner Signature	/LYNDSEY M BECKHARDT/	Date Considered	07/31/2017

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Sheet 2 of 4

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

U.S. PATENT DOCUMENTS

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	10	WO 2005/046663	05-26-2005	KIDANE		
	11	WO 2005/121102	12-22-2005	TORKELSON		
	12	JP 2005-519099	06-30-2005	BRAUNS		
	13	WO 2007/092026	08-16-2007	LEIBOVICI		
	14	JP 2007-510655	04-26-2007	KIDANE		
	15	JP 2008-501702	01-24-2008	TORKELSON		

Examiner Signature	/LYNDSEY M BECKHARDT/	Date Considered	07/31/2017

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Sheet 3 of 4

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

U.S. PATENT DOCUMENTS

Examiner initial *	Cite No.	Document Number Number - Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear

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	16	JP 2008-534661	08-28-2008	LEIBOVICI		
	17	CA 2476054	09-12-2003	BRAUNS		
	18	WO 98/50019	11-12-1998	CHEN		
	19	JP H04103525	04-06-1992	MASATSUNE		✓

Examiner Signature	/LYNDSEY M BECKHARDT/	Date Considered	07/31/2017

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Sheet 4 of 4

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

NON PATENT LITERATURE DOCUMENTS

Examiner initial *	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	20	BELOUSOV, Yu. B., et al., RATIONAL PHARMACOTHERAPY IN CARDIOLOGY, VOL. 8, NO. 1, PG. 37-44, 2012, ENGLISH ABSTRACT	✓
	21	BOZHKOVA, S.A., TRAUMATOLOGY AND ORTHOPEDICS, VOL. 1, NO. 59, PG. 138-143, 2011, ENGLISH ABSTRACT.	✓

Examiner Signature	/LYNDSEY M BECKHARDT/	Date Considered	07/25/2017

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1. Applicants unique citation designation number. (optional) 2. Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 2

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	1613
Examiner Name	LYNDSEY MARIE BECKHARDT
Attorney Docket Number	ESTEVE 6 PCT US

U.S. PATENT DOCUMENTS

Examiner initial *	Cite No.	Document Number Number - Kind Code [2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US 2006/0074056	04-06-2006	Vaisburg, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Cite No. 1	Foreign Patent Document Country [3] Code Number [4] Kind Code (if known) [5]	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	2	WW WO 03/074056	09-12-2003	BOEHRINGER INGELHEIM		

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Sheet 2 of 2

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	1613
Examiner Name	LYNDSEY MARIE BECKHARDT
Attorney Docket Number	ESTEVE 6 PCT US

NON PATENT LITERATURE DOCUMENTS

Examiner initial *	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T [2]
	3	Stangier, Clin Pharmacokinet 2008; 47 (5); 285-295.	

Examiner Signature	/LYNDSEY M BECKHARDT/	Date Considered	07/25/2017

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14379613	PILGAONKAR ET AL.
	Examiner	Art Unit
	LYNDSEY BECKHARDT	1613

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
	No Classified Search		

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SEARCH NOTES		
Search Notes	Date	Examiner
East (keyword and Inventor) see attached	9/24/2015	LMB
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East (keyword and Inventor) see attached	3/7/2016	LMB
Google (keyword) see attached East search terms	3/7/2016	LMB
East (keyword and Inventor) see attached	7/25/2017	LMB

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	9	L1 or L2 or L3	USPAT	OR	OFF	2017/07/25 14:47
L5	42	L1 or L2 or L3	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L7	26	L5 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L9	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2017/07/25 14:47
L10	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L16	1948029	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L17	43039	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L18	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L20	8079	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L22	1943	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L23	1943	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L25	39456	(drug or active or pharmaceutical) same (particle or microsphere) same (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L26	5933	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L27	2099222	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend) same organic acid	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L31	40	((Pratibha) near2 (Pilgaonkar)).INV.	US-	OR	OFF	2017/07/25

			PGPUB; USPAT			14:47
L32	36	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L33	36	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L34	42	L31 or L32 or L33	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L37	0	("20060183779").PN.	USPAT; USOCR	OR	OFF	2017/07/25 14:47
L38	0	("200600183779").PN.	USPAT; USOCR	OR	OFF	2017/07/25 14:47
L39	0	("200600183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L41	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L46	9	L43 or L44 or L45	USPAT	OR	OFF	2017/07/25 14:47
L47	42	L43 or L44 or L45	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L49	26	L47 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L51	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2017/07/25 14:47
L52	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L58	1948029	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L59	43039	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L60	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L62	8079	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L64	1943	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47

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MSN Exhibit 1002
Page 384 of 680

L65	1943	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L67	39456	(drug or active or pharmaceutical) same (particle or microsphere) same (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L68	5933	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L72	40	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L73	36	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L74	36	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2017/07/25 14:47
L75	42	L72 or L73 or L74	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L78	0	("20060183779").PN.	USPAT; USOCR	OR	OFF	2017/07/25 14:47
L79	0	("200600183779").PN.	USPAT; USOCR	OR	OFF	2017/07/25 14:47
L80	0	("200600183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47
L82	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/07/25 14:47

EAST Search History (Interference)

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7/25/2017 2:49:26 PM
C:\Users\Ishaak\Documents\EAST\Workspaces\14379613.wsp

OK TO ENTER: /LMB/

07/25/2017

AMENDMENTS TO THE SPECIFICATION

Please replace the passage appearing at page 21 with the following amended passage.

Example 3: Comparative evaluation of two formulation approaches for dabigatran etexilate mesylate

The two formulation approaches for dabigatran etexilate mesylate as shown below were evaluated:

(i) First approach being that of the present invention having two types of particles/pellets (one of dabigatran etexilate mesylate and the other of organic acid) and
(ii) Second approach having one type of particles/pellets having both dabigatran etexilate mesylate and organic acid. This formulation was prepared according to the teachings of ~~US 2006/074056~~ WO 03/074056 and, in particular, Example 1. Formulation (B)

(A) Preparation of formulation A having two types of particles/pellets (i.e. Dabigatran etexilate mesylate granules and seal coated tartaric acid pellets)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US	6655

25666 7590 08/11/2017
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EXAMINER	
BECKHARDT, LYNDSEY MARIE	

ART UNIT	PAPER NUMBER
1613	

MAIL DATE	DELIVERY MODE
08/11/2017	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/379,613	Applicant(s) PILGAONKAR ET AL.	
	Examiner LYNDSEY BECKHARDT	Art Unit 1613	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/01/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *21,23-30 and 32-39* is/are pending in the application.

5a) Of the above claim(s) *33-39* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *21,23-30 and 32* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *06/01/2016, 11/02/2016, 06/01/2017*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Claims 21, 23-30 and 32-39 are currently pending. Claims 21, 23-30 and 32 are currently under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/01/2016 has been entered.

Information Disclosure Statement

Applicant’s Informational Disclosure Statement, filed on 06/01/2016, 11/02/2016, 06/01/2017 has been considered. Please refer to Applicant's copy of the 1449 submitted herein.

Specification

The specification amendments filed 06/01/2016 is entered to correct a typographical error.

Examiner’s Note

Unless otherwise indicated, previous objection/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the 06/01/2016 response will be addressed to the extent they apply to current rejection(s).

Maintained Rejections:

The following rejections are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21, 23-30 and 32 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US 2006/0183779 (previously applied) in view of US 2008/0069891 (previously applied) as evidenced by PubChem (previously applied).

Regarding claim 21, the limitation of a composition comprising a) particles that comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salts; and b) particles that comprise at least one pharmaceutically acceptable organic acid is met by active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-mthyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmaceutically acceptable salts thereof (abstract), wherein PubChem evidences the structure of the ‘779 publication [0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The ‘779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1).

The limitation of wherein at least one type of particles is coated with a protective coating layer is met by the ‘779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]).

Regarding claim 23, the limitation of further comprising at least one pharmaceutically acceptable excipient is met by the ‘779 publication teaching polymer selected from gum Arabic included in the particles [0012]. The ‘779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient.

Regarding claims 24-25, the limitation of wherein the first type of particles is free from acids is met by the ‘779 publication teaching spatial separation of the organic acid and the active substance, wherein the organic acid and the active agent are taught to be in a particle ([0010], [0011]).

Regarding claim 26, the limitation of comprising from 0.01 wt% to 90% of dabigatran etexilate (expressed as dabigatran etexilate mesylate) is met by the '779 publication teaching dabigatran etexilate (abstract, [003]) wherein the active agent is taught to be present at 5-60% [0014].

Regarding claims 27 and 30, the limitation of wherein at least 90% by weight of the organic acid present in the composition is contained in the second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients and 2-95% of the at least one pharmaceutically acceptable organic acid is met by the ‘779 publication teaching 30-100% of the organic acid in the core [0012].

Regarding claims 28 and 29, the limitation of wherein the first type of particles is coated with a protective coating layer and the second type of particle is coated with a protective coating layer is met by the '779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]).

Regarding claim 32, the limitation of wherein the composition comprises form 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

The '779 publication does not specifically teach components a) and b) in two distinct types of particles (claim 21).

The '891 publication teaches a pharmaceutical composition may include granulate including at least one active pharmaceutical ingredient. The composition may include a coating on the granulate. The composition further comprises a second particle comprising a fat/wax. The granulate are formed into various dosage forms (abstract, [0018]). The invention comprises two particles, the first type containing the pharmaceutical agent and the second comprising fat/wax material [0020].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779 publication as two distinct particles as the '891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the

invention was made would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication.

Response to Arguments:

Applicant's arguments have been fully considered and are not deemed to be persuasive.

Applicant argues that the mere fact that it might be possible to select elements of an invention by combining elements of references does not make out an obviousness rejection.

In response, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779 publication as two distinct particles as the '891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a

pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the ‘779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. It would have been obvious to one of ordinary skill in the art to try the use of separated microparticles, as the prior art of the '779 publication and the '891 publication teach two possible solutions, layering of a microparticles or using separate microparticles, thus teaching a finite number of predictable solution.

Applicant argues the pellets having the specific configuration disclosed in the ‘779 publication confer a technical advantage in that they produce, upon dissolution following administration an acid microclimate resulting from the dissolution of the organic acid. The ‘779 publication teaches an improved formulation wherein both the tartaric acid and the active ingredients are present in the same pellet (Figure 1). The ‘779 publication discloses that this particular structure has the advantage that the organic acid does not go into solution until after the preparation has been taken and then produces an acid microclimate in which the active substance can dissolve.

In response, the use of two distinct particles, as taught by the ‘891 publication, would still results in the acid being present to dissolve and create a microenvironment of acid after administration.

Applicant argues there is no teaching or suggestion in the ‘779 publication that such characteristics could be provided by a dosage form wherein the active and organic acid are physically separated into two distinct particles. This deficiency is not cured by the ‘891 publication.

In response, the ‘779 publication teaches a particle containing a core material containing an acid and an insulating layer. An active substance layer and a coating layer are additional taught (Figure 1). Thus the use of two separate microparticles as taught by the ‘891 publication still contain the core containing an acid and an insulating or coating layer, thus the particle is still present and would still dissolve once administered to the body.

Applicant argues the provision of two distinct types of particles in the formulations disclosed in the ‘891 publication has the function of limiting the extent of solvent access to the active particles and thus it may help to retain the release rate consistent with the initial desired rate of active ingredient release and thereby frustrate dose dumping. One of skill in the art would not have been motivated to modify the single pellet compositions disclosed in the '779 publication, which compositions are designed to provide improved dissolution and absorption based on the generic disclosure in the ‘891 publication that the composition may comprise an API in the first particle and a fat/wax in a second particle.

In response, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the ‘779 publication as two distinct particles as the ‘891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the ‘779 publication teaches the need for spatial separation of the organic acid and the active

substance [0010]. It would have been obvious to one of ordinary skill in the art to try the use of separated microparticles, as the prior art of the '779 publication and the '891 publication teach two possible solutions, layering of a microparticles or using separate microparticles, thus teaching a finite number of predictable solution.

Applicant submit that the comparative data disclosed in the instant specification demonstrate superior and unexpected effects associated with the instant claimed compositions. Example 3 demonstrates that the instantly claimed composition exhibit a faster dissolution rate than the composition disclosed in WO 03/074056 (the international equivalent of the '779 publication). Applicant argues the limitations in the Ziauddin and Zhenguo declarations.

In response, the declarations and specification data are addressed below.

Applicant argues since the instant formulations comprise two distinct types of particles, one comprising the active ingredients and the other comprising the organic acid, they are physically separated when the dosage form is taken and both dissolve at the same time. Thus the acidic microenvironment is not generated as taught in the '779 publication.

In response, as Applicant has stated the active ingredients and the organic acid both dissolve at the same time and thus the acidic microenvironment would still be generated.

Applicant argues in the previous office action the Examiner notes the Affiant is the same as the Inventor of the instant application. Therefore the Affiant has an interest in the outcome of the application. Applicant states that MPEP 716.01(c) III states that an

applicant as to the advantage to his or claimed invention, while less persuasive than a disinterested person cannot be disregarded.

In response, Applicant did not disregard the provided the declaration, but specifically responded to each point presented in the previous declaration.

37 CFR 1.132 Declaration

The examiner acknowledges receipt of the Declaration under 37 CFR 1.132 by Ziauddin Tyebji, filed 06/01/2016 and Zhenggua Zu, filed 06/01/2016.

The Declarations under 37 CFR 1.132 filed 06/01/2016 are insufficient to overcome the rejection of claims 21, 23-30 and 32 based upon *obviousness* by the '779 publication and the '891 publication as evidenced by PubChem as set forth in the last Office action because:

The declaration states that Formulation A has two types of particles/pellets (one comprising dabigatran etexilate mesylate and the other comprising a coated organic acid) and Formulation B is described in Example 1 of the '779 publication, which is the same as that disclosed in WO 2003/074056. Formulation B has only one type of particles/pellets having both dabigatran etexilate mesylate and organic acid. Formulation A is taught to have dabigatran etexilate mesylate particles and tartaric acid pellets which are deal coated with a lubricated seal coat. The formulation of the present invention having two types of particles/pellets can provide faster dissolution particularly at earlier time points as compared to formulation having one type of particle/pellets.

In response, the Formulation A and B cannot be properly compared to each other, as the ratio and amount of tartaric acid and active substance are not the same in

the formulation A and B. Thus the comparison is not strictly between the use of two separate particles or a layered particle, but rather have additional factors differentiating the two formulations. As the formulations can be directly compared, a proper assessment cannot take place regarding the dissolution time of the active ingredient.

Additionally it is noted that the instant claims are not commensurate in scope with the provided results. The instant claims state wherein at least one type of particle is coated with a protective coating layer, wherein the active agent containing particle is coated and wherein the acid containing particle is coated. The Example presented contains a coating over the acid containing particle, however no coating layer is present over the active agent containing particles, thus the results are not commensurate in scope.

The Zhenggue Xu declaration demonstrates a bioequivalence study that was carried out using formulations A and B were administered in two different studies fed and fasting. The data shown above clearly demonstrate that in addition to exhibiting a faster dissolution profile than the composition disclosed in the ‘056 publication, the compositions of the present invention also exhibit the same bioavailability as the compositions disclosed in the ‘056 publication.

In response, the Formulation A and B cannot be properly compared to each other, as the ratio and amount of tartaric acid and active substance are not the same in the formulation A and B. Thus the comparison is not strictly between the use of two separate particles or a layered particle, but rather have additional factors differentiating

the two formulations. As the formulations can be directly compared, a proper assessment cannot take place regarding the dissolution time of the active ingredient.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949).

Upon consideration of the facts taught by the prior art and the information submitted by the Affiant, the balance of evidence indicates that the prior art teaches the instantly claimed inventions.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached on Monday, Tuesday and Thursday 7:30 am to 3:00 pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on (571) 272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LYNDSEY BECKHARDT/
Examiner, Art Unit 1613

/DENNIS J PARAD/
Primary Examiner, Art Unit 1612

PTO/SB/08a (07-09)
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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

U.S. PATENT DOCUMENTS

Examiner initial *	Cite No	Document Number Number - Kind Code [2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US-2004/0109890	06-10-2004	SUGIMOTO	
	2	US-2005/0123606	06-09-2005	KIDANE	
	3	US-2006/0183779	08-17-2006	BRAUNS	

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Cite No. 1	Foreign Patent Document Country [3] Code	Number [4]	Kind Code (if known) [5]	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	4	WO	00/12064		03-09-2000	CHEN		
	5	CN	101632668		01-27-2010	BRAUNS		
	6	EP	1366760		02-12-2002	SUGIMOTO		
	7	JP	2001-524131		11-27-2001	CHEN		
	8	JP	2002-316923		10-31-2002	SUGIMOTO		
	9	JP	2002-523443		07-30-2002	CHEN		

Examiner Signature		Date Considered	

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450 Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.
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Sheet 2 of 4

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Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
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Attorney Docket Number	ESTEVE 6 PCT US

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FOREIGN PATENT DOCUMENTS

Examiner Initial *	Cite No. [1]	Foreign Patent Document Country Code [3] Number [4] Kind Code (if known) [5]	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	10	WO 2005/046663	05-26-2005	KIDANE		
	11	WO 2005/121102	12-22-2005	TORKELSON		
	12	JP 2005-519099	06-30-2005	BRAUNS		
	13	WO 2007/092026	08-16-2007	LEIBOVICI		
	14	JP 2007-510655	04-26-2007	KIDANE		
	15	JP 2008-501702	01-24-2008	TORKELSON		

Examiner Signature		Date Considered	

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Sheet 3 of 4

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

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	16	JP 2008-534681	08-28-2008	LEIBOVICI		
	17	CA 2478054	09-12-2003	BRAUNS		
	18	WO 98/50019	11-12-1998	CHEN		
	19	JP H04103525	04-06-1992	MASATSUNE		✓

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 4

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

NON PATENT LITERATURE DOCUMENTS

Examiner initial *	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T 2
	20	BELOUSOV, Yu. B., et al., RATIONAL PHARMACOTHERAPY IN CARDIOLOGY, VOL. 8, NO. 1, PG. 37-44, 2012, ENGLISH ABSTRACT	✓
	21	BOZHKOVA, S.A., TRAUMATOLOGY AND ORTHOPEDICS, VOL. 1, NO. 59, PG. 138-143, 2011, ENGLISH ABSTRACT.	✓

Examiner Signature		Date Considered	

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Electronic Acknowledgement Receipt

EFS ID:	29366173
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	25666
Filer:	George Patrick Sage/Linda Wooden
Filer Authorized By:	George Patrick Sage
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	01-JUN-2017
Filing Date:	19-AUG-2014
Time Stamp:	12:24:42
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_TRANSMITTAL.pdf	1354293 b0bcf012fda1f4a7a5b71b3145c81c95bb2749ec	no	1

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	1449.pdf	5171759 87d15c97e566d5c0c87b8a3caf5e5b2613882c51	no	4
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Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	1_CA2476054A1.pdf	875711 282f9018b4f3ee4f5a3d6f75d1592a89c39c17b8	no	25
Warnings:					
Information:					
4	Foreign Reference	2_WO2007092026.PDF	1428251 a9b22b3e5d3b9c8e2b7b0a1f83571b4a04b1c84c	no	25
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Warnings:					
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6	Foreign Reference	4_EP1366760A1.PDF	1554594 6467c2a6451bdc1d876419634aac4a5dff50547f	no	29
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7	Foreign Reference	5_JPH04103525_WITH_TRANSLATION.pdf	1227600 4b3126571ad761a505e90941dad7a3d1283a46e7	no	15
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8	Foreign Reference	6_WO2000012064.PDF	855496 c963b3684eee9b7690fc7a107bbaa39f5e92b43a	no	24
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Information:					

9	Foreign Reference	7_WO1998050019.PDF	1073633 61f7fc1fe2d95a5a05765a0da7734138b6d6d9e1	no	28
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Information:					
10	Foreign Reference	8_WO2005121102.PDF	2196699 793a85bc2909f12beabbcc460a3db2ab95248fcb	no	43
Warnings:					
Information:					
11	Non Patent Literature	Belousov_RationalPharmacotherapyCardiology.PDF	286938 e6311064feefb556dea2d51ed5ba8079ee2bc670	no	8
Warnings:					
Information:					
12	Non Patent Literature	Bozhkova_Traumatology_Orthopedics_2011.PDF	2148308 a31e4b9f1e6afd4797ab3c58566d07a9b30427b6	no	6
Warnings:					
Information:					
13	Foreign Reference	CN101632668A.pdf	791670 a69461a8acf38d8aced14274d9eb06f5ef1356e1	no	16
Warnings:					
Information:					
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Warnings:					
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Information:					

16	Foreign Reference	3_JPA_2007510655.PDF	452227 9937cb068f3ac54cd99ab6e595cfc024172ebc09	no	12
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Information:					
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Warnings:					
Information:					
		Total Files Size (in bytes):	25114463		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

* * * * *

Applicants : Pratibha S. PILGAONKAR, et al.
Serial No. : 14/379,613
Filed : 19 August 2014
Title : ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
Art Unit : 1613

* * * * *

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

COMMUNICATION COVERING TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §§ 1.97 AND 1.98

Sir:

Herewith, in accord with the foregoing regulations, please find an Information Disclosure Statement which, it is respectfully submitted, should materially advance and accelerate the prosecution of the above-identified application. Attached hereto is a Form PTO/SB/08 and copies of the non-US patent/application documents and non-patent literature listed thereon. English language abstracts are provided for foreign language patent document(s) which are not available as US patent/application equivalents.

As will be noted, this Information Disclosure Statement calls a number of references, which might be considered relevant, to the attention of the Office. The fact that these are in fact "Prior Art" and/or relevant to the prosecution is, however, not admitted. In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. It is understood that, during examination, the Office will make an independent search and will identify any relevant prior art under 37 CFR § 1.104(a). Entry of this Information Disclosure Statement into the file of this application, initialing of each reference entry, making all of the references called to the Office's attention therein of record, listing such references among the "References Cited" on any patent to issue therefrom, and favorable action on the merits of this application are all respectfully solicited.

Respectfully submitted,
THE FIRM OF HUESCHEN AND SAGE

Michele M. CUDAHY, Reg. No. 55,093

Dated : 01 June 2017
Customer No. : 25,666
Seventh Floor, Kalamazoo Building
107 West Michigan Avenue
Kalamazoo, MI 49007
(269) 382-0030

* * * * *

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Sheet 1 of 1

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	1613
Examiner Name	LYNDSEY MARIE BECKHARDT, Esq.
Attorney Docket Number	ESTEVE 6 PCT US

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	1	US-6,087,380	07-11-2000	Hauel, et al.	
	2	US 2005/0234104	10-20-2005	Schmid, et al.	
	3	US 2011/0129538	06-02-2011	Landerer, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Cite No. 1	Foreign Patent Document Country [3] Code Number [4] Kind Code (if known) [5]	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	4	WO WO 2005/028468	03-31-2005	BOEHRINGER INGELHEIM PH		
	5	WO WO 2012/001156	01-05-2012	KRKA TOVARNA ZDRAVIL		
	6	WO WO 98/37075	08-27-1998	BOEHRINGER INGELHEIM PH		

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Electronic Acknowledgement Receipt

EFS ID:	27399277
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	25666
Filer:	George Patrick Sage/Michele Cudahy
Filer Authorized By:	George Patrick Sage
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	02-NOV-2016
Filing Date:	19-AUG-2014
Time Stamp:	15:43:11
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	IDS_TRANSMITTAL_2NOV16.pdf	1696015 9e9778ed4fadc6c5b9ae9c61fd5b8990c003e80f	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	PTO_SB08_2NOV16.pdf	1398114 15ef4cb9c0309c0500ca5add640191979bae1fc2	no	1
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Information:					
This is not an USPTO supplied IDS fillable form					
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Information:					
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Information:					
5	Foreign Reference	REF6_2NOV16.pdf	7709556 93785fcb931ec40bc033c84ad4c6d21dac130393	no	201
Warnings:					
Information:					
		Total Files Size (in bytes):	13162230		

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* * * * *

Applicants : Pratibha S. PILGAONKAR, Maharukh T. RUSTOMJEE, and Anilkumar S. GANDHI

Serial No. : 14/379,613

Filed : 19 August 2014

Title : ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Art Unit : 1613

Examiner : LYNDSEY MARIE BECKHARDT, Esq.

* * * * *

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

COMMUNICATION COVERING TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §§ 1.97 AND 1.98

Sir:

Herewith, in accord with the foregoing regulations, please find an Information Disclosure Statement which, it is respectfully submitted, should materially advance and accelerate the prosecution of the above-identified application. Attached hereto is a Form PTO/SB/08 and copies of the non-US patent/application documents and non-patent literature listed thereon. English language abstracts are provided for foreign language patent document(s) which are not available as US patent/application equivalents.

As will be noted, this Information Disclosure Statement calls a number of references, which might be considered relevant, to the attention of the Office. The fact that these are in fact "Prior Art" and/or relevant to the prosecution is, however, not admitted. In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no

other material information as defined in 37 CFR 1.56(a) exists. It is understood that, during examination, the Office will make an independent search and will identify any relevant prior art under 37 CFR § 1.104(a).

Entry of this Information Disclosure Statement into the file of this application, initialing of each reference entry, making all of the references called to the Office's attention therein of record, listing such references among the "References Cited" on any patent to issue therefrom, and favorable action on the merits of this application are all respectfully solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE



Michele M. CUDAHY, Reg. No. 55,093

Dated : 2 November 2016
Customer No. : 25,666
Seventh Floor, Kalamazoo Building
107 West Michigan Avenue
Kalamazoo, MI 49007
(269) 382-0030
Enclosure(s) : Form PTO/SB/08 and Accompanying References.

* * * * *

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PTO/SB/08a (07-09)
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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	1613
Examiner Name	LYNDSEY MARIE BECKHARDT
Attorney Docket Number	ESTEVE 6 PCT US

U.S. PATENT DOCUMENTS

Examiner initial *	Cite No.	Document Number Number - Kind Code [2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US 2006/0074056	04-06-2006	Vaisburg, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Cite No. 1	Foreign Patent Document Country [3] Code Number [4] Kind Code (if known) [5]	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	2	WW WO 03/074056	09-12-2003	BOEHRINGER INGELHEIM		

Examiner Signature		Date Considered	

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not Considered. Include copy of this form with next communication to applicant. 1. Applicant's unique citation design number (optional). 2 See Kinds Codes of USPTO patent Documents. at www.uspto.gov or MPEP 901.04. 3. Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5. Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. 6. Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450 Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

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PTO/SB/08b (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	14/379,613
Filing Date	August 19, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	1613
Examiner Name	LYNDSEY MARIE BECKHARDT
Attorney Docket Number	ESTEVE 6 PCT US

NON PATENT LITERATURE DOCUMENTS

Examiner initial *	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T [2]
	3	Stangier, Clin Pharmacokinet 2008; 47 (5); 285-295.	

Examiner Signature		Date Considered	

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1. Applicants unique citation designation number. (optional) 2. Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Cheif Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450 Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

Adapted from PTO/SB/30EFS (07-14)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	14/379,613	Filing Date	19 August 2014	Docket Number (if applicable)	ESTEVE 6 PCT US	Art Unit	1613
First Named Inventor	Pratibha S. PILGAONKAR			Examiner Name	LYNDSEY MARIE BECKHARDT		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV.

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☒ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 08-3220

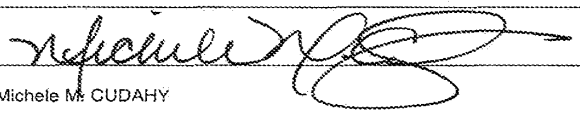
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature
☐ Applicant Signature

P262US rev. 10/2015

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

Adapted from PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Signature of Registered U.S. Patent Practitioner			
Signature		Date (DD-MM-YYYY)	01 June 2016
Name	Michele M. CUDAHY	Registration Number	55,093

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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Electronic Patent Application Fee Transmittal

Application Number:	14379613
Filing Date:	19-Aug-2014
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Filer:	George Patrick Sage/Michele Cudahy
Attorney Docket Number:	ESTEVE 6 PCT US

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt	
EFS ID:	25936552
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	25666
Filer:	George Patrick Sage/Michele Cudahy
Filer Authorized By:	George Patrick Sage
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	01-JUN-2016
Filing Date:	19-AUG-2014
Time Stamp:	14:00:10
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1200
RAM confirmation Number	325
Deposit Account	083220
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response After Final Action	RESPONSE_1JUN16.pdf	11369103 c787d82d3884e9f293765fd848a01b1e866e96f6	no	11
Warnings:					
Information:					
2	Specification	SPEC_AMENDMENT_1JUN16.pdf	688864 38f06f659990de9be670730d0cc6913dc1107d6f	no	1
Warnings:					
Information:					
3	Affidavit-traversing rejectns or objectns rule 132	132_DECLARATION_XU_1JUN16.pdf	2469888 bc714f5d67951964aad18e1979ef06a2cc11bc8d	no	3
Warnings:					
Information:					
4	Affidavit-traversing rejectns or objectns rule 132	132_DECLARATION_TYEBJI_1JUN16.pdf	4027473 75d262e5aa79a0747d4e4de4bb2e3c7b0776f086	no	4
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	PTO_SB08_1JUN16.pdf	2376721 9a6f3ecdee7588b14b58c5749ae4234350001910	no	2
Warnings:					
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6	Foreign Reference	REF2_1JUN16.pdf	1253042 c3316db4df7b4a954664d2acd30150d6e0062c37	no	28
Warnings:					
Information:					
7	Non Patent Literature	REF3_1JUN16.pdf	18281749 1121d9c370f7f2e9bd15698c89eac7945cb4e5ef	no	12
Warnings:					
Information:					

8	Request for Continued Examination (RCE)	PTO_SB30_1JUN16.pdf	1813600 86c3fad550938003ff4f67b9ec80308fc49655ea	no	2
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	30952 360542152bb56c4a013f9c381f4ac12e28ab2657	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	42311392		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

* * * * *

Applicants	:	Pratibha S. PILGAONKAR, Maharukh T. RUSTOMJEE, and Anilkumar S. GANDHI
Serial No.	:	14/379,613
Filed	:	19 August 2014
Title	:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
Art Unit	:	1613
Examiner	:	LYNDSEY MARIE BECKHARDT, Esq.

* * * * *

Honorable Commissioner for Patents
PO Box 1450
Alexandria, VA 22313

RESPONSE AND AMENDMENT AFTER FINAL
UNDER 37 CFR §§ 1.113 AND 1.116
PRESENTATION OF A DECLARATION UNDER 37 CFR § 1.132
REQUEST FOR CONTINUED EXAMINATION UNDER 37 CFR §1.114

Sir:

Responsive to the Office Action, **a Final Rejection**, dated 23 March 2016, and in accordance with the foregoing regulations, kindly amend as follows.

IN THE SPECIFICATION: See Amendments to the Specification attached hereto.

IPR2025-01107
MSN Exhibit 1002
Page 427 of 680

REMARKS

The Applicants acknowledge the Examiner's comprehensive Office Action, **a Final Rejection**, with appreciation. Claims 21-39 are pending in the application; however, Claims 33-39 remain withdrawn from consideration as a result of the previously issued Restriction Requirement. The previous rejections for lack of written description and anticipation have been withdrawn in view of the Response and Amendment filed on 29 December 2015; however, the Office maintains the prior art rejection under 35 USC § 103. The Office states that the modified obviousness rejection was made in view of the Applicant's previously submitted amendment and that since the modified rejection was necessitated by the Applicant's amendment, the instant Office Action is made Final.

To begin, with the instant Amendment, Example 3 (at pages 21-23 of the instant specification) has been amended to correct an obvious typographical error. Specifically, Example 3 has been amended to accurately reflect that the disclosed comparative data relates to a comparison between the instant composition and Example 1 of **WO 03**/074056 (rather than a comparison between the instant composition and Example 1 of **US 2006**/074056).

The Applicants note that WO 03/074056 (which reference is enclosed herewith and listed on the enclosed Form PTO-SB08) discloses a novel oral dosage form for dabigatran and is an international equivalent of US 2006/0183779, which US publication is discussed at page 3 of the instant specification. Moreover, US 2006/074056 (which reference is also listed on the enclosed Form PTO-SB08) relates to compounds acting as inhibitors of VEGF and HGF receptor signaling for the treatment of cell proliferative diseases and conditions. The US '056 publication discloses a generic class of compounds which is structurally unrelated to dabigatran etexilate, and Example 1 of the US '056 publication relates to the synthesis of a representative species of the disclosed compounds.

Thus, one skilled in the art would recognize that the citation of **US 2006**/074056 represents a clear typographical error. The Applicants respectfully submit that no

new matter has been introduced by the instant amendment to correct the error in the specification.

Claims 21, 23-30, and 32 are rejected for obviousness under 35 USC § 103(a) based on the disclosure of US 2006/0183779 in view of US 2008/0069891, as evidenced by PubChem (PubChem, Dabigatran Etexilate, (accessed 21 March 2016), pages 1-25). The PubChem entry is cited to demonstrate that the compound/chemical structure disclosed in the '779 publication is dabigatran etexilate.

The Office reiterates its position that the '779 publication discloses that dabigatran etexilate combined with organic acids provides improved formulation. The Office further reiterates that the '779 publication discloses pellets comprising a core containing an organic acid, a separating layer, and a layer containing the active substance (specifically citing paragraph [0010] and Figure 1 of the '779 publication). The Office goes on to reiterate that the disclosure in the '779 publication related to an optional outermost layer meets the limitation of a "protective coating layer."

The Office goes on to reiterate that the '779 publication meets (or renders obvious) the limitations of the dependent claims as discussed at pages 4-5 of the instant Final Rejection.

The Office again acknowledges that the '779 publication does not specifically disclose instant components a) and b) in two distinct types of particles; however, it remains the position of the Office that this deficiency is cured by the '891 publication.

The Office reiterates its position that the '891 publication discloses a pharmaceutical composition which may include a granulate comprising at least one pharmaceutical ingredient, which composition may include a coating on the granulate. The Office goes on to reiterate that the disclosed composition may further comprise a second particle comprising a fat/wax and that the composition may be formed into various dosage forms. The Office further reiterates that the invention disclosed in the '891

publication comprises two particles, the first type containing the pharmaceutical agent and the second comprising a fat/wax material.

It remains the position of the Office that it would have been obvious to formulate the oral composition disclosed in the '779 publication as two distinct particles since the '891 publication discloses pharmaceutical compositions comprising two distinct particles, one of which includes a pharmaceutical agent. The Office states that one skilled in the art would have been motivated to do so since the '779 publication discloses the need for spatial separation of the organic acid and the active substance and that there would have been a reasonable expectation of success since the '779 publication discloses an oral pharmaceutical formulation in the form of particles and since the '891 publication discloses that it was known to formulate active agents and excipients for oral dosage forms in separate particles.

The Applicants respectfully submit that the Office characterization of the cited references is not completely accurate in that the Office has not considered the cited references in their entirety.

The Applicants further submit that the courts have held that the mere fact that it might be ***possible*** to select elements of an invention by combining elements of references does not make out an obviousness rejection. See In re Bergel, 130 USPQ 206, 208 (CCPA) 1961). More recently, the Court of Appeals for the Federal Circuit has held that "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole." In re Kahn, 78 USPQ2d 1329 (CAFC 2006)(cited with approval by the court in KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385 (2007)).

Under 35 USC § 103, in order to establish a *prima facie* showing of obviousness, it must be demonstrated that "...the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art to which the subject matter pertains..."

The Applicants respectfully submit that the Office has not made the required demonstration to establish *prima facie* obviousness.

The '779 publication discloses (at paragraph [0006]) that the aim of the invention is to provide an improved formulation for oral use of the compound of formula (I).

The unexpected effect obtained by the disclosed invention is disclosed in paragraph [0007] of the '779 publication, which is reproduced below:

> Surprisingly it has now been found that the use of pharmaceutically acceptable organic acids with a water solubility of >1 g/250 ml at 20 °C., preferably >1 g/160 ml at 25 °C., in solid oral preparations leads to a significantly improved formulation of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate as well as the pharmaceutically acceptable salts thereof.

The pellets having the specific configuration disclosed in the '779 publication confer a technical advantage in that they produce, upon dissolution following administration, an acid microclimate resulting from the dissolution of the organic acid. This acid microclimate facilitates the dissolution of the active substance.

The '779 publication teaches an improved formulation wherein both the tartaric acid and the active ingredient are present in the same pellet (see Figure 1). The '779 publication discloses that this particular structure has the advantage that the organic acid does not go into solution until after the preparation has been taken and then produces an acid microclimate in which the active substance can dissolve (see paragraph [0011]).

This disclosure is confirmed in an article by the patent proprietor of the '779 publication: "Clinical Pharmacokinetics and Pharmacodynamics of the Oral Direct Thrombin Inhibitor Dabigatran Etexilate", Clin Pharmacokinet 2008; 47 (5): 285-2951 (which reference is enclosed herewith and listed on the enclosed Form PTO-SB08).

Pages 287 and 288 of the above-mentioned article state the following (emphasis added):

2. Pharmacokinetics

In early phase I clinical trials in healthy volunteers, dabigatran etexilate was administered in tartaric acid solution or as tablets. In the solid oral dosage form intended to be marketed, dabigatran etexilate is presented as capsules containing multiple pellets approximately 0.8 mm in diameter. The pellets contain a tartaric acid core coated by dabigatran etexilate. Using this approach, an acidic microenvironment is generated, which increases drug dissolution and absorption and renders the extent of absorption of dabigatran etexilate independent of variations in the gastric pH.[21,22] After oral administration to healthy volunteers, the prodrug dabigatran etexilate was rapidly absorbed and converted via two intermediates, BIBR 951 and BIBR 1087, to the active form, dabigatran.[23]

Thus, the acidic microclimate generated by the single pellet formulation is the critical feature of the improved formulation disclosed in the '779 publication in terms of providing good dissolution characteristics and bioavailability.

The Applicants respectfully submit that there is no teaching or suggestion in the '779 publication that such characteristics could be provided by a dosage form wherein the active ingredient and organic acid are physically separated into two distinct particles. The Applicants further submit that this deficiency is not cured by the '891 publication.

The '891 publication discloses (at paragraph [0020], which is specifically cited by the Office) "the present invention may be a pharmaceutical composition comprising two particles. The first particle comprises an API in a pharmaceutically effective amount wherein the first particle is coated with a polymer. The second particle comprises a fat/wax material present in an amount sufficient to inhibit administration abuse of the API from the first particle."

The provision of the of two distinct types of particles in the formulations disclosed in the '891 publication has the function of limiting the extent of solvent access to the active particles and, thus, it may help to retain the release rate consistent with the initial desired rate of active ingredient release, thereby frustrating dose dumping

attempts associated with abuse (see paragraphs [0110], [0111], and [0117] of the '891 publication).

The Applicants respectfully submit that one skilled in the art would not have been motivated to modify the single pellet compositions disclosed in the '779 publication, which compositions are designed to provide improved dissolution and absorption, based on the generic disclosure in the '891 publication that a composition may comprise an API in a first particle and a fat/wax material (to inhibit administration of abuse of the API) in a second particle, to arrive at the instantly claimed compositions with any reasonable expectation of success.

Thus, the Applicants respectfully submit that the Office allegation of *prima facie* obviousness is not made out.

Notwithstanding the Applicants' demonstration that the Office's allegation of *prima facie* obviousness is not made out, the Applicants further submit that the comparative data disclosed in the instant specification demonstrate the superior and unexpected effects associated with the instantly claimed compositions.

Specifically, Example 3 (at pages 21-23) demonstrates that the instantly claimed compositions exhibit a faster dissolution rate than the compositions disclosed in WO 03/074056 (an international equivalent of the '779 publication).

The Applicants also provide a Declaration by Ziauddin TYEBJI, a scientist skilled in this particular art, which confirms that the comparative example disclosed in the instant specification employs the composition of Example 1 of WO 03/074056 as the reference example (i.e., Formulation B). The Declaration further confirms that the instantly claimed compositions exhibit a faster dissolution rate than the compositions disclosed in WO 03/074056.

Moreover, the Applicants also provide a Declaration by Zhenguo XU, a scientist skilled in this particular art, which demonstrates that the instant compositions have the same bioavailability as the compositions disclosed in the '779 publication.

The Applicants respectfully submit that the formulations of the present invention do not function in the same way as the formulation disclosed in the '779 publication. Since the instant formulations comprise two distinct types of particles, one comprising the active ingredient and the other comprising the organic acid, they are physically separated when the dosage form is taken and both dissolve at the same time. Thus, an acidic microenvironment is not generated as taught in the '779 publication.

This fact is particularly pronounced under fed conditions wherein the presence of food will make the distance between acid particles and dabigatran particles even bigger. **Surprisingly**, on one side the dissolution profile of the formulation of the invention is faster than the dissolution profile of the formulation disclosed in the '779 publication (see comparative example in the instant specification and in the TYEBJI Declaration), and on the other side the *in vivo* results (see comparative example in the XU Declaration) demonstrate that both formulations have the same bioavailability.

Such results would not have been predicted based on the disclosure of the '779 publication, alone or in combination with the '891 publication.

Thus, the Applicants respectfully submit that the data provided in the instant specification (and the TYEBJI Declaration) as well as the data provided in the XU Declaration demonstrate the superior and unexpected effects associated with the instantly claimed compositions and further distinguish the instant claims over the disclosure of the references of record in the instant application.

The Applicants further submit that the TYEBJI Declaration and the XU Declaration address the Office statement at page 10 of the instant Final Rejection that the applicant has not compared the claimed invention with the closest prior art.

Moreover, as discussed in the previous Response, the previously submitted GANDHI Declaration provided comparative data demonstrating that the instantly

claimed compositions provide improved stability of dabigatran etexilate, which results would not have been predicted based on the disclosure of the references of record in the instant application.

With respect to the Office statement (at page 10 of the instant Final Rejection) "[i]n addition to the facts provided above, the examiner notes that the Affiant is the same as the Inventor of the instant application. Therefore, the Affiant has an interest in the outcome of the instant application," the Applicants respectfully submit that, according to MPEP § 716.01(c) III, "[a]n affidavit of an applicant as to the advantages of his or her claimed invention, while less persuasive than that of a disinterested person, cannot be disregarded for this reason alone."

Additionally, with respect to the Office statement (at page 11 of the instant Final Rejection) "[a]ffidavits or declarations are provided as evidence and must set forth facts, not merely conclusions," the Applicants respectfully submit that the GANDHI Declaration provided comparative data as well as conclusions based on this data.

To summarize, one skilled in the art would not have been motivated to modify the single pellet compositions disclosed in the '779 publication, which compositions are designed to provide improved dissolution and absorption, based on the generic disclosure in the '891 publication that a composition may comprise an API in a first particle and a fat/wax material (to inhibit administration of abuse of the API) in a second particle, to arrive at the instantly claimed compositions with any reasonable expectation of success; the comparative data disclosed in the instant specification, the TYEBJI Declaration, and the XU Declaration demonstrate that the instant compositions exhibit a faster dissolution rate and equivalent bioavailability compared to the compositions disclosed in the '779 publication, which results would not have been predicted based on the disclosure of the '779 publication, alone or in combination with the '891 publication; and the previously submitted GHANDI Declaration demonstrates that the instantly claimed compositions provide improved stability of dabigatran etexilate, which results would not have been predicted based on the disclosure of the '779 publication, alone or in combination with the '891 publication.

In view of the foregoing, the Applicants respectfully submit that the instant claims are not rendered obvious by the disclosure of the references of record in the instant application, alone or in combination. Reconsideration and withdrawal of the obviousness rejection under 35 USC § 103(a) is respectfully requested.

Finally, in accordance with MPEP § 821.04, the Applicants request rejoinder of withdrawn Claims 33-39 upon the identification of allowable subject matter.

* * * * *

Accordingly, entry of the present amendment, entry of the TYEBJI Declaration and the XU Declaration into the record of the application, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned agent has made an earnest effort to place this application into condition for immediate allowance. If she can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call her at her below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: _____
MICHELE M. CUDAHY, Reg. No. 55,093

Dated: 1 June 2016
Customer No.: 25,666
Seventh Floor, Kalamazoo Building
107 West Michigan Avenue
Kalamazoo, MI 49007
(269) 382-0030

Enclosure(s) : TYEBJI Declaration;
XU Declaration;
Amendments to the Specification;
Form PTO-SB08 and Accompanying References;
Request for Continued Examination (Form PTO/SB/30) and Accompanying Fee

* * * * *

THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.

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MSN Exhibit 1002
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AMENDMENTS TO THE SPECIFICATION

Please replace the passage appearing at page 21 with the following amended passage.

Example 3: Comparative evaluation of two formulation approaches for dabigatran etexilate mesylate

The two formulation approaches for dabigatran etexilate mesylate as shown below were evaluated:

(i) First approach being that of the present invention having two types of particles/pellets (one of dabigatran etexilate mesylate and the other of organic acid) and
(ii) Second approach having one type of particles/pellets having both dabigatran etexilate mesylate and organic acid. This formulation was prepared according to the teachings of ~~US 2006/074056~~ WO 03/074056 and, in particular, Example 1. Formulation (B)

(A) Preparation of formulation A having two types of particles/pellets (i.e. Dabigatran etexilate mesylate granules and seal coated tartaric acid pellets)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		**Docket No.:**	**ESTEVE 6 PCT US**
Applicant(s):	**LABORATORIOS DEL DR. ESTEVE S.A.**	**Examiner:**	**Beckhardt, Lyndsey Marie**
Application No.:	**14/379,613**	**Art Unit:**	**1613**
U.S. Filing Date:	**August 19, 2014**	**Conf. No.:**	**6655**
Title:	**ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE**	**Customer No.:**	**25,666**

DECLARATION UNDER 37 CFR 1.132 IN U.S. PATENT APPLICATION NO. 14/379,613

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Zhengguo XU, a citizen of China and residing at Spain, do hereby declare

1. THAT I am familiar with the invention described and claimed in the patent application 14/379,613. I am submitting this declaration in support of the patentability of the claims of the application.

2. THAT I received the degree of MSc. of Biopharmacy.

3. THAT I have worked from 2004 in Laboratorios del Dr. Esteve as a pharmacokineticist.

4. THAT under my supervision and/or with my participation, the experiments described below were carried out which illustrate the advantages of the presently claimed compositions.

In-vivo bioequivalence study of formulation of the present invention having two types of particles/pellets (Formulation A) and formulation having one type of particles/pellets (Formulation B)

An in-vivo bioequivalence study (relative bioavailability study) was carried out wherein the two different formulations (Formulations A and B described in paragraph [0119] o the patent application) were administered in two different studies (fed and fasting). The study consists of a randomized, balanced, open label, two treatment, four period, two sequence, single dose, crossover, fully replicate, bioequivalence study of two different formulations of Dabigatran Etexilate Mesylate capsules (Formulation A and B as per the present application) in healthy adult human subjects under fed and fasting conditions.

The geometric least squares mean, ratio of formulation A (A) and formulation B (B) i.e. (A/B) %, Intra Subject CV(%) and 90% confidence intervals for the ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-inf of Free Dabigatran are summarized in the following tables.

Results in fasting study:

Pharmacokinetic parameter	Geometric Least Squares Means (Formulation A)	Geometric Least Squares Means (Formulation B)	Ratio (A/B) (%)	90% Confidence Limits (A vs. B)	Intra Subject CV %
Ln(Cmax)(ng/mL)	192.9271	191.9106	100.45	87.13 , 115.84	44.41
Ln(AUC0-t)(ng hr/mL)	1636.1942	1602.6370	102.09	89.60 , 117.37	46.07
Ln(AUC0-inf)(ng hr/mL)	1680.8333	1646.7486	102.44	89.84 , 117.20	43.48

Results in fed study:

Pharmacokinetic parameter	Geometric Least Squares Means (Formulation A)	Geometric Least Squares Means (Formulation B)	Ratio (A/B) (%)	90% Confidence Limits (A vs. B)	Intra Subject CV %
Ln(Cmax)(ng/mL)	144.7350	138.8756	104.22	98.53 , 112.04	22.88
Ln(AUC0-t)(ng hr/mL)	1486.0219	1444.3907	102.47	99.42 , 106.68	14.27
Ln(AUC0-inf)(ng hr/mL)	1521.5415	1476.3162	102.52	99.06 , 106.84	13.51

The data shown above clearly demonstrate that, in addition to exhibiting a faster dissolution profile than the compositions disclosed in WO 03/074056 (see comparative data in the present application at pages 21-23), the compositions of the present invention also exhibit the same bioavailability as the compositions disclosed in WO 03/074056.

The superior properties associated with the compositions of the present invention would not have been predicted based on the teachings of WO 03/074056 (or its US equivalent, US 2006/0183779).

The undersigned declarant declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this May 5th, 2016



Zhengguo XU

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		**Docket No.:**	**ESTEVE 6 PCT US**
Applicant(s):	**LABORATORIOS DEL DR. ESTEVE S.A.**	**Examiner:**	**Beckhardt, Lyndsey Marie**
Application No.:	**14/379,613**	**Art Unit:**	**1613**
U.S. Filing Date:	**August 19, 2014**	**Conf. No.:**	**6655**
Title:	**ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE**	**Customer No.:**	**25,666**

DECLARATION UNDER 37 CFR 1.132 IN U.S. PATENT APPLICATION NO. 14/379,613

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ziauddin TYEBJI, a citizen of India and residing at Spain, do hereby declare

1. THAT I am familiar with the invention described and claimed in the patent application 14/379,613. I am submitting this declaration in support of the patentability of the claims of the application.

2. THAT I received the degree of M. Pharm. (Pharmaceutical Technology).

3. THAT I have worked from 2009 at Laboratorios del Dr. Esteve as Global Director of Product Development.

4. THAT under my supervision and/or with my participation, the experiments described below were carried out which illustrate the advantages of the presently claimed compositions.

Comparative Evaluation of Two Formulation Approaches for Dabigatran Etexilate Mesylate

The dissolution profiles of two formulations comprising dabigatran etexilate mesylate were evaluated.

Formulation A is a according to the present invention and has two types of particles/pellets (one of them comprising dabigatran etexilate mesylate and the other one comprising a coated organic acid)

Formulation B is the formulation described in example 1 of US 2006/0183779 A1. This formulation is exactly the same one disclosed in example 1 of PCT application WO 2003/074056 which is and equivalent of US'779. This formulation is also the one which has been tested in example 3 of the present invention. In said example it is stated that "*the formulation was prepared according to the teachings of **US** 2006/074056*". This quote is erroneous and it was meant to say "*the formulation was prepared according to the teachings of **WO** 2003/074056*". Formulation B has only one type of particles/pellets having both dabigatran etexilate mesylate and organic acid.

Formulation A

Dabigatran etexilate granules	
Ingredient	mg/capsule
Intragranular	
Dabigatran etexilate mesylate equivalent to 150 mg dabigatran etexilate	172.95
Isopropyl alcohol (IPA)	q.s.
Extragranular	
Microcrystalline cellulose	67.05
Croscarmellose sodium	50
Total weight	290
Seal coated tartaric acid granules	
Ingredient	mg/capsule
Core	
Tartaric acid (TAP® 600)	196.34
Coating	

Hydroxypropylmethyl cellulose	5.62
Lactose	5.62
Talc	8.42
Isopropyl alcohol/water	q.s.
Total weight	216

Procedure:

(i) Preparation of Dabigatran Etexilate Mesylate Granules Portion

The weighed quantity of dabigatran etexilate mesylate was loaded in the granulator and granulated using isopropyl alcohol. The granules were further dried in a fluidized bed drier. The granules were then sized, sifted and blended with microcrystalline cellulose, croscarmellose sodium in a suitable blender to give dabigatran etexilate mesylate granules portion.

(ii) Preparation of Seal Coated Tartaric Acid Pellets

Hydroxypropyl cellulose was added to the isopropyl alcohol/water mixture under continuous stirring to obtain a clear solution. Lactose was added to this solution and mixed, followed by addition of talc and stirring. The suspension thus formed was filtered through a suitable sieve and sprayed under continuous stirring on tartaric acid pellets using a fluidized bed coater with Wurster column to achieve desired weight gain. The coated tartaric acid pellets were then dried.

The lubricated seal coated tartaric acid pellets and dabigatran etexilate mesylate granules were filled in capsules using the automatic capsule filling machine in HPMC size 0 capsules.

Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A) and formulation having one type of particles/pellets (Formulation B)

Dissolution profiles of the two formulations were determined in 0.01N HCl pH 2 media at 100 rpm USP type I (basket). The results are shown in the table below:

	% Release	
Time (minutes)	Formulation A (two types of pellets)	Formulation B (one type of pellets)
10	65.1	19.2

15	79.2	57
20	86.7	86.1
30	92	97
45	95.5	97.6
60	96.8	98.5

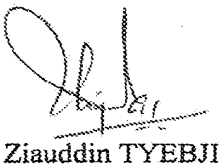
Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A above) and formulation having one type of particles/pellets (Formulation B above) indicates that formulations of the present invention having two types of particles/pellets can provide faster dissolution particularly at earlier time points as compared to formulation having one type of particles/pellets.

The data shown above clearly demonstrate that the compositions disclosed in WO 03/074056 (see comparative data in the present application at pages 21-23), the compositions of the present invention exhibit a faster dissolution profile.

The superior properties associated with the compositions of the present invention would not have been predicted based on the teachings of WO 03/074056 (or its US equivalent, US 2006/0183779).

The undersigned declarant declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this May 5th, 2016



Ziauddin TYEBJI

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/379,613	Filing Date 08/19/2014	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **06/01/2016**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 17	Minus	** 20	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**0**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/HENRIETT K. DENDY/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

CONSIDERED: /L.M.B/

03/07/2016

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		Docket No.:	ESTEVE 6 PCT US
Applicant(s):	Pilgaonkar, et al.	Examiner:	Beckhardt, Lyndsey Marie
Application No.:	14/379,613	Art Unit:	1613
U.S. Filing Date:	August 19, 2014	Conf. No.:	6655
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	Customer No.:	25666

DECLARATION UNDER 37 CFR 1.132 IN U.S. PATENT APPLICATION NO. 14/379,613

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

I, Anilkumar S. Gandhi, Ph.D. a citizen of India and residing at A-403, Shreenath Complex, P.K. Extension Road, Near Raja Industries, Mulund (West), MUMBAI - 400080, India, as Applicant, do hereby state:

1. THAT I am a co-inventor of the invention described and claimed in the above-identified patent application. I am submitting this declaration in support of the patentability of the claims of the application.

2. I received a Doctor of Philosophy degree from the Institute of Chemical Technology (ICT), Mumbai (previously known as University Department of Chemical Technology, UDCT) in 2002.

3. I have worked since March 2002 at Rubicon Research Pvt. Ltd. I currently serve as Director, Operations at Rubicon Research Pvt. Ltd., the assignee of the present application. I was previously Group Leader, Formulation Development from March 2002 to March 2005; Manager, Product Innovations from April 2005 to March 2008; Sr. Manager, IP and Formulation Research from May 2008 to August 2010; General Manager, IP & Formulation Research from September 2010 to March 2012

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and Director, Product Innovations from April 2012 to April 2013 at Rubicon Research Pvt. Ltd. I am responsible for leading operations and product development activities for various projects, supporting business development activities of the Organization, ensuring compliance to system SOPs, technical problem solving and driving continuous improvement and process excellence. Additionally I am co-inventor of more than 40 patent applications and co-author of more than 30 research publications and scientific presentations in the field of pharmaceutical drug delivery.

4. Under my supervision and/or with my participation, the experiments described below were carried out which illustrate the advantages of the presently claimed compositions.

5. Experiments were performed comparing the stability of compositions comprising dabigatran etexilate particles and coated organic acid particles (according to the present invention) and compositions without said coating. The stability studies were performed exposing the formulations to 40 °C and 75% relative humidity (RH) for up to 4 weeks in closed vials.

Formulation	*Initial*	*After 4 weeks*
Example 1 of the present application (i.e. coated tartaric acid pellets)	Light yellow free flowing powder	NC
Example 1 of the present application but with uncoated tartaric acid pellets	Light yellow free flowing powder	Stuck to the bottom of the vial

NC = no change

Sticky agglomerations were observed when uncoated tartaric acid pellets were used in combination with uncoated dabigatran etexilate mesylate granules, whereas the composition according to the present invention (comprising at least one type of particles coated with a protective coating layer) were stable at the tested conditions.

6. The stability of the above formulations was also assessed by analyzing the impurity content of said formulations after storage for up to 4 weeks at 40 °C and 75% RH.

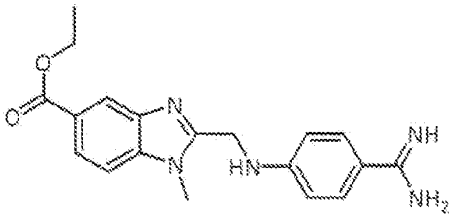
Formulation	*Storage conditions*	*Impurity A*	*Impurity B*	*Unspecified impurity*	*Total impurity*
Impurity limits	-	0.2%	0.2%	0.2%	1.0%

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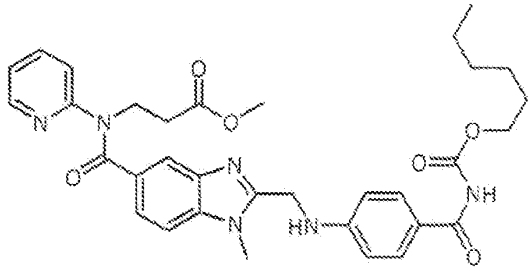
Example 1 of the present application (i.e. coated tartaric acid pellets)	Initial	ND	0.03	0.03	0.19
	After 4 weeks	0.03	0.07	0.05	0.13
Example 1 of the present application but with uncoated tartaric acid pellets	Initial	ND	0.03	0.11	0.32
	After 4 weeks	**0.46**	**3.28**	**0.56**	**7.19**

ND = not detected; BQL = below quantification limit

Impurities A and B have the chemical structure shown below:



Impurity A



Impurity B

The results gathered in the table above show that compositions that do not comprise at least one type of particles (the dabigatran etexilate particles or the organic acid particles) coated with a protective coating layer had a higher increase in the impurity content, even above the established impurity limits, when compared to the compositions according to the present invention, wherein at least one type of particles are coated with a protective coating layer.

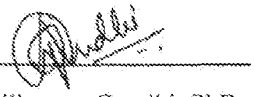
7. The undersigned declarant declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code

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and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: December 17, 2015

Respectfully submitted,

By: 

Anilkumar Gandhi, PhD

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S42	1	("20060074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 10:34
S41	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 10:34
S84	1	("20060074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S83	0	("2006074056").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S82	1	("20060183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S81	0	("200600183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S80	0	("200600183779").PN.	USPAT; USOCR	OR	OFF	2016/03/07 12:35
S79	0	("20060183779").PN.	USPAT; USOCR	OR	OFF	2016/03/07 12:35
S78	1	"14379613"	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S77	2	S76 and dabigatran	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S76	35	S73 or S74 or S75	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S75	29	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S74	31	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S73	34	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB;	OR	OFF	2016/03/07 12:35

			USPAT			
S72	1	"14379613"	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S71	5263	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	ADJ	OFF	2016/03/07 12:35
S70	7	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend) same organic acid	US-PGPUB; USPAT	ADJ	OFF	2016/03/07 12:35
S69	1934962	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend) same organic acid	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S68	5263	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S67	35181	(drug or active or pharmaceutical) same (particle or microsphere) same (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S66	57	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle) same (types or separate or distinct)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S65	1695	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S64	1695	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S63	82	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle) and multiparticulate	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S62	7168	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S61	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S60	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S59	38283	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S58	1768162	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S57	7	((landerer) near2 (sabine)).INV.	US-	OR	OFF	2016/03/07

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MSN Exhibit 1002
Page 452 of 680

			PGPUB; USPAT			12:35
S56	10	((brauns) near2 (ulrich)).INV.	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S55	2	(("20060183779") or ("20110129538")).PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S54	1	("20080039391").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S53	1	("20050038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S52	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S51	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2016/03/07 12:35
S50	6	S47 and particle same acid	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S49	22	S47 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S48	2	S47 and dabigatran	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S47	35	S43 or S44 or S45	US-PGPUB; USPAT; USOCR	OR	OFF	2016/03/07 12:35
S46	4	S43 or S44 or S45	USPAT	OR	OFF	2016/03/07 12:35
S45	29	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S44	31	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35
S43	34	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2016/03/07 12:35

EAST Search History (Interference)

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3/7/2016 2:48:23 PM
C:\Users\Ishaak\Documents\EAST\Workspaces\14379613.wsp

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MSN Exhibit 1002
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14379613	PILGAONKAR ET AL.
	Examiner	Art Unit
	LYNDSEY BECKHARDT	1613

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
	No Classified Search		

SEARCH NOTES		
Search Notes	Date	Examiner
East (keyword and Inventor) see attached	9/24/2015	LMB
Google (keyword) see attached East search terms	9/24/2015	LMB
East (keyword and Inventor) see attached	3/7/2016	LMB
Google (keyword) see attached East search terms	3/7/2016	LMB

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US	6655

25666 7590 03/23/2016
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EXAMINER	
BECKHARDT, LYNDSEY MARIE	

ART UNIT	PAPER NUMBER
1613	

MAIL DATE	DELIVERY MODE
03/23/2016	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/379,613	Applicant(s) PILGAONKAR ET AL.	
	Examiner LYNDSEY BECKHARDT	Art Unit 1613	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/29/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *21,23-30 and 32-39* is/are pending in the application.

5a) Of the above claim(s) *33-39* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *21, 23-30 and 32* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Claims 21, 23-30, 32-39 are currently pending. Claims 21, 23-30 and 32 are currently under examination.

Examiner's Note

Unless otherwise indicated, previous objection/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the 12/29/2015 response will be addressed to the extent they apply to current rejection(s).

Modified Rejections:

The following rejections are modified based on Applicant's claim amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21, 23-30 and 32 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US 2006/0183779 (previously applied) in view of US 2008/0069891 (previously applied) as evidenced by PubChem (PubChem, Dabigatran Etexilate, (accessed 03/21/2016), pgs. 1-25).

Regarding claim 21, the limitation of a composition comprising a) particles that comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salts; and b) particles that comprise at least one pharmaceutically acceptable organic acid is met by active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-mthyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmaceutically acceptable salts thereof (abstract), wherein PubChem evidences the structure of the ‘779 publication

[0003] is Dabigatran etexilate (page 1, right column, page 3, structure). The '779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1).

The limitation of wherein at least one type of particles is coated with a protective coating layer is met by the '779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]).

Regarding claim 23, the limitation of further comprising at least one pharmaceutically acceptable excipient is met by the '779 publication teaching polymer selected from gum Arabic included in the particles [0012]. The '779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient.

Regarding claims 24-25, the limitation of wherein the first type of particles is free from acids is met by the '779 publication teaching spatial separation of the organic acid and the active substance, wherein the organic acid and the active agent are taught to be in a particle ([0010], [0011]).

Regarding claim 26, the limitation of comprising from 0.01 wt% to 90% of dabigatran etexilate (expressed as dabigatran etexilate mesylate) is met by the '779 publication teaching dabigatran etexilate (abstract, [003]) wherein the active agent is taught to be present at 5-60% [0014].

Regarding claims 27 and 30, the limitation of wherein at least 90% by weight of the organic acid present in the composition is contained in the second type of particles

and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients and 2-95% of the at least one pharmaceutically acceptable organic acid is met by the '779 publication teaching 30-100% of the organic acid in the core [0012].

Regarding claims 28 and 29, the limitation of wherein the first type of particles is coated with a protective coating layer and the second type of particle is coated with a protective coating layer is met by the '779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]).

Regarding claim 32, the limitation of wherein the composition comprises form 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

The '779 publication does not specifically teach components a) and b) in two distinct types of particles (claim 21).

The '891 publication teaches a pharmaceutical composition may include granulate including at least one active pharmaceutical ingredient. The composition may include a coating on the granulate. The composition further comprises a second particle comprising a fat/wax. The granulate are formed into various dosage forms (abstract, [0018]). The invention comprises two particles, the first type containing the pharmaceutical agent and the second comprising fat/wax material [0020].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the '779

publication as two distinct particles as the ‘891 publication teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the ‘779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the ‘779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the ‘891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the ‘779 publication could be via the layers taught by the ‘779 publication or through the use of separate particles as taught by the ‘891 publication.

Response to Arguments:

Applicant’s arguments have been fully considered and are not deemed to be persuasive.

Applicant argues the instant amendments remove the terms solvates and hydrates from instant claim 1. Additionally the instant specification teaches two polymorph forms thus the written description rejection is overcome.

In response, Examiner has found Applicant’s arguments and amendments persuasive and the Written Description rejection has been withdrawn.

Regarding the 102(b) rejection over the '779 publication, Applicant argues the instant claims have been amended to specify two distinct types of particles. The '779 publication does not teach two distinct types of particles and thus the rejection should be withdrawn.

In response, the 102(b) rejection over the '779 publication has been withdrawn based on Applicant's amendments to specify two distinct types of particles.

- 103 rejection over the '779 publication and the '891 publication

Applicant argues the instant claims have been amended to specify two distinct types of particles. The '891 publication discloses the present invention may be a pharmaceutical composition comprising two particles. The two distinct types of particles in the '891 publication has the function of limiting the extent of solvent access to the active particles. One skilled in the art would not have been motivated to modify the composition disclosed in the '779 publication based on the generic disclosure in the '891 publication that a composition may comprise an API in the first particle and a fat/wax material in the second particle and have any reasonable expectation of success.

In response, the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time

the invention was made that the separation of the organic acid and the active agent described by the ‘779 publication could be via the layers taught by the ‘779 publication or through the use of separate particles as taught by the ‘891 publication.

Applicant argues improved stability as demonstrated by the declaration by Anikumar S Gandhi.

In response, the declaration is addressed below.

Applicant argues the coating in the '779 publication refers to the presence of a protective coating layer as the outermost layer which serves to reduce any increase in abrasion during packaging into capsules or insulating layer separating the organic acid and the active substance which increases the durability of the finished product.

In response, the instant claims require a protective coating layer. As recited by Applicant the ‘779 publication does teach a protective coating layer to reduce abrasion, thus meeting the claim limitation.

Applicant argues the '779 publication does not teach two distinct types of particles wherein at least one type of particles is coated with a protective coating layer.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The ‘779 publication teaches particles containing the claimed active separated into layers with the organic acid (Figure 1, [0007]). The ‘891 publication teaches

granulate composition wherein coated granules comprise active agent and a second particle comprises a fat/wax (abstract, [0018]).

Applicant argues the '891 publication discloses a coating to improve crush-resistance of the formulations.

In response, coating to improve crush resistance would meet the instant claim limitations of 'protective coating layer'.

37 CFR 1.132 Declaration

The examiner acknowledges receipt of the Declaration under 37 CFR 1.132 by Anilkumar Gandhi filed on 12/29/2015.

The Declaration under 37 CFR 1.132 filed 12/29/2015 is insufficient to overcome the rejection of claims 21, 23-30 and 32 based upon obviousness over the '779 publication and the '891 publication as set forth in the last Office action because:

Declarant presents data regarding Example 1 of the present application with coated tartaric acid pellets compared to uncoated tartaric acid pellets, wherein the coated tablets do not stick to the bottom of the vial after 4 weeks of storage as a sticky agglomerate and have stability with lower formation of two tested impurities.

In response, the instant claims are directed to at least one type of the particles to be coated with a protective coating layer, wherein only instant claim 29 contains limitations of wherein the particle containing the organic acid contains the protective coating layer. Thus the presented results pertain only to claim 29, as the remainder of the examined claims do not require the acid containing particles to be coated, but rather the coating could be applied over either particle.

Further it is noted that the instant tested examples are directed to one specific coating material, hydroxypropyl cellulose and talc, whereas the instant claims are broadly directed to protective coating layer, and thus are not commensurate in scope.

Additionally the ‘779 publication teaches the use of an insulating layer over the organic acid (reading on protective layer) and a coating layer outside the active substance layer (Figure 1). The insulating layer includes hydroxypropyl cellulose [0013] and the coating layer may also be hydroxypropyl cellulose [0015]. Thus the ‘779 publication teaches the use of the hydroxypropyl cellulose is known to be used as a coating layer over the acid containing particle and additionally over the active agent containing layer. Further the use of insulating layer is so the organic acid does not go into solution until after the preparation has been taken [0011]. Thus the use of a coating layer containing the hydroxypropyl cellulose was known to stabilize the acid in the formulation.

Applicant has not compared the closet prior art to the claimed invention, as the closet prior art comprises the coating layers, wherein the active agent and the acid are in different layers of the same particles. Therefore the difference is in the particle being layered vs two separate particles, and is not regarding the protective layer being present.

In addition to the facts provided above, the examiner notes that the Affiant is the same as the Inventor of the instant application. Therefore, the Affiant has an interest in the outcome of the instant application.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949).

Upon consideration of the facts taught by the prior art and the information submitted by the Affiant, the balance of evidence indicates that the prior art teaches the instantly claimed inventions.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached on Monday thru Thursday 7:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on (571) 272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LYNDSEY BECKHARDT/
Examiner, Art Unit 1613

/DENNIS J PARAD/
Primary Examiner, Art Unit 1612

Notice of References Cited	Application/Control No. 14/379,613	Applicant(s)/Patent Under Reexamination PILGAONKAR ET AL.	
	Examiner LYNDSEY BECKHARDT	Art Unit 1613	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A	US-				
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	PubChem, Dabigatran Etexilate, (accessed 03/21/2016), pgs. 1-25
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

* * * * *

Applicants : Pratibha S. PILGAONKAR, Maharukh T. RUSTOMJEE, and Anilkumar S. GANDHI

Serial No. : 14/379,613

Filed : 19 August 2014

Title : ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Art Unit : 1613

Examiner : LYNDSEY MARIE BECKHARDT, Esq.

* * * * *

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT UNDER 37 CFR §§ 1.111 AND 1.115

AND

PRESENTATION OF A DECLARATION UNDER 37 CFR § 1.132

Sir:

Responsive to the Office Action, dated 30 September 2015, kindly amend as follows.

IN THE CLAIMS: See Listing of Claims. This listing will replace all prior versions of claims in the application.

REMARKS

The Applicants acknowledge the Examiner's comprehensive Office Action with appreciation. Claims 21-39 are pending in the application; however, Claims 33-39 have been withdrawn from consideration as a result of the previously issued Restriction Requirement. The Office raises rejections under USC § 112, first and second paragraphs, as well as prior art rejections under 35 USC § 102 and 35 USC § 103. The Office also raises formalistic objections.

The Office states that Claim 31 is objected to under 37 CFR §1.75 as being a substantial duplicate of Claim 27. With the instant Amendment, Claim 31 has been cancelled. Withdrawal of the objection is respectfully requested.

Claims 21-32 are rejected for lack of written description under 35 USC § 112, first paragraph. It is the position of the Office that formulations comprising dabigatran etexilate in the form of polymorphs, solvates, or hydrates lack written description. The Office states that the instant specification does not disclose to which polymorphs, solvates, or hydrates the applicant is referring nor does the instant specification disclose how to make any particular polymorphs, solvates, or hydrates of dabigatran etexilate.

The Office cites the Vippagunta, et al. (*Adv. Drug Delivery Rev.*, **2001**, *48*, 3-26) and Müller (*Inorganic Structural Chemistry*, **1993**, 14-15) references to support its position regarding the unpredictability associated with preparing such compounds. It is the position of the Office that based on such lack of predictability and the lack of disclosure in the instant specification, one of ordinary skill in the art would conclude that the applicants were not in possession of any particular polymorph, solvate, or hydrate of dabigatran etexilate and that, therefore, the claims lack written description.

With the instant Amendment, the terms "solvates" and "hydrates" have been deleted from the claims.

The Applicants respectfully submit that the instant specification discloses (at page 5) that dabigatran etexilate mesylate exists in two anhydrous polymorphic forms, Forms I and II, which polymorphic forms are described in WO 2005/028468. Thus, the Applicants further submit that one skilled in the art would recognize that the applicant was in possession of polymorphic forms of dabigatran etexilate at the time the invention was made.

Claims 26-27 are rejected for indefiniteness under 35 USC § 112, second paragraph, based on the parenthetical expressions (i.e., "(expressed as dabigatran etexilate mesylate)" and "(if any)") recited in these claims. The Office states that it is unclear whether the limitations contained in the parentheses are required by these claims. The Office suggests that these claims be amended to recite the above-mentioned limitations using commas rather than parentheses. With the instant Amendment, Claims 26 and 27 have been amended as suggested by the Office.

The Applicants respectfully submit that the instant claims, as presently amended, comply with the requirements of 35 USC § 112, first and second paragraphs. Reconsideration and withdrawal of the rejections under 35 USC § 112, first and second paragraphs, is respectfully requested.

Claims 21-23 and 26-32 are rejected under 35 USC § 102(b) as being anticipated by the disclosure of US 2006/0183779, as evidenced by Wikipedia (Wikipedia, Dabigatran, 25 September 2015, pages 1-4).

The Office states that the '779 publication discloses that dabigatran etexilate combined with organic acids provides improved formulation. The Office further states that the '779 publication discloses pellets comprising a core containing an organic acid, a separating layer, and a layer containing the active substance (specifically citing paragraph [0010] and Figure 1 of the '779 publication). The Office goes on to state that the '779 publication discloses "multiple particles" used in a capsule formulation (specifically citing paragraph [0072]) which meets the limitation

"two types of particles" recited in instant Claim 21 since the instant claims "do not make the distinction between the two particles being different."

The Office goes on to allege that the '779 publication meets the limitations of dependent Claims 22-23 and 26-32 as discussed in detail at pages 7-8 of the instant Office Action.

With the instant Amendment, Claim 21 has been amended to recite "two ***distinct*** types of particles" to clarify the meaning of the instant claims. Claim 21 has also been amended to incorporate the limitation of Claim 22 (i.e., wherein at least one type of particles is coated with a protective coating layer), and Claim 22 has been cancelled. Support for these amendments may be found throughout the originally filed specification (including in the specific examples disclosed) and claims, and the Applicants respectfully submit that no new matter has been introduced by these amendments.

The Applicants respectfully submit that (as acknowledged by the Office at page 11 of the instant Office Action, in its discussion with respect to the obviousness rejection) the '779 publication does not disclose compositions comprising two distinct types of particles wherein one type of particles comprises dabigatran etexilate, or a pharmaceutically acceptable salt or polymorph thereof, and another type of particles comprises at least one pharmaceutically acceptable organic acid.

The Applicants further submit that, since the '779 publication does not meet all the limitations of the instant claims, as presently amended, the instant claims are not anticipated by the disclosure of the '779 publication. Reconsideration and withdrawal of the anticipation rejection under 35 USC § 102(b) is respectfully requested.

Claims 21-32 are further rejected for obviousness under 35 USC § 103(a) based on the disclosure of US 2006/0183779 in view of US 2008/0069891, as evidenced by Wikipedia (Wikipedia, Dabigatran, 25 September 2015, pages 1-4). The Office reiterates its position that the '779 publication discloses that dabigatran etexilate

combined with organic acids provides improved formulation. The Office further reiterates that the '779 publication discloses pellets comprising a core containing an organic acid, a separating layer, and a layer containing the active substance (specifically citing paragraph [0010] and Figure 1 of the '779 publication).

The Office acknowledges that the '779 publication does not specifically disclose instant components a) and b) in two types of particles; however, it is the position of the Office that this deficiency is cured by the '891 publication.

The Office states that the '891 publication discloses a pharmaceutical composition which may include granulate including at least one pharmaceutical ingredient, which composition may include a coating on the granulate. The Office goes on to state that the disclosed composition may further comprise a second particle comprising a fat/wax and that the composition may be formed into various dosage forms. The Office further states that the invention disclosed in the '891 publication comprises two particles, the first type containing the pharmaceutical agent and the second comprising a fat/wax material.

It is the position of the Office that it would have been obvious to formulate the oral composition disclosed in the '779 publication as two distinct particles since the '891 publication discloses pharmaceutical compositions comprising two distinct particles, one of which includes a pharmaceutical agent. The Office states that one skilled in the art would have been motivated to do so since the '779 publication discloses the need for spatial separation of the organic acid and the active substance and that there would have been a reasonable expectation of success since the '779 publication discloses an oral pharmaceutical formulation in the form of particles and since the '891 publication discloses that it was known to formulate active agents and excipients for oral dosage forms in separate particles.

As discussed above, the instant claims, as presently amended, recite the limitation two ***distinct*** types of particles, one type comprising dabigatran etexilate or a

pharmaceutically acceptable salt or polymorph thereof, and another type comprising at least one pharmaceutically acceptable organic acid, which limitation is not taught or suggested by the '779 publication.

Moreover, the '891 publication discloses (at paragraph [0020], which is specifically cited by the Office) "the present invention may be a pharmaceutical composition comprising two particles. The first particle comprises an API in a pharmaceutically effective amount wherein the first particle is coated with a polymer. The second particle comprises a fat/wax material present in an amount sufficient to inhibit administration abuse of the API from the first particle."

The provision of the of two distinct types of particles in the formulations disclosed in the '891 publication has the function of limiting the extent of solvent access to the active particles and, thus, it may help to retain the release rate consistent with the initial desired rate of active ingredient release, thereby frustrating dose dumping attempts associated with abuse (see paragraphs [0110], [0111], and [0117] of the '891 publication).

The Applicants respectfully submit that one skilled in the art would not have been motivated to modify the compositions disclosed in the '779 publication based on the generic disclosure in the '891 publication that a composition may comprise an API in a first particle and a fat/wax material (to inhibit administration of abuse of the API) in a second particle, to arrive at the instantly claimed compositions with any reasonable expectation of success.

The Applicants further submit that the instant claims, as presently amended, require that at least one of the two distinct types of particles is coated with a protective coating layer.

The instantly claimed compositions provide ***improved stability*** of dabigatran etexilate, as demonstrated by the comparative data provided in the enclosed Declaration by Anilkumar S. GANDHI, a scientist skilled in this particular art.

Specifically, the Declarant provides comparative experimental evidence demonstrating the improved stability of compositions comprising dabigatran etexilate particles and coated organic acid particles (according to the present invention) compared to compositions without said coating. The comparative data are discussed in detail in sections 5 and 6 of the GANDHI Declaration.

The Applicants respectfully submit that the provision of a coating in the '779 publication (teaching compositions comprising only one type of particles) refers a) to the presence of a protective coating layer as an outermost layer, which serves to reduce any increased abrasion during packaging into capsules (see paragraphs [0010], [0015]), or b) to an insulating layer separating the organic acid and active substance, which increases the durability of the finished product (see paragraph [0013]).

The aim of the compositions disclosed in the '779 publication is to provide an improved galenic form of dabigatran etexilate. This is achieved by using pharmaceutically acceptable organic acids with a specific solubility in water (see paragraphs [0006]-[0007] of the '779 publication). Moreover, the examples of the '779 publication relate to tablets comprising both dabigatran etexilate mesylate and tartaric acid, which tablets were prepared by directly mixing and compressing the ingredients or by dry granulation and compression (see Examples 1-2 of the 779 publication), i.e., dabigatran etexilate and the organic acid are mixed together without providing any coating.

The '779 publication discloses (at paragraphs [0029] and [0034]-[0035]) that one advantage of the disclosed formulations is that they guarantee sufficient bioavailability of the active substance, which is better than that obtained with a conventional pharmaceutical preparation.

This disclosure does not teach or suggest that the instantly claimed compositions, which comprise two ***distinct*** types of particles, wherein at least one type of particles is coated with a protective coating layer, would result in compositions having improved stability of the active ingredient.

The Applicants respectfully submit that the provision of a coating in the '891 publication is to improve the crush-resistance of the formulations to provide an increase to possible abuse by crushing the resulting particles (see, for example, paragraph [0024] of the '891 publication).

This disclosure does not teach or suggest that the instantly claimed compositions, which comprise two ***distinct*** types of particles, wherein at least one type of particles is coated with a protective coating layer, would result in compositions having improved stability of the active ingredient.

Therefore, the Applicants respectfully submit that one skilled in the art would not have expected the ***improved stability*** of dabigatran etexilate provided by the instantly claimed compositions based on the disclosure of the '779 publication and/or the '891 publication.

The Applicants respectfully submit that the superior and unexpected effects associated with the instantly claimed compositions ***further distinguish*** the instant claims over the disclosure of the '779 and '891 publications.

In view of the foregoing, the Applicants respectfully submit that the instant claims are not rendered obvious by the references of record in the instant application. Reconsideration and withdrawal of the obviousness rejection under 35 USC § 103(a) is respectfully requested.

Finally, in accordance with with MPEP § 821.04, the Applicants request rejoinder of withdrawn Claims 33-39 upon the identification of allowable subject matter.

* * * * *

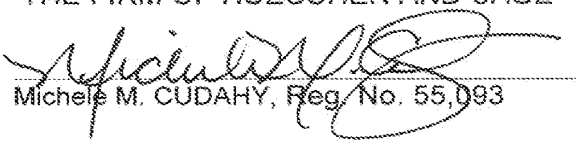
Accordingly, entry of the present amendment and the GANDHI Declaration, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned agent has made an earnest effort to place this application into condition for immediate allowance. If she can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call her at her below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE



Michele M. CUDAHY, Reg. No. 55,093

Dated : 29 December 2015
Customer No. : 25,666

Seventh Floor, Kalamazoo Building
107 West Michigan Avenue
Kalamazoo, MI 49007
(269) 382-0030

Enclosure(s) : GANDHI Declaration
Listing of Claims

* * * * *

THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.

LISTING OF CLAIMS

1-20 (canceled)

21. (currently amended) A composition comprising a mixture of at least two distinct types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or ~~salts, polymorph[[s,]] solvates or hydrates~~ thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein at least one type of particles is coated with a protective coating layer.

22. (canceled)

23. (previously presented) The composition according to claim 21, further comprising at least one pharmaceutically acceptable excipient.

24. (previously presented) The composition according to claim 21, wherein the first type of particles is free from acids.

25. (previously presented) The composition according to claim 21, wherein the second type of particles is free from dabigatran etexilate.

26. (currently amended) The composition according to claim 21, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, (expressed as dabigatran etexilate mesylate).

27. (currently amended) The composition according to claim 21, wherein at least 90% by weight of the organic acid present in the composition is contained in the second type of particles and the rest, (if any), of the organic acid forms part of the pharmaceutically acceptable excipients.

28. (previously presented) The composition according to claim 21, wherein the first type of particles is coated with a protective coating layer.

29. (previously presented) The composition according to claim 21, wherein the second type of particles is coated with a protective coating layer.

30. (previously presented) The composition according to claim 21, comprising from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

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31. (canceled)

32. (previously presented) A unit dosage form prepared from the composition according to claim 21, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

33. (withdrawn) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a composition according to claim 21.

34. (withdrawn) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a unit dose according to claim 32.

35. (withdrawn) A process for the preparation of the composition according to claim 23, comprising the step of mixing the first type of particles and the second type of particles with the at least one at least one pharmaceutically acceptable excipient.

36. (withdrawn) The process of claim 35, wherein the first type of particles are prepared by granulation.

37. (withdrawn – currently amended) The process according to claim 36, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable ~~salts,~~ salt or polymorph[[s,]] ~~solvates or hydrates~~ thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

v) coating the organic acid granules with a protective coating layer;

vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

38. (withdrawn – currently amended) The process according to claim 36, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable ~~salts,~~ salt or polymorph[[s,]] ~~solvates or hydrates~~ thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

v) coating the granules of dabigatran etexilate with a protective coating layer;

vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

39. (withdrawn – currently amended) The process according to claim 36, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable ~~salts,~~ salt or polymorph[[s,]] ~~solvates or hydrates~~ thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

v) coating the organic acid pellets of step (iv) with a protective coating layer;

vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		Docket No.:	ESTEVE 6 PCT US
Applicant(s):	Pilgaonkar, et al.	Examiner:	Beckhardt, Lyndsey Marie
Application No.:	14/379,613	Art Unit:	1613
U.S. Filing Date:	August 19, 2014	Conf. No.:	6655
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	Customer No.:	25666

DECLARATION UNDER 37 CFR 1.132 IN U.S. PATENT APPLICATION NO. 14/379,613

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

I, Anilkumar S. Gandhi, Ph.D, a citizen of India and residing at A-403, Shreenath Complex, P.K. Extension Road, Near Raja Industries, Mulund (West), MUMBAI - 400080, India, as Applicant, do hereby state:

1. THAT I am a co-inventor of the invention described and claimed in the above-identified patent application. I am submitting this declaration in support of the patentability of the claims of the application.

2. I received a Doctor of Philosophy degree from the Institute of Chemical Technology (ICT), Mumbai (previously known as University Department of Chemical Technology, UDCT) in 2002.

3. I have worked since March 2002 at Rubicon Research Pvt. Ltd. I currently serve as Director, Operations at Rubicon Research Pvt. Ltd., the assignee of the present application. I was previously Group Leader, Formulation Development from March 2002 to March 2005; Manager, Product Innovations from April 2005 to March 2008; Sr. Manager, IP and Formulation Research from May 2008 to August 2010; General Manager, IP & Formulation Research from September 2010 to March 2012

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and Director, Product Innovations from April 2012 to April 2013 at Rubicon Research Pvt. Ltd. I am responsible for leading operations and product development activities for various projects, supporting business development activities of the Organization, ensuring compliance to system SOPs, technical problem solving and driving continuous improvement and process excellence. Additionally I am co-inventor of more than 40 patent applications and co-author of more than 30 research publications and scientific presentations in the field of pharmaceutical drug delivery.

4. Under my supervision and/or with my participation, the experiments described below were carried out which illustrate the advantages of the presently claimed compositions.

5. Experiments were performed comparing the stability of compositions comprising dabigatran etexilate particles and coated organic acid particles (according to the present invention) and compositions without said coating. The stability studies were performed exposing the formulations to 40 °C and 75% relative humidity (RH) for up to 4 weeks in closed vials.

Formulation	*Initial*	*After 4 weeks*
Example 1 of the present application (i.e. coated tartaric acid pellets)	Light yellow free flowing powder	NC
Example 1 of the present application but with uncoated tartaric acid pellets	Light yellow free flowing powder	Stuck to the bottom of the vial

NC = no change

Sticky agglomerations were observed when uncoated tartaric acid pellets were used in combination with uncoated dabigatran etexilate mesylate granules, whereas the composition according to the present invention (comprising at least one type of particles coated with a protective coating layer) were stable at the tested conditions.

6. The stability of the above formulations was also assessed by analyzing the impurity content of said formulations after storage for up to 4 weeks at 40 °C and 75% RH.

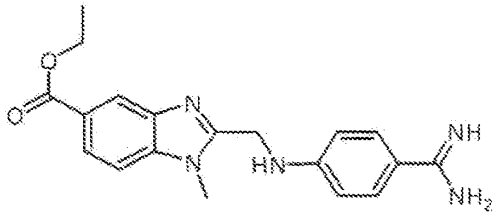
Formulation	*Storage conditions*	*Impurity A*	*Impurity B*	*Unspecified impurity*	*Total impurity*
Impurity limits	-	0.2%	0.2%	0.2%	1.0%

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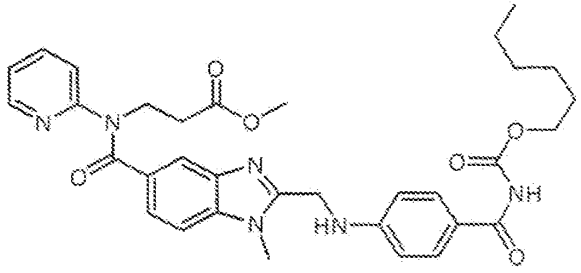
Example 1 of the present application (i.e. coated tartaric acid pellets)	Initial	ND	0.03	0.03	0.19
	After 4 weeks	0.03	0.07	0.05	0.13
Example 1 of the present application but with uncoated tartaric acid pellets	Initial	ND	0.03	0.11	0.32
	After 4 weeks	**0.46**	**3.28**	**0.56**	**7.19**

ND = not detected; BQL = below quantification limit

Impurities A and B have the chemical structure shown below:



Impurity A



Impurity B

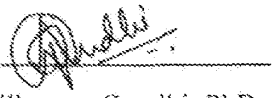
The results gathered in the table above show that compositions that do not comprise at least one type of particles (the dabigatran etexilate particles or the organic acid particles) coated with a protective coating layer had a higher increase in the impurity content, even above the established impurity limits, when compared to the compositions according to the present invention, wherein at least one type of particles are coated with a protective coating layer.

7. The undersigned declarant declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code

and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: December 17, 2015

Respectfully submitted,

By: 

Anilkumar Gandhi, PhD

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Electronic Acknowledgement Receipt

EFS ID:	24475674
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	25666
Filer:	George Patrick Sage/Michele Cudahy
Filer Authorized By:	George Patrick Sage
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	29-DEC-2015
Filing Date:	19-AUG-2014
Time Stamp:	11:35:50
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	RESPONSE_29DEC15.pdf	5233471 895359549360c8350b67d475231e80b9f6dce2ff	no	9
Warnings:					
Information:					

2	Claims	CLAIMS_29DEC15.pdf	1980127 baa9ec7b555722328d4f0fc162a4962b3c59437f	no	4
Warnings:					
Information:					
3	Affidavit-traversing rejectns or objectns rule 132	132_DEC_29DEC15.pdf	1885407 3f32317f5075f660700876082fd9a01764ba19a3	no	4
Warnings:					
Information:					
			Total Files Size (in bytes):	9099005	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/379,613	Filing Date 08/19/2014	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/29/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 17	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US	6655

25666 7590 09/30/2015
THE FIRM OF HUESCHEN AND SAGE
SEVENTH FLOOR, KALAMAZOO BUILDING
107 WEST MICHIGAN AVENUE
KALAMAZOO, MI 49007

EXAMINER	
BECKHARDT, LYNDSEY MARIE	

ART UNIT	PAPER NUMBER
1613	

MAIL DATE	DELIVERY MODE
09/30/2015	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/379,613	Applicant(s) PILGAONKAR ET AL.	
	Examiner LYNDSEY BECKHARDT	Art Unit 1613	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/27/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *21-39* is/are pending in the application.

5a) Of the above claim(s) *33-39* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *21-32* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☒ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *08/19/2014*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Claims 21-39 are currently pending. Claims 21-32 are currently under examination.

Election/Restrictions

Applicant's election without traverse of Group I, Tartaric acid and Lubricant in the reply filed on 07/27/2015 is acknowledged.

Claims 33-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07/27/2015.

Priority

The instant application is a national stage entry of PCT/EP2013/053426, filed 02/21/2013, which claims foreign priority to India application 461/MUM/2012, filed 02/21/2012.

Information Disclosure Statement

Applicant's Informational Disclosure Statement, filed on 08/19/2014 has been considered. Please refer to Applicant's copy of the 1449 submitted herein.

Claim Objections

Claim 31 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 27. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is

proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112 – first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 and dependent claims 22-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification, while complies with the written description requirement for a formulation comprising a dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts**,** does not reasonably comply with the written description requirement a formulation comprising dabigatran etexilate in the form of polymorphs, solvates or hydrates thereof.

Determination of Claim Scope

Claim 21 of the instant application claims a composition comprising dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof.

Review of Applicants' Disclosure

The instant specification does not disclose, to which polymorphs, solvates or hydrates of dabigatran etexilate applicants are referring. Applicants' specification does not disclose how to make any particular polymorphs, solvates or hydrates of dabigatran etexilate, nor do Applicants depict chemical structures of any particular polymorphs, solvates or hydrates of dabigatran etexilate in their disclosure.

Possession Based Ordinary Skilled Artisan's Determination/ State of the Prior Art

It is generally accepted in the art that the structure of a particular polymorph, solvate or hydrate for a given compound or series of compounds is unclear. It is also generally accepted in the art that the formation of a particular solvate or hydrate or crystal for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, 2001, *48*, pp 18), and which polymorphic form of a compound is form depends on the preparation and crystallization conditions: method of synthesis, temperature, pressure, kind of solvent, cooling or heating rate, crystallization from solution, fusion or gas phase, and presence of seed are some of the factors of influence (Müller, Inorganic Chemistry, page 14-15, 1993). In other words, one can't arbitrarily make these things so they have to disclose to us how they did it. Therefore, an ordinary skilled artisan would conclude that Applicants were not in possession of any particular polymorph, solvate or hydrate of corresponding to any one or more dabigatran etexilate. Furthermore, because Applicants' generic reference to particular polymorph, solvate or hydrate does not permit the ordinary skilled artisan to clearly envisage what specific any one or more of dabigatran etexilate were in Applicants' possession, the only reasonable conclusion

said artisan would make was that Applicants were not in possession of a particular polymorph, solvate or hydrate of any one or more of dabigatran etexilate and had not reduced to practice the preparation, isolation, and characterization of said particular polymorph, a solvate and a hydrate of one or more of dabigatran etexilate.

In conclusion, the instant claim 21 and dependent claims 22-32 fails to comply with the written description requirement.

Claim Rejections - 35 USC § 112 – second paragraph

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-27 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 26 contains the limitation of “from 0.01 wt% to 90 wt% of dabigatran etexilate (expressed as dabigatran etexilate mesylate)”. It is unclear if the limitations contained in the parenthesis are required by the claim.

Claim 27 contains the limitation of “in the second type of particles and the rest (if any) of the organic acids forms part of the pharmaceutically acceptable excipients”. It is

unclear if the limitations contained in the parenthesis are required by the claim. It is suggested Applicant use commas in place of the parenthesis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-23 and 26-32 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by US 2006/0183779 as evidenced by Wikipedia (Wikipedia, Dabigatran, (09/25/2015), pgs. 1-4).

Regarding claim 21, the limitation of a composition comprising a) particles that comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salts; and b) particles that comprise at least one pharmaceutically acceptable organic acid is met by active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-mthyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmaceutically acceptable salts thereof (abstract), wherein Wikipedia evidences the structure of the ‘779 publication [0003] is Dabigatran etexilate (page 1, right column). The ‘779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1). The ‘779 publication teaches multiple particles used in a capsule formulation [0072], which meets

the limitation for two types of particles as more than two particles are present, and the instant claims do not make the distinction between the two types of particles being different.

Regarding claim 22, the limitation of wherein at least one type of particles is coated with a protective coating layer is met by the ‘779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]).

Regarding claim 23, the limitation of further comprising at least one pharmaceutically acceptable excipient is met by the ‘779 publication teaching polymer selected from gum Arabic included in the particles [0012].

Regarding claim 26, the limitation of comprising from 0.01 wt% to 90% of dabigatran etexilate (expressed as dabigatran etexilate mesylate) is met by the '7‘9 publication teaching dabigatran etexilate (abstract, [003]) wherein the active agent is taught to be present at 5-60% [0014].

Regarding claims 27 and 30-31, the limitation of wherein at least 90% by weight of the organic acid present in the composition is contained in the second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients and 2-95% of the at least one pharmaceutically acceptable organic acid is met by the ‘779 publication teaching 30-100% of the organic acid in the core [0012].

Regarding claims 28 and 29, the limitation of wherein the first type of particles is coated with a protective coating layer and the second type of particle is coated with a

protective coating layer is met by the '779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]).

Regarding claim 32, the limitation of wherein the composition comprises form 50 mg to 200 mg of dabigatran etexilate mesylate is met by the '779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21-32 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US 2006/0183779 in view of US 2008/0069891 as evidenced by Wikipedia (Wikipedia, Dabigatran, (09/25/2015), pgs. 1-4).

Regarding claim 21, the limitation of a composition comprising a) particles that comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salts; and b) particles that comprise at least one pharmaceutically acceptable organic acid is met by active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-mthyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmaceutically acceptable salts thereof (abstract), wherein Wikipedia evidences the structure of the ‘779 publication [0003] is Dabigatran etexilate (page 1, right column). The ‘779 publication teaches dabigatran etexilate and organic acids provides a significantly improved formulation [0007]. Wherein the core of the pellet containing an organic acid, a separating layer followed by a layer containing the active substance ([0010], Figure 1).

Regarding claim 22, the limitation of wherein at least one type of particles is coated with a protective coating layer is met by the ‘779 publication teaching the optional outermost layer, which serves to reduce any increased abrasion during packing into capsules ([0013]-[0015]).

Regarding claim 23, the limitation of further comprising at least one pharmaceutically acceptable excipient is met by the ‘779 publication teaching polymer selected from gum Arabic included in the particles [0012]. The ‘779 publication teaches embodiments wherein talc is present (Table 1), wherein the instant specification teaches lubricants include talc [0053], the elected excipient.

Regarding claims 24-25, the limitation of wherein the first type of particles is free from acids is met by the ‘779 publication teaching spatial separation of the organic acid and the active substance, wherein the organic acid and the active agent are taught to be in a particle ([0010], [0011]).

Regarding claim 26, the limitation of comprising from 0.01 wt% to 90% of dabigatran etexilate (expressed as dabigatran etexilate mesylate) is met by the '7‘9 publication teaching dabigatran etexilate (abstract, [003]) wherein the active agent is taught to be present at 5-60% [0014].

Regarding claims 27 and 30-31, the limitation of wherein at least 90% by weight of the organic acid present in the composition is contained in the second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients and 2-95% of the at least one pharmaceutically acceptable

organic acid is met by the ‘779 publication teaching 30-100% of the organic acid in the core [0012].

Regarding claims 28 and 29, the limitation of wherein the first type of particles is coated with a protective coating layer and the second type of particle is coated with a protective coating layer is met by the ‘779 publication teaching the core layer containing an insulating layer and the drug coating layer containing a coating material to reduce abrasion ([0011], [0013], [0015]).

Regarding claim 32, the limitation of wherein the composition comprises form 50 mg to 200 mg of dabigatran etexilate mesylate is met by the ‘779 publication teaching the mesylate of the compound of form I, present at 50 mg in the capsules (Table 1, [0014], [0030]).

The ‘779 publication does not specifically teach components a) and b) in two types of particles (claim 21).

The ‘891 publication teaches a pharmaceutical composition may include granulate including at least one active pharmaceutical ingredient. The composition may include a coating on the granulate. The composition further comprises a second particle comprising a fat/wax. The granulate are formed into various dosage forms (abstract, [0018]). The invention comprises two particles, the first type containing the pharmaceutical agent and the second comprising fat/wax material [0020].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by the ‘779 publication as two distinct particles as the ‘891 publication teaches pharmaceutical

composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as the '779 publication teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as the '779 publication teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and the '891 publication teaches it was known to formulate active agents and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by the '779 publication could be via the layers taught by the '779 publication or through the use of separate particles as taught by the '891 publication.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached on Monday thru Thursday 7:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on (571) 272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LYNDSEY BECKHARDT/
Examiner, Art Unit 1613
/SCOTT LONG/
Primary Examiner, Art Unit 1633

Notice of References Cited	Application/Control No. 14/379,613	Applicant(s)/Patent Under Reexamination PILGAONKAR ET AL.	
	Examiner LYNDSEY BECKHARDT	Art Unit 1613	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2006/0183779 A1	08-2006	Brauns; Ulrich	C07D401/12	514/338
*	B	US-2008/0069891 A1	03-2008	Habib; Walid	A61K9/1652	424/494
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Vippagunta et al. "Crystalline Solids," Advanced Drug Delivery Reviews, (2001), 48, pgs. 3-26
	V	Müller, Inorganic Chemistry, (1993) pgs. 14-15
	W	Wikipedia, Dabigatran, (09/25/2015), pgs. 1-4
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

IPR2025-01107
MSN Exhibit 1002
Page 505 of 680

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CONFIRMATION NO. 6655

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/379,613	08/19/2014	424	1613	ESTEVE 6 PCT US

APPLICANTS

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INVENTORS

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Anilkumar S. Gandhi, Mumbai, INDIA;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP2013/053426 02/21/2013

**** FOREIGN APPLICATIONS ***************************

INDIA 461/MUM/2012 02/21/2012

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

10/16/2014

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /LYNDSEY MARIE BECKHARDT/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		INDIA	0	19	1

ADDRESS

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UNITED STATES

TITLE

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

FILING FEE RECEIVED		
1480	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14379613	PILGAONKAR ET AL.
	Examiner	Art Unit
	LYNDSEY BECKHARDT	1613

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
	No Classified Search		

SEARCH NOTES		
Search Notes	Date	Examiner
East (keyword and Inventor) see attached	9/24/2015	LMB
Google (keyword) see attached East search terms	9/24/2015	LMB

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/SCOTT LONG/ Primary Examiner, Art Unit 1633

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L6	0	("20060183779").PN.	USPAT; USOCR	OR	OFF	2015/09/25 10:56
L7	0	("200600183779").PN.	USPAT; USOCR	OR	OFF	2015/09/25 10:56
L8	0	("200600183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/25 10:56
L9	1	("20060183779").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/25 10:56
S1	31	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/21 09:45
S2	28	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/21 09:45
S3	26	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/21 09:45
S4	3	S1 or S2 or S3	USPAT	OR	OFF	2015/09/21 09:48
S5	32	S1 or S2 or S3	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/21 09:48
S6	2	S5 and dabigatran	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/21 09:49
S7	20	S5 and particle	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/21 10:09
S8	4	S5 and particle same acid	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/21 10:09
S9	0	("2005038077").PN.	USPAT; USOCR	OR	OFF	2015/09/21 10:38
S10	0	("2005038077").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/21 10:39
S11	1	("20050038077").PN.	US-PGPUB; USPAT;	OR	OFF	2015/09/21 10:39

			USOCR			
S12	1	("20080039391").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/21 10:50
S13	2	(("20060183779") or ("20110129538")).PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/21 11:14
S14	10	((brauns) near2 (ulrich)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/21 11:30
S15	7	((landerer) near2 (sabine)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/21 11:35
S16	1706484	(organic acid near5 particle)	US-PGPUB; USPAT	OR	OFF	2015/09/21 11:36
S17	36653	(organic acid near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2015/09/21 11:36
S18	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical) near3 particle)	US-PGPUB; USPAT	OR	OFF	2015/09/21 12:27
S19	6	(tartaric near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2015/09/21 12:27
S20	6858	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2015/09/21 12:31
S21	77	((tartaric or organic acid) near5 particle) and ((drug or active agent or pharmaceutical or dabigatran) near3 particle) and multiparticulate	US-PGPUB; USPAT	OR	OFF	2015/09/21 12:31
S22	1621	((tartaric or organic acid) near5 particle) same((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2015/09/21 12:51
S23	1621	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle)	US-PGPUB; USPAT	OR	OFF	2015/09/21 12:51
S24	56	((tartaric or organic acid) near5 particle) same ((drug or active agent or pharmaceutical or dabigatran) near3 particle) same (types or separate or distinct)	US-PGPUB; USPAT	OR	OFF	2015/09/21 12:52
S25	33811	(drug or active or pharmaceutical) same (particle or microsphere) same (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2015/09/24 07:57
S26	5011	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	OR	OFF	2015/09/24 07:57
S27	1879983	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture	US-PGPUB;	OR	OFF	2015/09/24 07:58

IPR2025-01107
MSN Exhibit 1002
Page 509 of 680

		or combination or dual or types or blend) same organic acid	USPAT			
S28	7	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend) same organic acid	US-PGPUB; USPAT	ADJ	OFF	2015/09/24 07:58
S29	5011	(drug or active or pharmaceutical) near10 (particle or microsphere) near10 (mixture or combination or dual or types or blend)	US-PGPUB; USPAT	ADJ	OFF	2015/09/24 08:00
S30	1	"14379613"	US-PGPUB; USPAT	OR	OFF	2015/09/24 16:26
S31	31	((Pratibha) near2 (Pilgaonkar)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/24 17:01
S32	28	((Maharukh) near2 (Rustomjee)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/24 17:01
S33	26	((Anilkumar) near2 (Gandhi)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/24 17:01
S34	32	S31 or S32 or S33	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/24 17:01
S35	2	S34 and dabigatran	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/24 17:01
S36	1	"14379613"	US-PGPUB; USPAT; USOCR	OR	OFF	2015/09/25 08:23

9/25/2015 11:05:48 AM
C:\Users\Ishaak\Documents\EAST\Workspaces\14379613.wsp

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14379613	PILGAONKAR ET AL.
	Examiner	**Art Unit**
	LYNDSEY BECKHARDT	1613

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/24/2015								
	21	✓								
	22	✓								
	23	✓								
	24	✓								
	25	✓								
	26	✓								
	27	✓								
	28	✓								
	29	✓								
	30	✓								
	31	✓								
	32	✓								
	33	N								
	34	N								
	35	N								
	36	N								
	37	N								
	38	N								
	39	N								

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	
Filing Date	August 21, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

U.S. PATENT DOCUMENTS

Examiner Initial *	Cite No.	Document Number Number - Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US 2005/038077	02-17-2005	KOHLRAUSCH	

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Cite No. 1	Foreign Patent Document Country[3] Code Number[4] Kind Code (if known)[5]	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear	T

Examiner Signature	/Lyndsey Beckhardt/	Date Considered	09/25/2015

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1. Applicant's unique citation design number (optional). 2 See Kinds Codes of USPTO patent Documents. at www.uspto.gov or MPEP 901.04. 3. Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5. Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. 6. Applicant is to place a check mark here if English language Translation is attached

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450 Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.M.B./

PTO/SB/08b (07-09)
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Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete If Known	
Application Number	
Filing Date	August 21, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

NON PATENT LITERATURE DOCUMENTS

Examiner Initial *	Cite No. 1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T 2
	2	INTERNATIONAL SEARCH REPORT FOR PCT/EP2013/053426 OF 16 APRIL 2013.	

Examiner Signature	/Lyndsey Beckhardt/	Date Considered	09/25/2015

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1. Applicants unique citation designation number (optional) 2. Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450 Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.M.B./

* * * * *

Applicants : Pratibha S. PILGAONKAR, Maharukh T. RUSTOMJEE, and Anilkumar S. GANDHI

Serial No. : 14/379,613

Filed : 19 August 2014

Title : ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Art Unit : 1613

Examiner : LYNDSEY MARIE BECKHARDT, Esq.

* * * * *

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND ELECTION UNDER 37 CFR §§ 1.111 AND 1.142

Sir:

Responsive to the Office Action, a Restriction Requirement, dated 2 June 2015, it is the position of the Office that the instant application lacks unity of invention and consists of three (3) distinct inventions: **Group I** (Claims 21-32), drawn to a composition comprising a mixture of two types of particles; **Group II** (Claims 33-34), drawn to a method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events; and **Group III** (Claims 35-39), drawn to a process for the preparation of the composition comprising a mixture of two types of particles.

It is the further position of the Office that the application contains claims directed to more than one species of the generic invention.

The Office states that the following species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under

PCT Rule 13.1: 1) organic acid; 2) excipient; 3) treatment; and 4) method of making. The Office further states that the applicant must elect a single disclosed specific organic acid; a single disclosed specific excipient, or combination of excipients; a single specific type of treatment; and a single disclosed method of making, including whether granulation or extrusion is used and whether the drug containing particles are coated and/or if the organic acid containing particles are coated.

With the instant Response, the Applicants elect **Group I** (Claims 21-32), drawn to a composition comprising a mixture of two types of particles.

With respect to the requirement for species elections, the Applicants presume that, since **Group I** has been elected, only organic acid and excipient species elections are required, and the Applicants elect "tartaric acid" as the species organic acid, and "lubricant" as the excipient species.

The Applicants note that Claims 21-32 encompass the elected organic acid species, and Claims 23, 27, and 31 encompass the elected excipient species.

It is assumed that the Office will continue to expand its search in the absence of relevant art.

Moreover, the Applicants further designate "venous thromboembolic event" as the treatment species and "granulation and the organic acid containing particles" as the method of making species to facilitate expansion of the search.

The Examiner may withdraw all non-elected method claims, without prejudice to their rejoinder during later examination and/or prosecution in a Divisional Application.

Accordingly, entry of the present Election into the record of this application and favorable action on the merits thereof, are respectfully solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

Michele M. CUDAHY, Reg. No. 55,093

Dated : 27 July 2015
Customer No. : 25,666

Seventh Floor, Kalamazoo Building
107 West Michigan Avenue
Kalamazoo, MI 49007
(269) 382-0030

* * * * *

THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.

Electronic Acknowledgement Receipt

EFS ID:	23026537
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	25666
Filer:	George Patrick Sage/Michele Cudahy
Filer Authorized By:	George Patrick Sage
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	27-JUL-2015
Filing Date:	19-AUG-2014
Time Stamp:	11:26:41
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	RESPONSE_ELECTION_27JUL15.pdf	1329103 3cbd0e2eeb402fac8cc92f28ec474c2b8f911f4f	no	3
Warnings:					
Information:					

Total Files Size (in bytes):	1329103

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/379,613	Filing Date 08/19/2014	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	07/27/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/JACQUELYN WILLIAMS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US	6655

25666 7590 06/02/2015
THE FIRM OF HUESCHEN AND SAGE
SEVENTH FLOOR, KALAMAZOO BUILDING
107 WEST MICHIGAN AVENUE
KALAMAZOO, MI 49007

EXAMINER	
BECKHARDT, LYNDSEY MARIE	

ART UNIT	PAPER NUMBER
1613	

MAIL DATE	DELIVERY MODE
06/02/2015	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/379,613	Applicant(s) PILGAONKAR ET AL.	
	Examiner LYNDSEY BECKHARDT	Art Unit 1613	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/19/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *21-39* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *21-39* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

IPR2025-01107
MSN Exhibit 1002
Page 521 of 680

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

REQUIREMENT FOR UNITY OF INVENTION

As provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. See 37 CFR 1.475(e).

WHEN CLAIMS ARE DIRECTED TO MULTIPLE CATEGORIES OF INVENTIONS

As provided in 37 CFR 1.475(b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Otherwise, unity of invention might not be present. See 37 CFR 1.475(c).

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 21-32, drawn to a composition comprising a mixture of two types of particles.

Group II, claim(s) 33-34, drawn to a method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events.

Group III, claim(s) 35-39, drawn to a process for the preparation of the composition comprising a mixture of two types of particles.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

1) Organic Acid: (elect a single disclosed specific organic acid).

2) Excipient: (elect a single disclosed specific excipient or a single disclosed specific combination of excipients).

3) Treatment: (elect a single specific type of treatment or a single specific combination of treatments from reducing the risk of stroke, systemic embolism and/or preventing venous thromboembolic events).

4) Method of making: (elect a single disclosed specific method of making, including the if granulation or extrusion is used and if the drug containing particles are coated and/or if the organic acid containing particles are coated).

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply

must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise require all the limitations of an allowed generic claim. Currently, the following claim(s) are generic: Claims 21-27, 30-35 are generic.

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I-III lack unity of invention because even though the inventions of these groups require the technical feature of a composition comprising a mixture of at least two types of particles wherein the first type comprises dabigatran etexilate and the second type of particles comprise at least one pharmaceutically acceptable organic acid, this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of US 2005/038077. The '077 publication teaches dabigatran etexilate ([0003], as evidenced by page 2, lines 5-15 of the instant specification). The composition is taught to be a powder mixture comprising the active substance and fumeric acid ([0022], [0029]).

A telephone call was not made to Applicant due to the complexity of the Restriction Requirement.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention or species.

Should applicant traverse on the ground that the inventions have unity of invention (37 CFR 1.475(a)), applicant must provide reasons in support thereof. Applicant may submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. Where such evidence or admission is provided by applicant, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the

product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDSEY BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached on Monday thru Thursday 7:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on (571) 272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LYNDSEY BECKHARDT/
Examiner, Art Unit 1613

/BRIAN-YONG KWON/
Supervisory Patent Examiner, Art Unit 1613

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US

CONFIRMATION NO. 6655

25666
THE FIRM OF HUESCHEN AND SAGE
SEVENTH FLOOR, KALAMAZOO BUILDING
107 WEST MICHIGAN AVENUE
KALAMAZOO, MI 49007

POA ACCEPTANCE LETTER

OC000000074874124

Date Mailed: 04/29/2015

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/24/2015.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/sleutchit/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

ES78-1205 / WP10 S

Doc Code: PA..

Document Description: Power of Attorney

Adapted from PTO/AIA/82B 07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in the attached transmittal letter.

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent): **25,666**

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

Name	Registration Number		Name	Registration Number

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant:

☐ Inventor or Joint Inventor

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (*e.g.*, a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date	12/12/2014
Name	Eduard VALENTI VALL	Telephone	
Title / Company	Legal Representative	/ LABORATORIOS DEL DR. ESTEVE S.A.	

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms for more than one signature, see below *.

☐ *Total of _____ forms are submitted.

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be Filed in each application filed on behalf of an assignee applicant. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

(PTO/AIA - rev 5 03/2014)
Created from PTO_AIA-96S.doc

Electronic Acknowledgement Receipt

EFS ID:	22164002
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	25666
Filer:	George Patrick Sage/Linda Wooden
Filer Authorized By:	George Patrick Sage
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	24-APR-2015
Filing Date:	19-AUG-2014
Time Stamp:	15:48:33
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	TRANSMITTAL.pdf	618481 c0e3f24da12e9ef46c0feceb24e4b09486444244	no	1
Warnings:					
Information:					

2	Assignee showing of ownership per 37 CFR 3.73	AIA96_ASSIG.pdf	1199436 01d02249043df8b47ca3e90e53ffe8bf17607edf	no	2
Warnings:					
Information:					
3	Power of Attorney	SIGNED_POA_ESTEVE.pdf	47097 12fd04f9aa0b379bf096fbcbf43ff61c49ade2c0	no	1
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
			Total Files Size (in bytes):	1865014	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: PA..

Document Description: Power of Attorney

PTO/AIA/82A (07-12)

Approved for use through 11/30/2014. OMB 0651-0035

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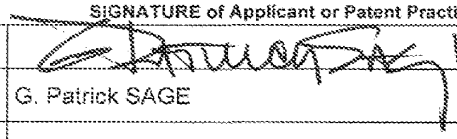
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B or equivalent) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5. If the Power of Attorney by Applicant form is not accompanied by this transmittal form or an equivalent, the Power of Attorney will not be recognized in the application.

Application Number	14/379,613
Filing Date	19 August 2014
First Named Inventor	Pratibha S. PILGAONKAR, et al.
Title	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

SIGNATURE of Applicant or Patent Practitioner

Signature		Date	24 April 2015
Name	G. Patrick SAGE	Telephone	269-382-0030
Registration Number	37,710		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

(F152US - rev. 11/2012)

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: LABORATORIOS DEL DR. ESTEVE S.A.

Application No./Patent No.: 14/379,613 Filed/Issue Date: 19 August 2014

Titled: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

LABORATORIOS DEL DR. ESTEVE S.A. ,

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose one of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose one of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel/Frame 035424/0104, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel/Frame _____ or for which a copy thereof is attached.

2. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel/Frame _____ or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2. (P154US - rev. 11/2012)

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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4. From: _____ To: _____

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5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel /Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at:

Reel/Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	24 April 2015 Date
G. Patrick SAGE Printed or Typed Name	37,710 Title or Registration Number

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/379,613	08/19/2014	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US

CONFIRMATION NO. 6655

25666
THE FIRM OF HUESCHEN AND SAGE
SEVENTH FLOOR, KALAMAZOO BUILDING
107 WEST MICHIGAN AVENUE
KALAMAZOO, MI 49007

PUBLICATION NOTICE

OC000000073101160

Title:ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Publication No.US-2015-0030680-A1
Publication Date:01/29/2015

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/379,613	08/19/2014	1615	1480	ESTEVE 6 PCT US	19	1

CONFIRMATION NO. 6655

CORRECTED FILING RECEIPT

25666
THE FIRM OF HUESCHEN AND SAGE
SEVENTH FLOOR, KALAMAZOO BUILDING
107 WEST MICHIGAN AVENUE
KALAMAZOO, MI 49007



Date Mailed: 11/07/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Pratibha S. Pilgaonkar, Mumbai, INDIA;
Maharukh T. Rustomjee, Mumbai, INDIA;
Anilkumar S. Gandhi, Mumbai, INDIA;

Applicant(s)

LABORATORIOS DEL DR. ESTEVE S.A., Barcelona, SPAIN

Power of Attorney: The patent practitioners associated with Customer Number 25666

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2013/053426 02/21/2013

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
INDIA 461/MUM/2012 02/21/2012

If Required, Foreign Filing License Granted: 10/16/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/379,613**

Projected Publication Date: 01/29/2015

Non-Publication Request: No

Early Publication Request: No

Title

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

IPR2025-01107
MSN Exhibit 1002
Page 539 of 680

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

CONFIDENTIAL
ATTORNEY-CLIENT PRIVILEGE

Michele M. CUDAHY
mmc@hueschen-sage.us

05 November 2014

DOCKET NO. : ESTEVE 6 PCT US
SERIAL NO. : 14/379,613
FILING DATE : 19 August 2014
TITLE : ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Honorable Commissioner of Patents and Trademarks

REQUEST FOR CORRECTED FILING RECEIPT

Sir :

Your undersigned agent has received the Filing Receipt for the above-identified application. However, there is an error as follows:

Inventor Name: "AnilKumar S. Gandhi" should be --Anilkumar S. Gandhi--.

Correction of Inventor Name and issuance of a corrected Filing Receipt are respectfully solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

Michele M. CUDAHY, Agent #55,093

Enclosure(s): Filing Receipt.

Electronic Acknowledgement Receipt

EFS ID:	20612787
Application Number:	14379613
International Application Number:	
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S. Pilgaonkar
Customer Number:	25666
Filer:	George Patrick Sage/LINDA WOODEN
Filer Authorized By:	George Patrick Sage
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	05-NOV-2014
Filing Date:	19-AUG-2014
Time Stamp:	13:51:46
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	request_corrected_ofr.pdf	451283 a038b865fd220a4aeba1af0d9da0cc60e3bc5b42	no	1
Warnings:					
Information:					

Total Files Size (in bytes):	451283

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
14/379,613	Pratibha S. Pilgaonkar	ESTEVE 6 PCT US

25666
THE FIRM OF HUESCHEN AND SAGE
SEVENTH FLOOR, KALAMAZOO BUILDING
107 WEST MICHIGAN AVENUE
KALAMAZOO, MI 49007

INTERNATIONAL APPLICATION NO.	
PCT/EP2013/053426	
I.A. FILING DATE	PRIORITY DATE
02/21/2013	02/21/2012

CONFIRMATION NO. 6655
371 ACCEPTANCE LETTER

OC000000071407702

Date Mailed: 10/20/2014

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office, in its capacity as a Designated / Elected Office (37 CFR 1.495), has ACCEPTED the above identified international application for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above. A Filing Receipt will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE or 371(c) DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1) and (c)(2) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN BELOW.** The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)

08/19/2014
DATE OF RECEIPT OF 35 U.S.C.
371(c)(1) and (c)(2) REQUIREMENTS

The following items have been received:

- Copy of the International Application filed on 08/19/2014
- Copy of the International Search Report filed on 08/19/2014
- Preliminary Amendments filed on 08/19/2014
- Information Disclosure Statements filed on 08/19/2014
- Inventor's Oath or Declaration filed on 08/19/2014
- Request for Immediate Examination filed on 08/19/2014
- U.S. Basic National Fees filed on 08/19/2014
- Priority Documents filed on 08/19/2014
- Application Data Sheet (37 CFR 1.76) filed on 08/19/2014

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

FREDERICK SMITH

Telephone: (571) 272-8679

FORM PCT/DO/EO/903 (371 Acceptance Notice)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/379,613	08/19/2014		1480	ESTEVE 6 PCT US	19	1

CONFIRMATION NO. 6655

25666
THE FIRM OF HUESCHEN AND SAGE
SEVENTH FLOOR, KALAMAZOO BUILDING
107 WEST MICHIGAN AVENUE
KALAMAZOO, MI 49007

FILING RECEIPT

OC00000007140770 1

Date Mailed: 10/20/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Pratibha S. Pilgaonkar, Mumbai, INDIA;
Maharukh T. Rustomjee, Mumbai, INDIA;
AnilKumar S. Gandhi, Mumbai, INDIA;

Applicant(s)

LABORATORIOS DEL DR. ESTEVE S.A., Barcelona, SPAIN

Power of Attorney: The patent practitioners associated with Customer Number 25666

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2013/053426 02/21/2013

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
INDIA 461/MUM/2012 02/21/2012

If Required, Foreign Filing License Granted: 10/16/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/379,613**

Projected Publication Date: 01/29/2015

Non-Publication Request: No

Early Publication Request: No

Title

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where

the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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NOT GRANTED

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SelectUSA

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IPR2025-01107
MSN Exhibit 1002
Page 547 of 680

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/379,613

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	480
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	19 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1480

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
14379613	

Applicant(s) Pratibha PILGAONKAR

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1		---	---		
2		1	---	---		
3		2	---	---		
4		(1)	---	---		
5		(1)	---	---		
6		(1)	---	---		
7		(1)	---	---		
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Total Indep	1		1		0	
Total Depend	20	↵	18	↵	0	↵
Total Claims	21		19		0	

	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
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PTO-1390 (06-13)
Approved for use through 6/30/2013. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

Attorney Docket No.	
ESTEVE 6 PCT US	
U.S. Application No. (if known, see 37 CFR 1.5)	

International Application No.	International Filing Date	Priority Date Claimed
PCT/EP2013/053426	21 February 2013	21 February 2012

Title of Invention
ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

First Named Inventor
Pratibha S. PILGAONKAR, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). NOTE: The express request under 35 U.S.C. 371(f) will not be effective unless the requirements under 35 U.S.C. 371(c)(1), (2), and (4) for payment of the basic national fee, copy of the International Application and English translation thereof (if required), and the oath or declaration of the inventor(s) have been received.
2. [X] A copy of the International Application (35 U.S.C. 371(c)(2)) is attached hereto (not required if the International Application was previously communicated by the International Bureau or was filed in the United States Receiving Office (RO/US)).
3. An English language translation of the International Application (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
4. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
   a. [X] is attached.
   b. [ ] was previously filed in the international phase under PCT Rule 4.17(iv).

Items 5 to 8 below concern amendments made in the international phase.

PCT Article 19 and 34 amendments

5. [ ] Amendments to the claims under PCT Article 19 are attached (not required if communicated by the International Bureau) (35 U.S.C. 371(c)(3)).
6. [ ] English translation of the PCT Article 19 amendment is attached (35 U.S.C. 371(c)(3)).
7. [ ] English translation of annexes (Article 19 and/or 34 amendments only) of the International Preliminary Examination Report is attached (35 U.S.C. 371(c)(5)).

Cancellation of amendments made in the international phase

8a. [ ] Do not enter the amendment made in the international phase under PCT Article 19.

8b. [ ] Do not enter the amendment made in the international phase under PCT Article 34.

NOTE: A proper amendment made in English under Article 19 or 34 will be entered in the U.S. national phase application absent a clear instruction from applicant not to enter the amendment(s).

The following items 9 to 17 concern a document(s) or information included.

9. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. [X] A preliminary amendment.
11. [X] An Application Data Sheet under 37 CFR 1.76.
12. [ ] A substitute specification. NOTE: A substitute specification cannot include claims. See 37 CFR 1.125(b).
13. [ ] A power of attorney and/or change of address letter.
14. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821-1.825.
15. [ ] Assignment papers *(cover sheet and document(s))*. Name of Assignee: _____
16. [ ] 37 CFR 3.73(c) Statement *(when there is an Assignee)*.

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. (P017AFUS - rev. 01/2013)

U.S. APPLN. No. (if known – see 37 CFR 1.5)	INTERNATIONAL APPLICATION No.	ATTORNEY DOCKET No.
	PCT/EP2013/053426	ESTEVE 6 PCT US

17. [X] Other items or information:

Form PTO/SB/38

The following fees have been submitted.	CALCULATIONS	PTO USE ONLY
18. [X] Basic national fee (37 CFR 1.492(a)) **$280**	$ 280.00	
19. [X] Examination fee (37 CFR 1.492(c)) If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** All other situations **$720**	$ 720.00	
20. [X] Search fee (37 CFR 1.492(b)) If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... $0 Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority .....**$120** International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB .....**$480** All other situations **$600**	$ 480.00	
TOTAL OF 18, 19, and 20 =	$ 1,480.00	
[ ] Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)). Fee for each additional 50 sheets of paper or fraction thereof $400	0.00	

Total Sheets	Extra Sheets	Number of each addition 50 or fraction thereof (round up to a whole number)	RATE	
28 - 100 =	0 / 50 =	0	x $400	$
Surcharge of **$140.00** for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)).				$ 0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	19 - 20 =		x $80	$ 0.00	
Independent claims	1 - 3 =		x $420	$ 0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $780	$ 0.00	
Processing fee of **$140.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)). +				$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$ 0.00	
[ ] **Applicant asserts small entity status.** See 37 CFR 1.27. Fees above are reduced by ½.					
[ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Fees above are reduced by ¾. Applicant must attach form PTO/SB/15A or B or equivalent.					
TOTAL NATIONAL FEE =				$	1,480.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property. +				$	0.00
TOTAL FEES ENCLOSED =				$	1,480.00
				Amount to be refunded:	$
				Amount to be charged:	$

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b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.

c. ☒ The Director is hereby authorized to charge additional fees which may be required, or credit any overpayment, to Deposit Account No. 08-3220 as follows:

i. ☒ any required fee.

ii. ☐ any required fee except for excess claims fees required under 37 CFR 1.492(d) and (e) and multiple dependent claim fee required under 37 CFR 1.492(f).

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

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NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the international application to pending status.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File)Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013, and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

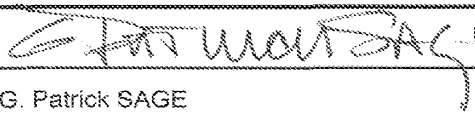
NOTE 1: By providing this statement under 37 CFR 1.55 or 1.76, **this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA**.

NOTE 2: A U.S. national stage application may not claim priority to the international application of which it is the national phase. The filing date of a U.S. national stage application is the international filing date. See 35 U.S.C. 363.

Correspondence Address

☒ The address associated with Customer Number: 25,666 **OR** ☐ Correspondence address below

Name	THE FIRM OF HUESCHEN AND SAGE				
Address	SEVENTH FLOOR, 107 WEST MICHIGAN AVENUE				
City	KALAMAZOO	State	MI	Zip Code	49007
Country	US			Telephone	269-382-0030
Email					

Signature		Date	19 August 2014
Name (Print/Type)	G. Patrick SAGE	Registration No. (Attorney/Agent)	37,710

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ESTEVE 6 PCT US
	Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Inventor Information:

Inventor 1				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Pratibha	S.	PILGAONKAR	
Residence Information				
City		State/Province	Country of Residence	
Mumbai			INDIA	
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City	Mumbai		State/Provinc	
Postal Code	400 078		Country	INDIA

Inventor 2				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Maharukh	T.	RUSTOMJEE	
Residence Information				
City		State/Province	Country of Residence	
Mumbai			INDIA	
Mailing Address of Inventor				
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City	Mumbai		State/Provinc	
Postal Code	400 078		Country	INDIA

Inventor 3				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Anilkumar	S.	GANDHI	
Residence Information				
City		State/Province	Country of Residence	
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Mailing Address of Inventor				
Address	221 Annexe Bldg, Goregaon-Mulund Link Road			
City	Mumbai		State/Provinc	
Postal Code	400 078		Country	INDIA

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ESTEVE 6 PCT US
	Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
☐ An Address is being provided for the correspondence Information of this application.	
Customer Number	25,666
Email Address	

Application Information:

Title of the Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
Attorney Docket Number	ESTEVE 6 PCT US	Small Entity	No
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if		Suggested Figure for Publication (if any)	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One	☑ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	25,666		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ESTEVE 6 PCT US
	Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Application Number	Continuity Type	Prior Application Number	Filing Date (DD-MMMM-YYYY)
This Application is a	a 371 of international	PCT/EP2013/053426	21 February 2013

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Application Number	Country	Filing Date (DD-MMMM-YYYY)	Priority Claimed
461/MUM/2012	INDIA	21 February 2012	☑ Yes ☐ No

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization to Permit Access:

☑ Authorization to Permit Access to the Instant Application by the Participating Offices.

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ESTEVE 6 PCT US
	Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

☑ Assignee	☐ Legal Representative under 35 U.S.C. 117
☐ Person to whom the inventor is obligated to assign	☐ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

☐ Deceased	☐ Legally Incapacitated

Name of the Deceased or Legally Incapacitated Inventor	
If the Assignee is an Organization check here	☑

Organization	LABORATORIOS DEL DR. ESTEVE S.A.

Mailing Address Information

Address	Avda. Mare de Déu de Montserrat, 221		
City	Barcelona	**State/Province**	
Country	SPAIN	Postal Code	E-08041
Phone Number		Fax Number	
Email Address			

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature				Date (DD-MMMM-YYYY)	19 August 2014
First Name	G. Patrick	Last Name	SAGE	Registration Number	37,710

Doc Code: Oath

Document Description: Oath or declaration filed

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

Attorney Docket Number	ESTEVE 6 PCT US
First Named Inventor	Pratibha PILGAONKAR, et al.
COMPLETE IF KNOWN	
Application Number	
Filing Date	21 August 2014
Art Unit	
Examiner Name	

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

(Title of the Invention)

As a below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application,

OR

☐ United States Application Number or PCT International application number _____

filed on _____.

Statement under 35 USC § 115

The above-identified application was made or authorized to be made by me.

I (we) believe I (we) am (are) the original inventor or an original joint inventor of a claimed invention in the application.

I (we) hereby acknowledge that any willful false statement made in this declaration is punishable under 18 USC § 1001 by fine or imprisonment of not more than five (5) years, or both.

And I (we) further authorize any member of The Firm of Hueschen and Sage, PLLC to insert or complete any information in this document to effect its submission in the United States Patent and Trademark Office, and countries foreign thereto.

Authorization To Permit Access To Application by Participating Office

☐ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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DECLARATION — Utility or Design Patent Application

Direct all correspondence to:	☒	The address associated with Customer Number:	25,666	OR ☐	Correspondence address below

Name		
Address		
City	State	Zip
Country	Telephone	Email

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files*. Documents not retained in an application file (such as the PTO-2038) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: *Deposit Accounts and Electronic Funds Transfer Profiles*.

LEGAL NAME OF SOLE OR FIRST INVENTOR:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Pratibha S. PILGAONKAR

Inventor's Signature	Date
	31st July 2014

Residence: City	State	Country
Mumbai		INDIA

Mailing Address

221 Annexe Bldg, Goregaon-Mulund Link Road

City	State	Zip	Country
Mumbai		400 078	INDIA

☒ Additional inventors are being named on the 2 supplemental sheet(s) PTO/AIA/10 attached hereto

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SUPPLEMENTAL SHEET FOR DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet (for PTO/AIA/08.09) Page 1 of 2

Legal Name of Additional Joint Inventor:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Maharukh T. RUSTOMJEE

Inventor's Signature	M. T. Rustomjee	Date	31/7/2014

Residence: City	State	Country
Mumbai		INDIA

Mailing Address: 221 Annexe Bldg, Goregaon-Mulund Link Road

City	State	Zip	Country
Mumbai		400 078	INDIA

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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SUPPLEMENTAL SHEET FOR DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet (for PTO/AIA/08,09) Page 2 of 2

Legal Name of Additional Joint Inventor: (*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname) Anilkumar S. GANDHI			
Inventor's Signature 			Date 31st July - 2014
Residence: City Mumbai	State	Country INDIA	
Mailing Address 221 Annexe Bldg, Goregaon-Mulund Link Road			
City Mumbai	State	Zip 400 078	Country INDIA

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Field of Invention

The present invention relates to oral pharmaceutical compositions comprising dabigatran etexilate or pharmaceutically acceptable salts thereof.

Background of the Invention

Atrial fibrillation is the most common cardiac arrhythmia which is characterized by abnormal heart rhythm. It is considered to be a common cause of irregular heart beat and can cause stroke and other systemic embolic events, eventually leading to death. It has been seen that the incidence of atrial fibrillation increases with age and nearly 6% of individuals over the age of 65 are affected while the prevalence is about 8% in individuals over the age of 80. The lack of organized cardiac contractions in atrial fibrillation generally results in some stagnant blood in the left atrium or left atrial appendage. This lack of movement of blood leads to thrombus formation or blood clotting. Patients with atrial fibrillation are therefore at greater risk of developing clots which increases the risk of stroke and other systemic embolic events. Since the consequence of stroke or systemic embolism is devastating, a primary aim of therapy for atrial fibrillation is to reduce the risk of arterial thrombus formation and thromboembolism. Anticoagulants such as warfarin are mainly used in case of atrial fibrillation along with other medications such as beta blockers and calcium channel blockers or some noninvasive rhythm control methods. Though anticoagulation therapy with warfarin has been shown to significantly reduce the incidence of stroke or systemic embolism, its use is found to be cumbersome due to multiple diet and drug interactions, chances of hemorrhage which are difficult to manage, requirement of frequent laboratory monitoring etc. Use of a newer safe and effective anticoagulant is therefore necessary.

Direct thrombin inhibitors, is another class of anticoagulants that act by directly inhibiting the enzyme thrombin and are expected to replace heparin (and derivatives) and warfarin in various clinical scenarios. Thrombin, a serine protease protein formed by proteolytic cleavage of prothrombin, converts soluble fibrinogen into insoluble strands of fibrin and further catalyzes many other coagulation-related reactions. Direct thrombin inhibitors inhibit thrombin including fibrin-bound thrombin, thereby delimiting thrombus growth, provide predictable anticoagulant responses because they are not

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MSN Exhibit 1002
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bound to plasma proteins and have no drug-drug interactions. Depending on their interaction with the thrombin molecule, there are bivalent as well as univalent types of direct thrombin inhibitors, with some being in clinical use, while others undergoing clinical development.

Dabigatran is a potent, reversible, univalent direct thrombin inhibitor. It reduces the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It is also useful in primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. Dabigatran was first disclosed in WO98/37075, which claimed compounds with a thrombin-inhibiting effect and the effect of prolonging the thrombin time, under the name 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino) phenyl] aminomethyl] benzimidazol-5-ylcarboxylic acid-N-(2-pyridyl)-N-(2 ethoxycarbonylethyl)amides.

Dabigatran is currently available as dabigatran etexilate mesylate (DEM) under the brand name Pradaxa® from Boehringer Ingelheim as immediate release oral capsules of 75 mg and 110 mg (in Europe) and 75 mg and 150 mg strengths (in the United States) to be administered twice daily. DEM is a salt form of the prodrug dabigatran etexilate which after oral administration is absorbed and converted to dabigatran by esterase-catalysed hydrolysis in the liver. DEM is a yellow-white to yellow non-hygroscopic powder that exists in two anhydrous polymorphic forms, Form I and II, which are described in WO 2005/028468. The aqueous solubility of DEM is strongly pH dependent with rather high solubility in acidic media and very poor solubility in neutral and basic media while solubility in water is 1.8mg/mL. The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately about 3-7% and elimination half life is 12-17 hours. DEM is BCS Class II drug, indicating poor aqueous solubility but good membrane permeability. DEM is stable in the solid state and not sensitive to light irradiation but it predominantly undergoes degradation by hydrolytic pathways in the presence of moisture. It is also acid sensitive.

Due to these physicochemical and biopharmaceutical properties of DEM, some attempts have been made to provide compositions of DEM that are stable and/or provide desirable *in vitro* release and bioavailability.

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U.S Patent Application 2006/0183779A1 describes pharmaceutical compositions of DEM for oral administration in the form of pellets comprising (a) substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1g/250ml at 20℃ such as tartaric acid; and (b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material. The separating agent layer or insulating layer separates the acid core from the active substance containing layer. The layer of active substance may in turn be enclosed in a coating which increases the abrasion resistance and shelf life of the pellets. Such layered pellets are later filled into hard capsules. However, the process of preparing layered pellets is cumbersome, time consuming and uneconomical.

U.S Patent Application 2005/0038077 discloses a tablet comprising dabigatran etexilate or pharmaceutically acceptable salt thereof; one or more pharmaceutically acceptable organic acids with a solubility in water of > 1g/250ml at 20℃ and a pharmaceutically acceptable excipient or filler. However due to the presence of an organic acid in close contact with the active in a tablet composition without any special steps taken to separate the two from each other, can make the active highly susceptible to hydrolysis in the presence of humidity.

The above attempts only provided compositions of DEM, which are either tedious or technologically demanding to prepare or are unlikely to remain stable over the shelf life of the product. Need therefore exists to prepare alternate compositions of dabigatran etexilate that are stable, easy or convenient to prepare, provide the desired *in vitro* release and bioavailability.

The present inventors after rigorous experimentation provide oral compositions of dabigatran etexilate comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein a) the first type of particles comprise the active agent; b) the second type of particles comprise at least one pharmaceutically acceptable organic acid; and c) optionally at least one type of particles are coated with a protective coating layer. Such compositions are chemically and polymorphically stable, provide desired in-vitro and in-vivo performance and can be prepared by simple, non-tedious and cost-effective process.In particular, the

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compositions of the present invention provide a quick dissolution particularly at earlier time points as compared to formulation having one type of particles/pellets. Such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster Tmax (~ 45 minutes – 1 hour), (b) significant bioactivation is involved and (c) negligible and variable absorption at higher pH.

Detailed Description of the Invention

The present invention provides, in one of its aspects, pharmaceutical compositions, preferably for oral administration, comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid.

In a particular embodiment, the present invention provides pharmaceutical compositions, preferably for oral administration, comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein a) the first type of particles comprise dabigatran etexilate in the form of free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; b) the second type of particles comprise at least one pharmaceutically acceptable organic acid; and c) optionally at least one type of particles are coated with a protective coating layer.

The compositions of the present invention are stable, easy to prepare, and provide the desired in-vitro release of the active.

The first type of particles present in the composition of the present invention, comprise dabigatran etexilate. Dabigatran etexilate may be used in the compositions of the present invention as the free base (3-[(2-{4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]methyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino-propionic acid ethyl ester) or in the form of pharmaceutically acceptable salts,, polymorphs, solvates, hydrates thereof. For the sake of conciseness, the term

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dabigatran etexilate is employed in this specification to designate any of the above-mentioned forms except when the term is further qualified (i.e. dabigatran etexilate mesylate). Whenever it is necessary to designate the free base of dabigatran etexilate the term "dabigatran etexilate (free base)" is employed.

The term "pharmaceutically acceptable salt" refers to those salts which are, according to medical judgement, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like. Pharmaceutically acceptable salts are well known in the art.

In one embodiment the amount of dabigatran etexilate (expressed as dabigatran etexilate mesylate) in the composition can vary from about 0.01 weight % to about 90 weight %, based on the total weight of the composition. In another embodiment the amount of dabigatran etexilate in the composition can vary from about 0.02 weight % to about 85 weight %, based on the total weight of the composition. In still another embodiment, the amount of dabigatran etexilate in the composition can vary from about 0.05 weight % to about 80 weight %, based on the total weight of the composition.

In one embodiment the compositions of the present invention may be in the form of unit dose forms comprising from 50 mg to 200 mg of dabigatran etexilate mesylate, preferably from 75 mg to 150 mg, more preferably 75 mg, 110 mg or 150 mg.

In one embodiment of the present invention dabigatran etexilate is used in the form of the mesylate salt, i.e. dabigatran etexilate mesylate.

In a particular embodiment of the present invention dabigatran etexilate is used in the form of polymorphic form I of dabigatran etexilate mesylate (as described in WO 2005/028468).

In another particular embodiment of the present invention dabigatran etexilate is used in the form of polymorphic form II of dabigatran etexilate mesylate (as described in WO 2005/028468).

The oral pharmaceutical composition of the present invention comprises a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable

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excipient, with a first type of particles comprising dabigatran etexilate and second type of particles comprising at least one pharmaceutically acceptable organic acid.

In a preferred embodiment of the present invention the first type of particles comprising dabigatran etexilate is free from organic and inorganic acids.

In a preferred embodiment of the present invention the first type of particles comprising dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof also comprise at least one pharmaceutical excipient.

In a most preferred embodiment of the present invention, the said first type of particles comprising dabigatran etexilate mesylate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof also comprise one or more excipients selected from the group consisting of binders, diluents and/or lubricants.

In a particular embodiment said first type of particles comprise at least one binder, preferably microcrystalline cellulose.

In another particular embodiment, said first type of particles comprises at least one disintegrant, preferably selected from sodium croscarmellose or crospovidone.

In another particular embodiment, said first type of particles comprise at least one diluent, preferably selected from mannitol or lactose.

In another particular embodiment, said first type of particles comprise at least one binder, preferably microcrystalline cellulose, a disintegrant, preferably selected from sodium croscarmellose or crospovidone and a diluent, preferably selected from mannitol or lactose.

In another preferred embodiment of the present invention the second type of particles comprising at least one pharmaceutically acceptable organic acid is free from dabigatran etexilate.

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In a most preferred embodiment of the present invention the first type of particles comprising dabigatran etexilate is free from acids and the second type of particles comprising at least one pharmaceutically acceptable organic acid is free from dabigatran etexilate.

In another preferred embodiment of the present invention the second type of particles comprise tartaric acid, preferably in the form of pellets with a particle size between 100 and 900 microns, more preferably between 400 and 700 microns.

An acid is a substance that releases hydrogen ions and decreases the pH of an aqueous solution.

Organic acids that may be employed in the present composition include, but are not limited to, tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, aspartic acid and the like or combinations thereof including the hydrates and acid salts thereof.

In one embodiment the organic acid is present in the composition of the present invention in an amount of about 2% by weight to about 95% by weight of the composition. In another embodiment the organic acid is present in the composition of the present invention in an amount of about 5% by weight to about 90% by weight of the composition. In a further embodiment the organic acid is present in the composition of the present invention in an amount of about 10% by weight to about 85% by weight of the composition.

In one embodiment at least 90% by weight, preferably at least 95% by weight, more preferably at least 99% by weight and still more preferably 100% by weight of the organic acid present in the composition is contained in the second type of particles which comprise at least one pharmaceutically acceptable organic acid, the rest (if any) of the organic acid being added as part of the excipients.

Further the oral pharmaceutical compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein optionally at least one type of particles are coated with a protective coating layer. In one embodiment, the first type of particles is coated with a

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protective coating layer. In another embodiment, the second type of particles is coated with a protective coating layer. In yet another embodiment, the first and the second type of particles are coated with a protective coating layer.

The term "protective coating layer" as used herein is intended to mean a layer of a polymeric or a non-polymeric material disposed on the surface of a particle core in order to avoid direct contact of the particle core with its environment.

In one embodiment, protective coating layer is formed of a polymeric or a non-polymeric pharmaceutically acceptable agent or any combination thereof.

The polymeric pharmaceutically acceptable agents used for the protective coating layer include, but are not limited to, cellulose derivatives, vinyl derivatives, polymers and copolymers, gums, acrylic or methacrylic acid polymers, copolymers, esters or derivatives thereof, and the like or combinations thereof. Cellulose derivatives that may be employed, include, but are not limited to, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, ethylcellulose, hydroxypropyl ethylcellulose, carboxymethylethyl cellulose, carboxy ethylcellulose, carboxymethyl hydroxyethylcellulose, hydroxyethylmethyl carboxymethyl cellulose, hydroxyethyl methyl cellulose, carboxymethyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, carboxymethyl sulfoethyl cellulose, sodium carboxymethyl cellulose, and the like or combinations thereof. Vinyl derivatives, polymers and copolymers thereof that may be employed include, but are not limited to copolymers of vinyl pyrrolidone, copolymers of polyvinyl alcohol (Kollicoat IR), polyvinylpyrrolidone or combinations thereof. Gums that may be employed include, but are not limited to, gum arabic, alginates, guar gum, locust bean gum, carrageenan, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, karaya, and the like, or combinations. Acrylic or methacrylic acid polymers, copolymers, esters or derivatives thereof, that may be employed include, but are not limited to, a) copolymer formed from monomers selected from methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters b) copolymer formed from monomers selected from butyl methacrylate, (2-dimethylaminoethyl)methacrylate and methyl methacrylate c) copolymer formed from monomers selected from ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride or d) copolymers of acrylate and

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methacrylates with/without quarternary ammonium group in combination with sodium carboxymethylcellulose, e.g. those available from Röhm GmbH under the trademark Eudragit ® like Eudragit EPO (dimethylaminoethyl methacrylate copolymer; basic butylated methacrylate copolymer), Eudragit RL and RS (trimethylammonioethyl methacrylate copolymer), Eudragit NE30D and Eudragit NE40D (ethylacrylate methymethacrylate copolymer), Eudragit RD 100 (ammoniomethacrylate copolymer with sodium carboxymethylcellulose); or the like or any combinations thereof.

The non-polymeric pharmaceutically acceptable agents used for the protective coating layer include, but are not limited to C8-C22 fatty acids, C8-C22 fatty alcohols, fats, in particular mono-, di- or triesters of glycerol and C8-C22 fatty acids, waxes, and the like, or combinations thereof. Fatty acids that may be employed include, but are not limited to, decenoic acid, docosanoic acid, stearic acid, palmitic acid, lauric acid, myristic acid, hydrogenated palm kernel oil, hydrogenated peanut oil, hydrogenated palm oil, hydrogenated rapeseed oil, hydrogenated rice bran oil, hydrogenated soybean oil, hydrogenated sunflower oil, hydrogenated castor oil, hydrogenated cottonseed oil, and the like, and mixtures thereof. Long chain monohydric alcohols that may be employed include, but are not limited to, cetyl alcohol, stearyl alcohol and mixtures thereof. Waxes that may be employed include, but are not limited to, spermaceti wax, carnauba wax, Japan wax, bayberry wax, flax wax, beeswax, Chinese wax, shellac wax, lanolin wax, sugarcane wax, candelilla wax, paraffin wax, microcrystalline wax, petrolatum wax, carbowax, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, glyceryl dipalmitate, glyceryl tripalmitate, glyceryl monopalmitate, glyceryl dilaurate, glyceryl trilaurate, glyceryl monolaurate, glyceryl trimyristate, glyceryl monodecenoate, glyceryl didecenoate, glyceryl tridecenoate, glyceryl behenate and the like, or mixtures thereof.

In a further embodiment, in addition to polymeric or non-polymeric pharmaceutically acceptable agent or any combination thereof, the protective coating layer may optionally further comprise one or more pharmaceutically acceptable excipients such as, but not limited to, plasticizer, anti-tacking agent, pigment, and the like, or combinations thereof. A plasticizer that may be employed includes, but is not limited to, triethyl citrate, acetyl triethyl citrate, propylene glycol, polyethylene glycol, acetyl tributyl citrate, acetylated monoglycerides, glycerin, triacetin, phthalate esters (*e.g.*, diethyl phthalate, dibutyl phthalate), castor oil, sorbitol and dibutyl seccate or a combination thereof. An anti-tacking agent that may be employed includes, but is not limited to, talc,

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or glyceryl monostearate. A pigment such as, but not limited to, titanium dioxide, iron oxide, or a mixture thereof may be employed.

The protective coating layer may be optionally applied onto at least one type of particles of the present invention. For example, the protective coating layer is applied onto the first type of particles which comprise dabigatran etexilate in the form of free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof.

In a preferred embodiment of the present invention the protective coating layer is coated onto the second type of particles which comprise at least one pharmaceutically acceptable organic acid. In a particular embodiment said coating layer comprises hydroxypropylmethyl cellulose and talc.

In another embodiment, both particles are coated with the said protective coating layer.

The protective coating layer may be optionally applied onto at least a type of particles of the present invention in any suitable equipment where coating can be achieved, such as, but not limited to, coating pan, conventional film coating apparatus or a fluidized bed apparatus, or the like. Furthermore, in one embodiment, the protective coating layer can be applied from an aqueous or organic solution or dispersion. In another embodiment, the particles being coated with the protective coating layer may be coated to a weight gain of about 2% to about 50% by weight.

In one embodiment, in order to reduce any damage to the protective coating layer during transfer into capsules, the particles coated with the protective coating layer may be further seal coated with conventional pharmaceutically acceptable film forming agents which may optionally be combined with plasticizers or pigments. Suitable film forming agents include, but are not limited to, hydroxypropyl cellulose, hydroxypropyl methylcellulose, acrylic and methacrylic acid polymers, copolymers or esters, and the like or combinations thereof. Plasticizers or pigments as discussed above may optionally be used with the film forming agents.

The compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient. In a further

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embodiment, the first type of particles comprising dabigatran etexilate may optionally further comprise at least one pharmaceutically acceptable excipient. In another embodiment, the second type of particles comprising at least one organic acid, may optionally further comprise at least one pharmaceutically acceptable excipient. In yet another embodiment, at least two types of particles that are present in the pharmaceutical composition optionally further comprise at least one pharmaceutically acceptable excipient.

The pharmaceutically acceptable excipients that may be incorporated in the composition of the present invention include, but are not limited to, binders, disintegrants, diluents, surfactants, glidants, lubricants, and the like or combinations thereof.

The term "disintegrant" as used herein is intended to mean a compound used in solid dosage formulations to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, natural, modified or pregelatinized starch, modified starches (such as sodium starch glycolate) and partially pregelatinized starches (such as Starch 1500), polyvinylpyrrolidone, crospovidone, croscarmellose sodium, calcium silicate clays, such as bentonite, microcrystalline cellulose, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, alginates, ion exange resins (such as Polacrilin potassium, Polacrilex) Neusilins, low substituted hydroxypropyl cellulose and the like, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in granulations. Examples of suitable binders include, but are not limited to celluloses such as microcrystalline cellulose, modified celluloses (such as low substituted hydroxypropyl cellulose, hydroxypropyl cellulose (or HPC), hydroxypropyl methylcellulose (or HPMC or hypromellose), hydroxyethylcellulose, hydroxyethyl methylcellulose, ethyl cellulose, cellulose gum, xanthan gum, sugars (such as sucrose, glucose, amilose, maltodextrin, dextrose and the like), starches such as corn or potato starch partially pregelatinized starches (such as Starch 1500), polyvinyl acetate (Kollicoat SR), polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat IR), copovidone, cross-linked polyvinylpyrrolidone, acrylic acid polymer

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(Carbopol), poloxamer, polycarbophil, polyethylene oxide, polyethylene glycol, and the like, combinations thereof and other material known to those of ordinary skill in the art.

The term "diluent" or "filler" as used herein is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of solid dosage formulations. Examples of suitable diluents include, but are not limited to microcrystalline cellulose, coprocessed microcrystalline celluloses (such as Avicel CI-611, Avicel RC-581, Avicel RC591, Avicel CE, Avicel DG, Avicel HFE), lactose, sucrose, xylitol, mannitol, maltose, polyols, fructose, guar gum, sorbitol, magnesium hydroxide, dibasic calcium phosphate, kaolin, calcium sulphate, carrageenan, chitosan, pectinic acid, sodium alginate, magnesium aluminium silicate, calcium carbonate and the like, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "lubricant" as used herein is intended to mean substances used in solid dosage formulations to reduce friction during compression of the solid dosage. Such compounds include, but are not limited to, magnesium stearate, calcium stearate, zinc stearate, stearic acid, talc, mineral oil and sodium stearyl fumarate, combinations thereof and other such materials known to those of ordinary skill in the art.

The tablet compositions of the invention may also include a glidant. The term "glidant" as used herein is intended to mean agents used in solid dosage formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, but not limited to, colloidal silica, silica gel, precipitated silica, calcium silicate, magnesium silicate, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "surfactant" as used herein is intended to mean substances used to reduce the surface tension of the aqueous solutions comprising them. Examples of surfactants include, but are not limited to, sodium docusate, glyceryl monooleate, polyethylene alkyl ether, polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, sorbic acid, sorbitan fatty acid ester, mixtures thereof and other such materials known to those of ordinary skill in the art.

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The compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, with first type of particles comprising dabigatran etexilate and second type of particles comprising at least one organic acid.

The term "particle" as used herein is intended to mean any solid or semi-solid portion of a substance or a composition having defined physical boundaries. Examples of particles particles include, but are not limited to, powder, granules, pellets, beads, minitablets or the like. The granules may be prepared by methods such as, but not limited to, wet granulation, melt granulation, dry granulation or roll compaction or the like. In an embodiment of the present invention, pellets may be prepared using extrusion spheronization. In another embodiment of the present invention, dabigatran etexilate present in the first set of particles or at least one organic acid present in the second set of particles can be loaded on an inert carrier. The inert carrier can be selected from, but not limited to, beads, pellets, spheres or similar particles that do not contain an active ingredient. Non-limiting examples of inert carrier include microcrystalline cellulose, sugar or silicon dioxide. In yet another embodiment, the particles of the present invention, in the powder form, may be incorporated in the compositions of the present invention.

In an embodiment of the present invention said first type of particles has a particle size comprised between 50 and 1000 microns and said second type of particles have a particle size comprised between 100 and 1000 microns.

The compositions of the present invention comprise from about 5% to about 100% by weight of the mixture of at least two types of particles. Ratio of the first and second types of particles is from about 1:99 to about 99:1.

The term "composition" or "formulation" has been employed interchangeably for the purpose of the present invention.

The term "dosage form" is as used herein is intended to mean a pharmaceutical composition which is suitable for administration to a patient. In one embodiment the compositions of the present invention can be in the form of capsules, tablets, minitablets, stick formulation, dispersible tablets, dry suspension for reconstitution,

powder or granule for solution or suspension, granules, and the like or any combinations thereof. Depending of the final dosage form the compositions of the present invention may comprise appropriate pharmaceutically acceptable excipients such as those mentioned above or some additional ones such as, but not limited to, sweeteners, flavors, colorants and the like or combinations thereof. Further it is contemplated within the scope of the invention that the dosage form can be encapsulated or coated. In one embodiment, the composition of the present invention is in the form of a capsule. Capsules include, for example, hard capsules of gelatine or hydroxypropylmethylcellulose and the like. In a further embodiment, the compositions of the present invention may be manufactured using conventional techniques known in the art.

The term "unit dosage form" refers to a physically discrete unit suitable as a unitary dosage for a human patient such as a capsule, a tablet or a vial.

In another aspect the present invention provides a unit dosage form prepared from the above mentioned compositions comprising two types of particles.

The compositions of the present invention provide flexibility of blending at least two types of particles to attain different release patterns. In one embodiment, the compositions of the present invention provide tailored in-vitro profiles and corresponding in-vivo profiles. In a further embodiment, the compositions of the present invention can provide tailored profiles wherein dissolution of the compositions of the present invention can be faster at initial time points when compared to formulations having only single type of particles comprising both dabigatran etexilate or pharmaceutically acceptable salts thereof and organic acid. Without being bound to any theory it is believed that such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster Tmax (~ 45 minutes – 1 hour), (b) significant bioactivation is involved for action of dabigatran and (c) negligible and variable absorption is observed at higher pH.

In another aspect the present invention provides a process for the preparation of a composition comprising the two types of particles described above comprising the step of mixing said first type of particles and said second type of particles with a at least one

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pharmaceutically acceptable excipient. In a particular embodiment of the present invention said first type of particles are prepared by granulation.

In one embodiment the process of preparing the compositions of the present invention comprises the steps of

(i) blending dabigatran etexilate and at least one pharmaceutically acceptable excipient such as diluent;

(ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the organic acid granules with a protective coating layer;

(vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) lubricating the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In another embodiment the process of preparing the compositions of the present invention comprises the steps of

(i) blending dabigatran etexilate and at least one pharmaceutically acceptable excipient such as diluent;

(ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the granules of active agent with a protective coating layer;

(vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;

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(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
(viii) lubricating the blend of step (vii);
(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In yet another embodiment the process of preparing the compositions of the present invention comprises the steps of

(i) blending dabigatran etexilate and at least one pharmaceutically acceptable excipient such as diluent;
(ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;
(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent or binder;
(iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;
(v) coating the organic acid pellets of step (iv) with a protective coating layer;
(vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;
(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;
(viii) lubricating the blend of step (vii);
(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In a further aspect the present invention provides the use of the pharmaceutical composition of dabigatran etexilate of the present invention for the manufacture of a medicament for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

In still another aspect the present invention provides a method of for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the subject in need thereof pharmaceutical compositions of dabigatran etexilate of the present invention.

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In another embodiment of the present invention the dabigatran etexilate may be combined with other active agents or pharmaceutically acceptable salts thereof including, but not limited to, atorvastatin, dipyridamole, mopidamole and the like or combinations thereof.

The invention is further illustrated by the following examples, which are for illustrative purposes and should not be construed as limiting the scope of the invention in any way.

Examples

Example 1: Oral capsule formulation of dabigatran etexilate mesylate

A) Preparation of coated tartaric acid pellets

(a) Preparation of tartaric acid pellets

Table 1: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid	80
Microcrystalline cellulose	30
Hydroxypropyl cellulose	10
Isopropyl alcohol*	q.s
Total	**120**

*not present in the final product

Procedure: Tartaric acid and microcrystalline cellulose were blended and to this blend was added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass was extruded, spheronized, dried and screened to give pellets. These pellets were then coated with a protective coating layer as follows to give coated tartaric acid pellets.

(b) Preparation of coated tartaric acid pellets

Table 2: Composition of tartaric acid pellets

Ingredients	mg/unit

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Tartaric acid pellets	120
Hydroxypropyl methylcellulose	10
Talc	6
Isopropyl alcohol*	q.s
Total	**136**

*not present in the final product

Procedure: Tartaric acid pellets prepared as above were coated with dispersion of hydroxypropyl cellulose and talc in isopropyl alcohol. The coated pellets were then dried to give coated tartaric acid pellets.

B) Preparation of dabigatran etexilate mesylate granules

Table 3: Composition of dabigatran etexilate mesylate granules

Ingredients	mg/unit
Dabigatran etexilate mesylate equivalent to 110 mg of dabigatran etexilate	126.83
Microcrystalline cellulose	40.17
Lactose anhydrous	30
Crospovidone	4
Hydroxypropyl cellulose	4
Isopropyl alcohol*	q.s
Total	**205**

*not present in the final product

Procedure: Dabigatran etexilate mesylate, microcrystalline cellulose, lactose anhydrous and crospovidone were blended. The blend was granulated using solution of hydroxypropyl cellulose in isopropyl alcohol. The granules were sized and screened to form dabigatran etexilate mesylate granules.

C) Preparation of oral capsule formulation of dabigatran etexilate mesylate

Table 4: Composition of capsule formulation of dabigatran etexilate mesylate

Ingredients	mg/unit

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Dabigatran etexilate mesylate granules	205
Coated tartaric acid pellets	136
Sodium stearyl fumarate	4
Total	**345**

Procedure: Dabigatran etexilate mesylate granules prepared as per composition of Table 3 above and coated tartaric acid pellets prepared as per Table 2 above were blended. Blend was lubricated with sodium stearyl fumarate and filled into capsules by means of a capsule filling machine.

Example 2: Oral capsule formulation of dabigatran etexilate mesylate

A) Preparation of tartaric acid pellets

Table 5: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid	60
Microcrystalline cellulose	18
Hydroxypropyl cellulose	4
Isopropyl alcohol*	q.s
Total	**82**

*not present in the final product

Procedure: Tartaric acid and microcrystalline cellulose were blended and to this blend was added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass was extruded, spheronized, dried and screened to give pellets. These pellets were then coated using with a protective coating layer as follows to give coated tartaric acid pellets.

B) Preparation of dabigatran etexilate mesylate coated granules

(a) Preparation of dabigatran etexilate mesylate granules

Table 6: Composition of dabigatran etexilate mesylate granules

Ingredients	mg/unit

Dabigatran etexilate mesylate equivalent to 110 mg of dabigatran etexilate	86.48
Microcrystalline cellulose	32.52
Lactose anhydrous	25
Crospovidone	3
Hydroxypropyl cellulose	3
Isopropyl alcohol*	q.s
Total	**150**

*not present in the final product

Procedure: Dabigatran etexilate mesylate, microcrystalline cellulose, lactose anhydrous and crospovidone were blended. The blend was granulated using solution of hydroxypropyl cellulose in isopropyl alcohol. The granules were sized and screened to form dabigatran etexilate mesylate granules.

(b) Preparation of dabigatran etexilate mesylate coated granules

Table 7: Composition of dabigatran etexilate mesylate coated granules

Ingredients	**mg/unit**
Dabigatran etexilate mesylate granules	150
Polyvinyl pyrrolidone	22
Talc	3
Isopropyl alcohol	q.s.
Total	**175**

*not present in the final product

Procedure: Dabigatran etexilate mesylate granules prepared as per the process mentioned above were coated with a coating dispersion of polyvinyl pyrrolidone and talc in isopropyl alcohol to form coated dabigatran etexilate mesylate granules.

C) Preparation of oral capsule formulation of dabigatran etexilate mesylate

Table 8: Composition of capsule formulation of dabigatran etexilate mesylate

Ingredients	**mg/unit**

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Coated dabigatran etexilate mesylate granules	175
Tartaric acid pellets	82
Sodium stearyl fumarate	3
Total	**260**

Procedure: Dabigatran etexilate mesylate granules prepared as per Table 7 above and coated tartaric acid pellets prepared as per table 5 above were blended. Blend was lubricated with sodium stearyl fumarate and filled into capsules by means of a capsule filling machine.

Example 3: Comparative evaluation of two formulation approaches for dabigatran etexilate mesylate

The two formulation approaches for dabigatran etexilate mesylate as shown below were evaluated:

(i) First approach being that of the present invention having two types of particles/pellets (one of dabigatran etexilate mesylate and the other of organic acid) and

(ii) Second approach having one type of particles/pellets having both dabigatran etexilate mesylate and organic acid. This formulation was prepared according to the teachings of US 2006/074056 and, in particular, Example 1. Formulation (B)

(A) Preparation of formulation A having two types of particles/pellets (i.e. Dabigatran etexilate mesylate granules and seal coated tartaric acid pellets)

Table 17: Composition of Dabigatran etexilate mesylate granules

Ingredients	**mg/capsule**
Intragranular	
Dabigatran etexilate mesylate equivalent to 150 mg dabigatran etexilate	172.95
IPA	q.s
Extragranular	

Microcrystalline cellulose	67.05
Croscarmellose Sodium	50
Total weight of the Dabigatran etexilate mesylate granules	290

Table 18: Composition of seal coated tartaric acid pellets

Ingredients	**mg/capsule**
Tartaric acid (TAP® 600)	196.34
Seal coating of Tartaric acid pellets	
Hydroxypropylmethyl cellulose	5.62
Lactose	5.62
Talc	8.42
Isopropyl alcohol- water	q.s
Total weight of seal coated pellets	216

Procedure:

(i) Preparation of Dabigatran etexilate mesylate granules portion

Loaded weighed quantity of dabigatran etexilate mesylate in the granulator and granulated it using isopropyl alcohol. The granules were further dried in fluidized bed drier. The granules were then sized, sifted and blended with microcrystalline cellulose, croscarmellose sodium in a suitable blender to give dabigatran etexilate mesylate granules portion.

(ii) Preparation of seal coated tartaric acid pellets

Hydroxypropyl cellulose was added to a suitable quantity of isopropyl alcohol water mixture under continuous stirring to obtain a clear solution. Lactose was added to this solution and mixed, followed by addition of talc and stirring. The suspension thus formed was filtered through a suitable sieve and sprayed under continuous stirring on tartaric acid pellets using a fluidized bed coater with Wurster column to achieve desired weight gain. The coated tartaric acid pellets were then dried.

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The lubricated seal coated tartaric acid pellets and dabigatran etexilate mesylate granules were filled in capsules using the automatic capsule filling machine in HPMC size 0 capsules.

(C) Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A above) and formulation having one type of particles/pellets (Formulation B above)

Dissolution profiles of the formulations in 0.01N HCl pH 2 media at 100 rpm USP type I (basket) are as depicted under A and B below:

Time (minutes)	% release	
	Formulation A (two types of particles/pellets)	Formulation B (one type of particles/pellets)
10	65.1	19.2
15	79.2	57
20	86.7	86.1
30	92	97
45	95.5	97.6
60	96.8	98.5

Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A above) and formulation having one type of particles/pellets (Formulation B above) indicates that formulations of the present invention having two types of particles/pellets can provide faster dissolution particularly at earlier time points as compared to formulation having one type of particles/pellets. Such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster Tmax (~ 45 minutes – 1 hour), (b) significant bioactivation is involved and (c) negligible and variable absorption at higher pH.

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Claims

1. A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid.

2. A composition according to claim 1 wherein at least one type of particles are coated with a protective coating layer.

3. A composition according to any one of claims 1 and 2 additionally comprising at least one pharmaceutically acceptable excipient.

4. A composition according to any preceeding claim wherein said first type of particles is free from acids.

5. A composition according to any preceding claim wherein said second type of particles is free from dabigatran etexilate.

6. A composition according to any preceeding claim comprising from 0.01 wt % to 90 wt % of dabigatran etexilate (expressed as dabigatran etexilate mesylate).

7. A composition according to any preceeding claim wherein at least 90% by weight of the organic acid present in the composition is contained in said second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients.

8. A composition according to any preceeding claim wherein said first type of particles is coated with a protective coating layer.

9. A composition according to any preceeding claim wherein said second type of particles is coated with a protective coating layer.

10. A composition according to any preceeding claim comprising from 2 wt % to 95 wt % of said at least one pharmaceutically acceptable organic acid.

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11. A composition according to any preceeding claim wherein at least 90% by weight, of the organic acid present in the composition is contained in said second type of particles, the rest (if any) of the organic acid forming part of said excipients.

12. A unit dosage form prepared from a composition according to any preceeding claim which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

13. Composition according to any one of claims 1 to 11 or a unit dose according to claim 12 for use in the reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or in the prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

14. Use of a composition according to any one of claims 1 to 11 or a unit dose according to claim 12 for the preparation of a medicament to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or to prevent venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery

15. A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the subject in need thereof a composition according to any one of claims 1 to 11 or a unit dose according to claim 12.

16. A process for the preparation of a composition according to any one of claims 3 to 11 comprising the step of mixing said first type of particles and said second type of particles with a at least one at least one pharmaceutically acceptable excipient.

17. The process of claim 16 wherein said first type of particles are prepared by granulation.

18. The process according to claim 17 comprising the steps of:

(i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;

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(ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the organic acid granules with a protective coating layer;

(vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) adding a lubricant to the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

19. The process according to claim 17 comprising the steps of:

(i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;

(ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the granules of dabigatran etexilate with a protective coating layer;

(vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) adding a lubricant to the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

20. A process according to claim 17 comprising the steps of:

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(i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;

(ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

(iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

(v) coating the organic acid pellets of step (iv) with a protective coating layer;

(vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) adding a lubricant to the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

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Abstract

Compositions comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, use of said compositions in the reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or in the prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery and processes for the preparation of said compositions.

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Page 588 of 680

* * * * *

Applicants: Pratibha S. PILGAONKAR
Maharukh T. RUSTOMJEE
Anilkumar S. GANDHI
Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

* * * * *

Honorable Commissioner for Patents
PO BOX 1450
Alexandria, VA 22313

PRELIMINARY AMENDMENT, CLAIM TO PRIORITY AND FILING OF PRIORITY DOCUMENT UNDER 37 CFR § 1.55 AND 35 USC § 119

Sir:

As soon as the Serial No. and Filing Date have been accorded the above-identified application, kindly enter the following amendment:

IN THE CLAIMS: See Listing of Claims. This listing will replace all prior versions and listing of claims in the application.

****

REMARKS:

A few constructive editorial changes have been made in the claims to bring them somewhat more into line with U.S. practice and requirements.

Applicants have cancelled all of the originally filed claims, 1-20. New claims, 21-39 have been added to better encompass the full scope and breadth of the invention, notwithstanding Applicants' belief that the claims would have been allowable as originally filed. The replacement Claims are attached hereto.

The instant application is filed as a National Stage entry under 35 USC § 371 from PCT International Application No. PCT/EP2013/053426, filed 21 February 2013, the benefit claim to which is hereby repeated. An image of the PCT International Application coversheet, published as WO 2013/124340, is submitted herewith as confirmation of the application filing particulars.

Applicant claims the benefit of Application No. 461/MUM/2012 filed on 21 February 2012 in INDIA. Form PTO/SB/38 Request to Retrieve Electronic Priority Application is filed herewith.

Entry of the amendments and favorable action on the merits are all hereby respectfully solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE



G. Patrick SAGE, Attorney #37,710

Dated: 19 August 2014
Customer No.: 25,666

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107 West Michigan Avenue
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Enclosure(s): Listing of Claims
An image of the PCT International Application coversheet, published as

* * * * *

THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.

LISTING OF CLAIMS

1-20 (canceled)

21. (new) A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid.

22. (new) The composition according to claim 21, wherein at least one type of particles is coated with a protective coating layer.

23. (new) The composition according to claim 21, further comprising at least one pharmaceutically acceptable excipient.

24. (new) The composition according to claim 21, wherein the first type of particles is free from acids.

25. (new) The composition according to claim 21, wherein the second type of particles is free from dabigatran etexilate.

26. (new) The composition according to claim 21, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate (expressed as dabigatran etexilate mesylate).

27. (new) The composition according to claim 21, wherein at least 90% by weight of the organic acid present in the composition is contained in the second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients.

28. (new) The composition according to claim 21, wherein the first type of particles is coated with a protective coating layer.

29. (new) The composition according to claim 21, wherein the second type of particles is coated with a protective coating layer.

30. (new) The composition according to claim 21, comprising from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

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31. (new) The composition according to claim 21, wherein at least 90% by weight of the organic acid present in the composition is contained in the second type of particles and the rest (if any) of the organic acid forms part of the excipients.

32. (new) A unit dosage form prepared from the composition according to claim 21, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

33. (new) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a composition according to claim 21.

34. (new) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the patient in need thereof a unit dose according to claim 32.

35. (new) A process for the preparation of the composition according to claim 23, comprising the step of mixing the first type of particles and the second type of particles with the at least one at least one pharmaceutically acceptable excipient.

36. (new) The process of claim 35, wherein the first type of particles are prepared by granulation.

37. (new) The process according to claim 36, comprising the steps of:
    i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;
    ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;
    iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;
    iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

v) coating the organic acid granules with a protective coating layer;

vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

38. (new) The process according to claim 36, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

v) coating the granules of dabigatran etexilate with a protective coating layer;

vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

39. (new) The process according to claim 36, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

v) coating the organic acid pellets of step (iv) with a protective coating layer;

vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	
Filing Date	August 21, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

U.S. PATENT DOCUMENTS

Examiner Initial *	Cite No	Document Number: Number - Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US 2005/038077	02-17-2005	KOHLRAUSCH	

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Cite No. 1	Foreign Patent Document: Country[3] Code — Number[4] Kind Code (if known)[5]	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, columns, Lines, Where Relevant Passages or Relevant Figures Appear	T

Examiner Signature		Date Considered	

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not Considered. Include copy of this form with next communication to applicant. 1. Applicant's unique citation design number (optional). 2 See Kinds Codes of USPTO patent Documents. at www.uspto.gov or MPEP 901.04. 3. Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5. Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. 6. Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450 Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	2

Complete if Known	
Application Number	
Filing Date	August 21, 2014
First Named Inventor	Pratibha S. PILGAONKAR
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

NON PATENT LITERATURE DOCUMENTS

Examiner Initial *	Cite No 1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T 2
	2	INTERNATIONAL SEARCH REPORT FOR PCT/EP2013/053426 OF 16 APRIL 2013.	

Examiner Signature		Date Considered	

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1. Applicants unique citation designation number (optional) 2. Applicant is to place a check mark here if English language Translation is attached.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/053426

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/50 A61K31/4439
ADD. A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, EMBASE, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/038077 A1 (KOHLRAUSCH ANJA [DE]) 17 February 2005 (2005-02-17) cited in the application paragraphs [0004], [0007] - [0008], [0013] - [0021] paragraph [0026] examples 1-2	1-3,6, 10,12-16

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 April 2013	26/06/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schwald, Claudia

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/053426

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3, 6, 10, 12-16

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3, 6, 10, 12-16

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein at least one type of particles are coated with a protective coating layer.

---

2. claim: 4

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein said first type of particles is free from acids.

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3. claim: 5

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein said second type of particles is free from dabigatran etexilate.

---

4. claims: 7, 11

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein at least 90% by weight of the organic acid present in the composition is contained in said second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients.

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5. claim: 8

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein said first type of particles is coated with a protective coating layer.

---

6. claim: 9

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein said second type of particles is coated with a protective coating layer.

---

7. claims: 17-20

A process comprising the step of mixing said first type of particles and said second type of particles with a at least one at least one pharmaceutically acceptable excipient, wherein said first type of particles are prepared by granulation.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/053426

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005038077 A1	17-02-2005	AR 045732 A1	09-11-2005
		AT 394094 T	15-05-2008
		CA 2535810 A1	03-03-2005
		DE 10337697 A1	24-03-2005
		DK 1658056 T3	08-09-2008
		EP 1658056 A1	24-05-2006
		ES 2307041 T3	16-11-2008
		JP 4977462 B2	18-07-2012
		JP 2007502788 A	15-02-2007
		PE 03422005 A1	17-06-2005
		PT 1658056 E	23-06-2008
		SI 1658056 T1	31-08-2008
		US 2005038077 A1	17-02-2005
		UY 28468 A1	31-03-2005
		WO 2005018615 A1	03-03-2005

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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29 August 2013 (29.08.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/124340 A1

(51) International Patent Classification:
A61K 9/16 (2006.01) *A61K 31/4439* (2006.01)
A61K 9/50 (2006.01) *A61P 7/02* (2006.01)

(21) International Application Number:
PCT/EP2013/053426

(22) International Filing Date:
21 February 2013 (21.02.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
461/MUM/2012 21 February 2012 (21.02.2012) IN

(71) Applicant: **LABORATORIOS DEL DR. ESTEVE, S.A.** [ES/ES]; Avda. Mare de Déu de Montserrat, 221, E-08041 Barcelona (ES).

(72) Inventors: **PILGAONKAR, Pratibha S.**; RUBICON RESEARCH PVT. LTD, 221 Annexe Building, Goregaon-Mulund Link Road, Off L.B.S. Marg, Bhandup (W), Mumbai 400 078 (IN). **RUSTOMJEE, Maharukh T.**; RUBICON RESEARCH PVT. LTD, 221 Annexe Building, Goregaon-Mulund Link Road, Off L.B.S. Marg, Bhandup (W), Mumbai 400 078 (IN). **GANDHI, Anilkumar S.**; RUBICON RESEARCH PVT. LTD, 221 Annexe Building, Goregaon-Mulund Link Road, Off L.B.S. Marg, Bhandup (W), Mumbai 400 078 (IN).

(74) Agent: **CARBONELL VALLÉS, Enric**; ABG Patentes, S.L., Avda. de Burgos 16D, Edificio Euromor, E-28036 Madrid (ES).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

(57) Abstract: Compositions comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, use of said compositions in the reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or in the prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery and processes for the preparation of said compositions.

WO 2013/124340 A1

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S PILGAONKAR
Filer:	George Patrick Sage/Linda Wooden
Attorney Docket Number:	ESTEVE 6 PCT US

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
National Stage Fee	1631	1	280	280
Natl Stage Search Fee - Report provided	1642	1	480	480
National Stage Exam - all other cases	1633	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1480**

Electronic Acknowledgement Receipt

EFS ID:	19903829
Application Number:	14379613
International Application Number:	PCT/EP2013/053426
Confirmation Number:	6655
Title of Invention:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
First Named Inventor/Applicant Name:	Pratibha S PILGAONKAR
Customer Number:	25666
Filer:	George Patrick Sage/Linda Wooden
Filer Authorized By:	George Patrick Sage
Attorney Docket Number:	ESTEVE 6 PCT US
Receipt Date:	19-AUG-2014
Filing Date:	
Time Stamp:	15:15:23
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1480
RAM confirmation Number	1485
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal of New Application	transmittal.pdf	2351058 fe3c0464b2bd2ec1bb9aa4d44e2152bbf69c085e	no	3
Warnings:					
Information:					
2	Application Data Sheet	ADS.pdf	3107735 760c022691ff16c5d8fdf60305e46b44f6a7f8fb	no	4
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Oath or Declaration filed	SIGNED_DECLARATION.pdf	2486972 475407f18ea850352280bcd2c7b4ca450f718b3b	no	4
Warnings:					
Information:					
4		APPLICATION_ESTEVE6PCTUS.pdf	133927 a4440e001d0d0181e6e63e2080e5cb630eee992a	yes	28

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	23
	Claims	24	27
	Abstract	28	28

Warnings:					
Information:					
5		PRELIM_AMEND_W_CLAIMS.pdf	2760402 0d5d68447bd62072e44aeea0b87a17016e161e8b	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	2
	Claims	3	6

Warnings:					
Information:					

6	Request for USPTO to retrieve priority docs	SB38_PRIORITY.pdf	963235 28452bf51644878098a23648335ecae27b8b814a	no	1
Warnings:					
Information:					
7	Information Disclosure Statement (IDS) Form (SB08)	SB08_1449.pdf	1312222 fb2548067de8f0fed7c98adfe31b5221e025f26c	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
8	Other Reference-Patent/App/Search documents	SEARCH_REPORT.pdf	2580138 390212cb8a26bcce5efdfb5026bb3df1c77d7b29	no	5
Warnings:					
Information:					
9	Miscellaneous Incoming Letter	WO2013124340_COVER_PG.pdf	831859 218079c952916012da4996dec2fd860c3c9a99b0	no	1
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	33471 8d3cf1231034de34b2da72df288aaea40a2d1dda	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	16561019		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: .REQ.RETR

PTO/SB/38 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Request to Retrieve Electronic Priority Application(s)

Send completed form to: Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

COMPLETE IF KNOWN	
Application Number	
Filing Date	
First Named Inventor	Pratibha S. PILGAONKAR, et al.
Art Unit	
Examiner Name	
Attorney Docket Number	ESTEVE 6 PCT US

The undersigned hereby requests the USPTO retrieve an electronic copy of each of the following foreign applications for which priority has been claimed under 35 U.S.C. 119(a)-(d) from a foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement:

Please retrieve (*check all that apply*)

☒ From EPO, JPO, or KIPO (participating foreign intellectual property office) a priority application
Column A. Participating office where application was originally filed
Column B. Application number and filing date of the application
From WIPO (participating foreign intellectual property office) a DAS registered priority application
Column A. DAS Depositing Office where application was originally filed
Column B. Application number and filing date of the application

☒ Copy of certified copy of non-participating office priority document from within a participating foreign intellectual property office application (EPO or JPO)
Column A. Participating office where certified copy of priority document is located
Column B. Application number and filing date of the EPO/JPO application
Column C. Two letter country code and application number of the non-EPO/JPO priority document

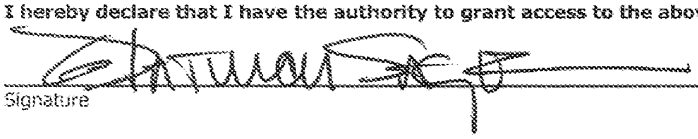
	A	B		C	
	Participating Office (e.g., EPO, JPO, KIPO) or DAS Depositing Office (e.g., IB)	Application to be retrieved or application containing the non-participating priority application		Non-participating priority application to be retrieved	
		App. No.	Filing Date	Country Code	App. No.
1	INDIA	461/MUM/2012	21 February 2012		
2					
3					
4					
5					
6					

This Request to Retrieve Electronic Priority Application(s) (Request) should be filed within the later of four months from the date of filing of the above-identified U.S. application claiming foreign priority, or sixteen months from the filing date of the foreign application to which priority is claimed.

This Request should be submitted concurrently with the claim for priority, or thereafter. The USPTO will not attempt to retrieve the identified priority application(s) until applicant indicates the identified priority application(s) on the oath or declaration or an application data sheet in compliance with 37 CFR 1.63(c).

Applicants are advised to consult Private PAIR (accessed through www.uspto.gov) to assure that the retrieval has been successful. The applicant remains ultimately responsible for the submission of the certified copy of the foreign application(s) within the period set forth in 37 CFR 1.55(a) (before the U.S. application issues as a patent) if the USPTO does not timely retrieve the identified priority application(s).

I hereby declare that I have the authority to grant access to the above-identified foreign application(s).



Signature

19 August 2014
Date

G. Patrick SAGE
Printed or Typed Name

269-382-0030
Telephone Number

Attorney
Title

37,710
Registration Number, if applicable

This collection of information is required by 37 CFR 1.55(d). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process an application). Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

(P022US - rev. 01/2008)

PCT REQUEST

Print Out (Original in Electronic Form)

VIII-3-1	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application LABORATORIOS DEL DR. ESTEVE, S.A. is entitled to claim priority of earlier application No. 461/MUM/2012 by virtue of the following:
VIII-3-1(iv)		an assignment from RUBICON RESEARCH PVT, LTD. to LABORATORIOS DEL DR. ESTEVE, S.A., dated 18 December 2012 (18.12.2012)

PCT REQUEST

Print Out (Original in Electronic Form)

0	**For receiving Office use only**	
0-1	International Application No.	**PCT/EP2013/053426**
0-2	International Filing Date	**21 FEB 2013 (21.02.2013)**
0-3	Name of receiving Office and "PCT International Application"	**RO/EP**

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	PCT Online Filing Version 3.5.000.232 MT/FOP 20020701/0.20.5.20
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	European Patent Office (EPO) (RO/EP)
0-7	**Applicant's or agent's file reference**	P9215PC00
I	**Title of Invention**	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
II	**Applicant**	
II-1	This person is	Applicant only
II-2	Applicant for	All designated States
II-4	Name	LABORATORIOS DEL DR. ESTEVE, S.A.
II-5	Address	Avda. Mare de Déu de Montserrat, 221 E-08041 BARCELONA Spain
II-6	State of nationality	ES
II-7	State of residence	ES
III-1	**Applicant and/or inventor**	
III-1-1	This person is	Inventor only
III-1-4	Name (LAST, First)	PILGAONKAR, Pratibha S.
III-1-5	Address	RUBICON RESEARCH PVT.LTD 221 Annexe Building Goregaon-Mulund Link Road Off L.B.S. Marg, Bhandup (W) 400078 Mumbai India

PCT REQUEST

Print Out (Original in Electronic Form)

III-2	**Applicant and/or inventor**	
III-2-1	This person is	Inventor only
III-2-4	Name (LAST, First)	RUSTOMJEE, Maharukh T.
III-2-5	Address	RUBICON RESEARCH PVT.LTD 221 Annexe Building Goregaon-Mulund Link Road Off L.B.S. Marg, Bhandup (W) 400078 Mumbai India
III-3	**Applicant and/or inventor**	
III-3-1	This person is	Inventor only
III-3-4	Name (LAST, First)	GANDHI, Anilkumar S.
III-3-5	Address	RUBICON RESEARCH PVT.LTD 221 Annexe Building Goregaon-Mulund Link Road Off L.B.S. Marg, Bhandup (W) 400078 Mumbai India
IV-1	**Agent or common representative; or address for correspondence**	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	Agent
IV-1-1	Name (LAST, First)	CARBONELL VALLÉS, Enric
IV-1-2	Address	ABG Patentes, S.L. Avda. de Burgos 16D Edificio Euromor E-28036 Madrid Spain
IV-1-3	Telephone No.	+ 34 91 417 13 00
IV-1-4	Facsimile No.	+ 34 91 417 13 00
IV-1-5	e-mail	informacion@abgpatentes.com
IV-1-5(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	as advance copies followed by paper notifications
IV-1-6	Agent's registration No.	09205730
V	**DESIGNATIONS**	
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**	

PCT REQUEST

Print Out (Original in Electronic Form)

VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	21 February 2012 (21.02.2012)	
VI-1-2	Number	461/MUM/2012	
VI-1-3	Country	IN	
VI-2	**Incorporation by reference :** where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.		
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	–	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	–	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	–	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	–	

PCT REQUEST

Print Out (Original in Electronic Form)

IX	Check list	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	5	✓
IX-2	Description	23	✓
IX-3	Claims	4	✓
IX-4	Abstract	1	✓
IX-5	Drawings	0	–
IX-7	TOTAL	33	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	–	✓
IX-18	PCT-SAFE physical media	–	–
IX-19	Other	Assignment	✓
IX-20	**Figure of the drawings which should accompany the abstract**		
IX-21	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**	(PKCS7 Digital Signature)	
X-1-1	Name (LAST, First)	CARBONELL VALLÉS, Enric	
X-1-2	Name of signatory	ES, ABG Patentes, S.L., E. Carbonell 24183	
X-1-3	Capacity (if such capacity is not obvious from reading the request)	(Representative)	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	**21 FEB 2013 (21.02.2013)**
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/EP
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference P9215PC00	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2013/053426	International filing date *(day/month/year)* 21 February 2013 (21.02.2013)	Priority date *(day/month/year)* 21 February 2012 (21.02.2012)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant LABORATORIOS DEL DR. ESTEVE, S.A.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 26 August 2014 (26.08.2014)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Nora Lindner e-mail: pt05.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2013/053426	21.02.2013	21.02.2012

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/16 A61K9/50 A61K31/4439 ADD. A61P7/02

Applicant
LABORATORIOS DEL DR. ESTEVE, S.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Schwald, Claudia Telephone No. +31 70 340-3381

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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MSN Exhibit 1002
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 4, 5, 7-9, 11, 17-20

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 4, 5, 7-9, 11, 17-20

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-3, 6, 10, 12-16

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2
	No:	Claims	1, 3, 6, 10, 12-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-3, 6, 10, 12-16
Industrial applicability (IA)	Yes:	Claims	1-3, 6, 10, 12-16
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Re Item IV

Lack of unity of invention

1.a. The subjective technical problem to be solved by the present invention is to provide a stable, easy and convenient to prepare composition of dabigatran which provides the desired in vitro release and bioavailability (p.3, l. 24-26).

1.b. Reference is made to the following document:

D1 US 2005/038077 A1 (KOHLRAUSCH ANJA [DE]) 17 February 2005 (2005-02-17)cited in the application

This document D1 discloses (D1, [0004, 0007, 0008, 0013-0021, 0026], ex.1-2) tablet compositions comprising a mixture of different types of particles, including solid (powder) particles of dabigatran etexilate in combination with solid (powder) particles of organic acids for the prophylaxis of deep vein thrombosis. The compositions guarantee sufficient bioavailability and prevents malabsorption.

Therefore it discloses the subject matter of claims 1, 3, 6, 10 and 12-16.

1.c. The subject matter of claim 2 differs in that it comprises a composition, **wherein at least one type of the particles are coated with a protective coating layer.**

No effect has been shown for said difference.

The problem underlying this claim is to provide an alternative composition.

The special technical feature is that at least one type of the particles are coated with a protective coating layer.

1.d. The subject matter of claim 4 differs in **that the first type of particles is free of acid**.

No effect has been shown for said difference.

The problem underlying this claim is to provide an alternative composition.

The special technical feature is that the first type of particles is free of acid.

1.e. The subject matter of claim 5 differs in **that the second type of particles is free of dabigatran etexilate**.

No effect has been shown for said difference.

The problem underlying this claim is to provide an alternative composition.

The special technical feature is that the second type of particles is free of dabiagtran etexilate.

1.f. The subject matter of claim 7 (together with claim11) differs in **that at least 90% by weight of the organic acid present in the composition is contained in said second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients.**

No effect has been shown for said difference.

The problem underlying this claim is to provide an alternative composition.

The special technical feature is that at least 90% by weight of the organic acid present in the composition is contained in said second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients.

1.g. The subject matter of claim 8 differs in that it comprises a composition, **wherein said first type of the particles is coated with a protective coating layer.**

No effect has been shown for said difference.

The problem underlying this claim is to provide an alternative composition.

The special technical feature is that wherein said first type of the particles is coated with a protective coating layer.

1.h. The subject matter of claim 9 differs in that it comprises a composition, **wherein said second type of the particles is coated with a protective coating layer.**

No effect has been shown for said difference.

The problem underlying this claim is to provide an alternative composition.

The special technical feature is that wherein said second type of the particles is coated with a protective coating layer.

1.i. The subject matter of claim 17 (together with claims 18-20) differs in that it is a process **wherein said first type of particles are prepared by granulation.**

No effect has been shown for said difference.

The problem underlying this claim is to provide an alternative composition.

The special technical feature is that it concerns a process wherein said first type of particles are prepared by granulation.

1.j The special technical features of claims 2, 4, 5, 7 (together with 11), 8, 9 and 17 (together with claims 18-20) are not the same special technical features according to Rule 13.2 PCT, since they are not identical and are not corresponding special technical features since they do not lead to the same effect over the prior art.

Accordingly, the present set of claims is considered not to be linked by a single general inventive concept as required by Rule 13.1 PCT. No other single general concept could be identified that could be a single general inventive concept in the sense of Rule 13.1 PCT and which could link the separate groups of inventions claimed. As a result the present set of claims lacks unity of invention.

1.k. The claimed inventions are grouped as follows and as indicated in the search report:

a) Invention 1: Claims 1, 3, 6, 10 and 12-16 (known from D1) and claim 2

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein at least one type of particles are coated with a protective coating layer.

b) Invention 2: Claim 4

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein said first type of particles is free from acids.

c) Invention 3: Claim 5

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein said second type of particles is free from dabigatran etexilate.

d) Invention 4: Claims 7 and 11

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein at least 90% by weight of the organic acid present in the composition is contained in said second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients.

e) Invention 5: Claims 8

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein said first type of particles is coated with a protective coating layer.

f) Invention 6: Claims 9

A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein said second type of particles is coated with a protective coating layer.

g) Invention 7: Claim 17 (together with claims 18-20)

A process comprising the step of mixing said first type of particles and said second type of particles with a at least one at least one pharmaceutically acceptable excipient, wherein said first type of particles are prepared by granulation.

1.I. Furthermore, searching this plurality of different inventions would have caused "major additional searching efforts".

The group of inventions first mentioned in the claims (Invention 1: Claims 1, 3, 6, 10 and 12-16 (known from D1) and claim 2) has been searched.

As the applicant did not pay any additional search fees, this opinion only relates to invention 1.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement for claims 1-3, 6, 10 and 12-16

1 Medical use

Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

2 Documents

Reference is made to the following document:

D1 US 2005/038077 A1 (KOHLRAUSCH ANJA [DE]) 17 February 2005 (2005-02-17)cited in the application

3 Novelty

a. The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1, 3, 6, 10 and 12-16. is not new.

b. The document D1 discloses (D1, [0004, 0007, 0008, 0013-0021, 0026], ex.1-2) tablet compositions comprising a mixture of different types of particles, including solid (powder) particles of dabigatran etexilate in combination with solid (powder) particles of organic acids for the prophylaxis of deep vein thrombosis. The compositions guarantee sufficient bioavailability and prevents malabsorption.

Therefore it discloses the subject matter of claims 1, 3, 6, 10 and 12-16.

c. It appears however that the subject matter of claim 2 is new in the meaning of Article 33 (1) PCT.

4 Inventive step

a. The subject-matter of claim 2 cannot be considered as involving an inventive step in the meaning of Article 33(3) PCT.

The document D1 is regarded as being the prior art closest to the subject-matter of claim 2, and discloses (D1, [0004, 0007, 0008, 0013-0021, 0026], ex.1-2) tablet compositions comprising a mixture of different types of particles, including solid (powder) particles of dabigatran etexilate in combination with solid (powder) particles of organic acids for the prophylaxis of deep vein thrombosis. The compositions guarantee sufficient bioavailability and prevents malabsorption..

The subject-matter of claim 2 therefore differs from this known D1 in that it comprises a protective coating layer on at least one type of the particles.

No effect of this difference versus the closest prior art has been demonstrated by the applicant.

The problem to be solved by the present invention may therefore be regarded as provision of an alternative.

The solution proposed in claim 2 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: Application of coating layers for different purposes like for the protection of an active ingredient, for

providing a certain release pattern or for the provision of non functional coatings as alternative compositions are very well known to the person skilled and are considered as a matter of common routine practice.

In the absence of any (surprising) technical effect must the application of a protective coating to at least one particle be considered a minor modification which the person skilled starting from D1 would have applied within his normal practice in order to provide alternative compositions, thereby arriving at the subject matter of claim 2.

For this reason is the subject matter of claim 2 considered as lacking an inventive step in the meaning of Article 33(3) PCT.

5. Industrial applicability

The subject matter of claims 1-3, 6, 10 and 12-16 appears to be industrially applicable in the meaning of Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

1. Clarity

1.a. The application does not meet the requirements of Article 6 PCT, because the subject matter of claim 6 is not clear.

1.b. The term bracketed terms e.g. "(expressed as dabigatran etexilate mesylate)" in claim 6 renders its scope unclear in the meaning of Article 6 PCT, since it in not evident to the person skilled whether said claim is meant to refer to this specific salt of dabigatran or not.

EP13/53426

सत्यमेव जयते
भारत सरकार
पेटेंट कार्यालय - बौद्धिक सम्पदा भवन
एस.एम. रोड, नजदीक अन्टॉप हिल डाकघर, अन्टॉप हिल, मुम्बई - 400 037
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THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Patent Application and Provisional Specification filed on 21/02/2012 in respect of Patent Application No. 461/MUM/2012 of RUBICON RESEARCH PVT.LTD. at 221, Annexe Building, Goregaon Mulund Link Road, Opposite Indira Container Yard, Off L.B.S. Road, Bhandup (West), Mumbai 400 078, Maharashtra, India.

This Certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 12th day of April 2013

(KISHOR R KADBE)
EXAMINER OF PATENTS AND DESIGNS
OFFICER INCHARGE-RMID

FORM 1 THE PATENTS ACT 1970 (39 OF 1970) & The Patent Rules, 2003 APPLICATION FOR GRANT OF A PATENT [*See* Section 7, 54 & 135 and Rule 20 (1)]	(FOR OFFICE USE ONLY) **Application No:** 461/MUM/2012 **Filing Date:** **Amount of Fee Paid:** 21-02-2012 **CBR No:** **Signature:**

1. APPLICANT(S)

NAME	NATIONALITY	ADDRESS
Rubicon Research Pvt. Ltd.	An Indian Company	221, Annexe Building, Goregaon Mulund Link Road, Opposite Indira Container Yard, Off L.B.S. Marg, Bhandup (West), Mumbai – 400 078, Maharashtra, India

2. **INVENTOR(S)**

NAME	NATIONALITY	ADDRESS
PILGAONKAR; PRATIBHA SUDHIR	An Indian	221, Annexe Building, Goregaon Mulund Link Road, Opposite Indira Container Yard, Off L.B.S. Marg, Bhandup (West), Mumbai – 400 078, Maharashtra, India
RUSTOMJEE; MAHARUKH TEHMASP	An Indian	221, Annexe Building, Goregaon Mulund Link Road, Opposite Indira Container Yard, Off L.B.S. Marg, Bhandup (West), Mumbai – 400 078, Maharashtra, India
GANDHI; ANILKUMAR SURENDRAKUMAR	An Indian	221, Annexe Building, Goregaon Mulund Link Road, Opposite Indira Container Yard, Off L.B.S. Marg, Bhandup (West), Mumbai – 400 078, Maharashtra, India

ORIGINAL

3. **TITLE OF THE INVENTION: ORAL PHARMACEUTICAL COMPOSITIONS OF DIRECT THROMBIN INHIBITORS**

4. **ADDRESS FOR CORRESPONDENCE OF APPLICANT IN INDIA** **Rubicon Research Private Limited, 221, Annexe Building,Goregaon – Mulund Link Road, Off L.B.S. Marg, Bhandup (W), Mumbai – 400 078**	**Telephone No.(022) 25661096/4385/7614** **Fax No.: 91-22-25661097** **Mobile No.:** **E-mail: anil@rubicon.co.in**

रूपये रुपये (चेक/पे ऑर्डर/मनी ऑर्डर द्वारा
CBR संख्या. 2257 दि. 21-02-2012
के तहत प्राप्त हुए।

461 MUM. 2012

21 FEB 2012

रोकड़िया

~~5. PRIORITY PARTICULARS OF THE APPLICATION (S) FILED IN CONVENTION COUNTRY~~

~~COUNTRY~~	~~APPLICATION NUMBER~~	~~FILING DATE~~	~~NAME OF THE APPLICANT~~	~~TITLE OF THE INVENTION~~

~~6.PARTICULARS FOR FILING PATENT COOPERATION TREATY (PCT) NATIONAL PHASE APPLICANT~~

~~International application number~~	~~International filing date as allotted by the receiving office~~

~~7. PARTICULARS FOR FILING DIVISIONAL APLICATION~~

~~ORIGINAL (FIRST) APPLICATION NUMBER~~	~~DATE OF FILING OF ORIGINAL (FIRST) APPLICATION~~

~~8. PARTICULARS FOR FILING PATENT OF ADDITION~~

~~Main application /patent Number~~	~~Date of filing of main application~~

9. DECLARATIONS:

(i) Declaration by the inventor(s)

We, the above named inventor(s) are the true and first inventor(s) for this invention and declare that the applicant(s) herein is our assignee or legal representative.

(a) Date 21/02/2012

(b) Signature(s) of the inventor(s)

(c) Name(s): **PILGAONKAR;** PRATIBHA SUDHIR

(a) Date 21/02/2012

(b) Signature(s) of the inventor(s)

(c) Name(s): **RUSTOMJEE;** MAHARUKH TEHMASP

(a) Date 21-02-2012

(b) Signature(s) of the inventor(s)

(c) Name(s): **GANDHI;** ANILKUMAR SURENDRAKUMAR

21 FEB 2012

~~(ii) Declaration by the applicant(s) in the convention country~~

~~We the applicants(s) in the convention country declare that the applicant (s) herein is/are my/our assignee or legal representative~~

~~(a) Date~~
~~(b) Signature (s)~~
~~(c) Name (s) of the signature~~

(iii) Declaration by the applicant(s):

We, the applicant(s) hereby declare(s) that: -

☑ We are in possession of the above mentioned invention

☑ The provisional specification relating to the invention is filed with this application.

☒ The invention as disclosed in the specification uses the biological material from India and the necessary permission from the competent authority shall be submitted by me/us before the grant of patent to me/us.

☑ There is no lawful ground of objection to the grant of the Patent to me/us.

☑ We are the assignee or legal representative of true and first inventors

☒ The application or each of the applications, particulars of which are given in Para-5 was the first application in convention country/countries in respect of our invention.

☒ We claim the priority from the above mentioned application (s) filed in convention country/countries and state that no application for protection in respect of the invention had been made in a convention country before that date by us or by any person from which we derive the title.

☒ Our application in India is based on international application under Patent Cooperation Treaty (PCT) as mentioned in Para-6.

☒ The application is divided out of our applications particulars of which are given in Para-7 and pray that this application may be treated as deemed to have been filed on under Sec.16 of the Act.

☒ The said invention is an improvement in or modification of the invention particulars of which are given in Para- 8.

21 FEB 2012

10. Following are the attachments with the application:

(a) Form – 2 with Provisional specification No. of pages: 20
(b) Statement and undertaking on Form 3
(c) Fee for excess pages exceeding 30 = Rs 00.00
(d) Fee for application = Rs 4,000.00

Fee Rs 4,000 /- in Cheque bearing No 643628 dated 17/02/2012 drawn on Thane Janata Sahakari Bank Ltd.

We hereby declare that to the best of our knowledge, information and belief the fact and matters stated herein are correct and we request that a patent may be granted to us for the said invention.

Dated this 21st day of February 2012

Pratibha S. Pilgaonkar
Chief Executive officer
Rubicon Research Pvt. Ltd

To:
The Controller of Patents
The Patent Office,
At Mumbai

21 FEB 2012

ORIGINAL

FORM 2

THE PATENTS ACT, 1970

(39 OF 1970)

&

The Patent Rules, 2003

PROVISIONAL SPECIFICATION

(See section 10; rule 13)

1. Title of the invention: **ORAL PHARMACEUTICAL COMPOSITIONS OF DIRECT THROMBIN INHIBITORS**

2. Applicant(s)

(a) NAME: **Rubicon Research Pvt. Ltd.**

(b) NATIONALITY: An Indian Company

(c) ADDRESS: 221, Annexe Building, Goregaon Mulund Link Road, Opposite Indira Container Yard, Off L.B.S. Marg, Bhandup (West), Mumbai – 400 078, Maharashtra, India.

3. PREAMBLE TO THE DESCRIPTION

The following specification describes the invention

461 | मुंबई MUM. | 2012
21 FEB 2012

Field of the Invention

The present invention relates to oral pharmaceutical compositions of direct thrombin inhibitors and processes for preparing such compositions. Particularly the present invention relates to oral pharmaceutical compositions comprising dabigatran etexilate or pharmaceutically acceptable salts thereof.

Background of the Invention

Atrial fibrillation is the most common cardiac arrhythmia which is characterized by abnormal heart rhythm. It is considered to be a common cause of irregular heart beat and can cause stroke and other systemic embolic events, eventually leading to death. It has been seen that the incidence of atrial fibrillation increases with age and nearly 6% of individuals over the age of 65 are affected while the prevalence is about 8% in individuals over the age of 80. The lack of organized cardiac contractions in atrial fibrillation generally results in some stagnant blood in the left atrium or left atrial appendage. This lack of movement of blood leads to thrombus formation or blood clotting. Patients with atrial fibrillation are therefore at greater risk of developing clots which increases the risk of stroke and other systemic embolic events. Since the consequence of stroke or systemic embolism is devastating, a primary aim of therapy for atrial fibrillation is to reduce the risk of arterial thrombus formation and thromboembolism. Anticoagulants such as warfarin are mainly used in case of atrial fibrillation along with other *medications such as beta blockers and* calcium channel blockers or some noninvasive rhythm control methods. Though anticoagulation therapy with warfarin has been shown to significantly reduce the incidence of stroke or systemic embolism, its use is found to be cumbersome due to multiple diet and drug interactions, chances of hemorrhage which are difficult to manage, requirement of frequent laboratory monitoring etc. Use of a newer safe and effective anticoagulant is therefore necessary.

Direct thrombin inhibitors, is another class of anticoagulants that act by directly inhibiting the enzyme thrombin and are expected to replace heparin (and derivatives) and warfarin in various clinical scenarios. Thrombin, a serine protease protein

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formed by proteolytic cleavage of prothrombin, converts soluble fibrinogen into insoluble strands of fibrin and further catalyzes many other coagulation-related reactions. Direct thrombin inhibitors inhibit thrombin including fibrin-bound thrombin, thereby delimiting thrombus growth, provide predictable anticoagulant responses because they are not bound to plasma proteins and have no drug-drug interactions. Depending on their interaction with the thrombin molecule, there are bivalent as well as univalent types of direct thrombin inhibitors, with some being in clinical use, while others undergoing clinical development.

Dabigatran is a potent, reversible, univalent direct thrombin inhibitor. It reduces the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It is also useful in primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. Dabigatran was first disclosed in WO98/37075, which claimed compounds with a thrombin-inhibiting effect and the effect of prolonging the thrombin time, under the name 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino) phenyl] aminomethyl] benzimidazol-5-ylcarboxylic acid-N-(2-pyridyl)-N-(2 ethoxycarbonylethyl)amides.

Dabigatran is currently available as dabigatran etexilate mesylate (DEM) in Europe and United States under the brand name Pradaxa® from Boehringer Ingelheim as immediate release oral capsules of 75 mg and 110 mg and 75 mg and 150 mg strengths respectively to be administered twice daily. DEM is a salt form of the prodrug dabigatran etexilate which after oral administration is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in the liver. DEM is a yellow-white to yellow non-hygroscopic powder that exists in two anhydrous polymorphic forms, Form I and II. The aqueous solubility of DEM is strongly pH dependent with rather high solubility in acidic media and very poor solubility in neutral and basic media while solubility in water is 1.8mg/mL. The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is

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approximately about 3-7% and elimination half life is 12-17 hours. DEM is BCS Class II drug, indicating poor aqueous solubility but good membrane permeability. DEM is stable in the solid state and not sensitive to light irradiation but it predominantly undergoes degradation by hydrolytic pathways in the presence of moisture. It is also acid sensitive.

Due to these physicochemical and biopharmaceutical properties of DEM, some attempts have been made to provide compositions of DEM that are stable and/or provide desirable *in vitro* release and bioavailability.

U.S Patent Application 2006/0183779A1 describes pharmaceutical compositions of DEM for oral administration in the form of pellets comprising (a) substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1g/250ml at 20°C such as tartaric acid; and (b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material. The separating agent layer or insulating layer separates the acid core from the active substance containing layer. The layer of active substance may in turn be enclosed in a coating which increases the abrasion resistance and shelf life of the pellets. Such layered pellets are later filled into hard capsules. However, the process of preparing layered pellets is cumbersome, time consuming and uneconomical.

U.S Patent Application 2005/0038077 discloses a tablet comprising dabigatran etexilate or pharmaceutically acceptable salt thereof; one or more pharmaceutically acceptable organic acids with a solubility in water of > 1g/250ml at 20°C and a pharmaceutically acceptable excipient or filler. However due to the presence of an organic acid in close contact with the active in a tablet composition without any special steps taken to separate the two from each other, can make the active highly susceptible to hydrolysis in the presence of humidity.

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The above attempts have however been made to provide compositions of DEM, that are either tedious or technologically demanding to prepare or are unlikely to remain stable over the shelf life of the product. Need therefore exists to prepare alternate compositions of dabigatran etexilate that are stable, easy or convenient to prepare, provide the desired *in vitro* release and bioavailability.

The present inventors after rigorous experimentation provide oral compositions of direct thrombin inhibitors comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein a) first type of particles comprise active agent; b) second type of particles comprise at least one pharmaceutically acceptable organic acid; and c) optionally at least one type of particles are coated with a protective coating layer. Such compositions are stable, provide desired in-vitro and in-vivo performance and can be prepared by simple, non-tedious and cost-effective process. These compositions are independent of the pH of the stomach and show reduced inter-patient and intra-patient variability.

Detailed Description of the Invention

The present invention provides oral pharmaceutical compositions comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein a) first type of particles comprise one or more direct thrombin inhibitors; b) second type of particles comprise at least one pharmaceutically acceptable organic acid; and c) optionally at least one type of particles are coated with a protective coating layer. The compositions of the present invention are stable, easy to prepare, and provide the desired in-vitro release of the active.

The first type of particles present in the composition of the present invention, comprise one or more direct thrombin inhibitors. The term "direct thrombin inhibitor/s" as employed herein refers to any compound that acts by directly inhibiting the enzyme thrombin, both free and fibrin-bound thrombin as well as thrombin-induced platelet aggregation; including, but not limited to, dabigatran, argatroban, inogatran,

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melagatran and the like, in the form of free acid or free base or pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts, pharmaceutically acceptable salts of prodrugs, active metabolites, polymorphs, solvates, hydrates, enantiomers, optical isomers, tautomers or racemic mixtures thereof. In one embodiment, the direct thrombin inhibitors employed in the compositions of the present invention include, but are not limited to, univalent inhibitors such as, but not limited to, dabigatran, argatroban, melagatran and the like; or bivalent inhibitors such as, but not limited to hirudin, bivalirudin, lepirudin, desirudin and the like; and various combinations thereof in the form of free acid or free base or pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts, pharmaceutically acceptable salts of prodrugs, active metabolites, polymorphs, solvates, hydrates, enantiomers, optical isomers, tautomers or racemic mixtures thereof.

Pharmaceutically effective amount of direct thrombin inhibitor is employed in the composition of the present invention. The term "effective amount" refers to an amount effective to achieve desired preventive, therapeutic and/or beneficial effect, such as but not limited to reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, and the like. In one embodiment the amount of direct thrombin inhibitor in the composition can vary from about 0.01 weight % to about 90 weight %, based on the total weight of the composition. In another embodiment the amount of direct thrombin inhibitor in the composition can vary from about 0.02 weight % to about 85 weight %, based on the total weight of the composition. In still another embodiment, the amount of direct thrombin inhibitor in the composition can vary from about 0.05 weight % to about 80 weight %, based on the total weight of the composition. In one embodiment the compositions of the present invention may be administered at a dose of about 0.01 mg to about 400 mg of direct thrombin reductase inhibitor. In another embodiment the compositions of the present invention may be administered at a dose of about 0.1 mg to about 350 mg of direct thrombin inhibitor. In still another embodiment the compositions of the

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present invention may be administered at a dose of about 0.2 mg to about 300 mg of direct thrombin inhibitor. In one embodiment, the direct thrombin inhibitor employed for the present invention is dabigatran in the form of free acid or free base or pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts, pharmaceutically acceptable salts of prodrugs, active metabolites, polymorphs, solvates, hydrates, enantiomers, optical isomers, tautomers or racemic mixtures thereof. In a further embodiment, the direct thrombin inhibitor employed in the present invention is dabigatran etexilate mesylate.

The oral pharmaceutical composition of the present invention comprises a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, with a first type of particles comprising one or more direct thrombin inhibitors and second type of particles comprising at least one pharmaceutically acceptable organic acid. Organic acids that may be employed in the present composition include, but are not limited to, tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, aspartic acid and the like or combinations thereof including the hydrates and acid salts thereof.

In one embodiment the organic acid is present in the composition of the present invention in an amount of about 2% by weight to about 95% by weight of the composition. In another embodiment the organic acid is present in the composition of the present invention in an amount of about 5% by weight to about 90% by weight of the composition. In a further embodiment the organic acid is present in the composition of the present invention in an amount of about 10% by weight to about 85% by weight of the composition.

Further the oral pharmaceutical compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein optionally at least one type of particles are coated with a protective coating layer. In one embodiment, the first type of particles is coated with a protective coating layer. In another embodiment, the second type of particles

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is coated with a protective coating layer. In yet another embodiment, the first and the second type of particles are coated with a protective coating layer.

In one embodiment, protective coating layer is formed of a polymeric or a non-polymeric pharmaceutically acceptable agent or any combination thereof.

The polymeric pharmaceutically acceptable agents used for the protective coating layer include, but are not limited to, cellulose derivatives, vinyl derivatives, polymers and copolymers, gums, acrylic or methacrylic acid polymers, copolymers, esters or derivatives thereof, and the like or combinations thereof. Cellulose derivatives that may be employed, include, but are not limited to, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, ethylcellulose, hydroxypropyl ethylcellulose, carboxymethylethyl cellulose, carboxy ethylcellulose, carboxymethyl hydroxyethylcellulose, hydroxyethylmethyl carboxymethyl cellulose, hydroxyethyl methyl cellulose, carboxymethyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, carboxymethyl sulfoethyl cellulose, sodium carboxymethyl cellulose, and the like or combinations thereof. Vinyl derivatives, polymers and copolymers thereof that may be employed include, but are not limited to copolymers of vinyl pyrrolidone, copolymers of polyvinyl alcohol (Kollicoat IR), polyvinylpyrrolidone or combinations thereof. Gums that may be employed include, but are not limited to, gum arabic, alginates, guar gum, locust bean gum, carrageenan, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, karaya, and the like, or combinations. Acrylic or methacrylic acid polymers, copolymers, esters or derivatives thereof, that may be employed include, but are not limited to, a) copolymer formed from monomers selected from methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters b) copolymer formed from monomers selected from butyl methacrylate, (2-dimethylaminoethyl)methacrylate and methyl methacrylate c) copolymer formed from monomers selected from ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride or d) copolymers of acrylate and methacrylates with/without quarternary ammonium

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group in combination with sodium carboxymethylcellulose, e.g. those available from Röhm GmbH under the trademark Eudragit ® like Eudragit EPO (dimethylaminoethyl methacrylate copolymer; basic butylated methacrylate copolymer), Eudragit RL and RS (trimethylammonioethyl methacrylate copolymer), Eudragit NE30D and Eudragit NE40D (ethylacrylate methymethacrylate copolymer), Eudragit RD 100 (ammoniomethacrylate copolymer with sodium carboxymethylcellulose); or the like or any combinations thereof.

The non-polymeric pharmaceutically acceptable agents used for the protective coating layer include, but are not limited to, fatty acids, long chain alcohols, fats, waxes, and the like, or combinations thereof. Fatty acids that may be employed include, but are not limited to, decenoic acid, docosanoic acid, stearic acid, palmitic acid, lauric acid, myristic acid, hydrogenated palm kernel oil, hydrogenated peanut oil, hydrogenated palm oil, hydrogenated rapeseed oil, hydrogenated rice bran oil, hydrogenated soybean oil, hydrogenated sunflower oil, hydrogenated castor oil, hydrogenated cottonseed oil, and the like, and mixtures thereof. Long chain monohydric alcohols that may be employed include, but are not limited to, cetyl alcohol, stearyl alcohol and mixtures thereof. Waxes that may be employed include, but are not limited to, spermaceti wax, carnauba wax, Japan wax, bayberry wax, flax wax, beeswax, Chinese wax, shellac wax, lanolin wax, sugarcane wax, candelilla wax, paraffin wax, microcrystalline wax, petrolatum wax, carbowax, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, glyceryl dipalmitate, glyceryl tripalmitate, glyceryl monopalmitate, glyceryl dilaurate, glyceryl trilaurate, glyceryl monolaurate, glyceryl trimyristate, glyceryl monodecenoate, glyceryl didecenoate, glyceryl tridecenoate, glyceryl behenate and the like, or mixtures thereof.

In a further embodiment, in addition to polymeric or non-polymeric pharmaceutically acceptable agent or any combination thereof, the protective coating layer may optionally further comprise one or more pharmaceutically acceptable excipients such as, but not limited to, plasticizer, anti-tacking agent, pigment, and the like, or combinations thereof. A plasticizer that may be employed includes, but is not limited

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to, triethyl citrate, acetyl triethyl citrate, propylene glycol, polyethylene glycol, acetyl tributyl citrate, acetylated monoglycerides, glycerin, triacetin, phthalate esters (*e.g.*, diethyl phthalate, dibutyl phthalate), castor oil, sorbitol and dibutyl seccate or a combination thereof. An anti-tacking agent that may be employed includes, but is not limited to, talc, or glyceryl monostearate. A pigment such as, but not limited to, titanium dioxide, iron oxide, or a mixture thereof may be employed.

The protective coating layer may be optionally applied onto at least a type of particles of the present invention in any suitable equipment where coating can be achieved, such as, but not limited to, coating pan, conventional film coating apparatus or a fluidized bed apparatus, or the like. Furthermore, in one embodiment, the protective coating layer can be applied from an aqueous or organic solution or dispersion. In another embodiment, the particles being coated with the protective coating layer may be coated to a weight gain of about 2% to about 50% by weight.

In one embodiment, in order to reduce any damage to the protective coating layer during transfer into capsules, the particles coated with the protective coating layer may be further seal coated with conventional pharmaceutically acceptable film forming agents which may optionally be combined with plasticizers or pigments. Suitable film forming agents include, but are not limited to, hydroxypropyl cellulose, hydroxypropyl methylcellulose, acrylic and methacrylic acid polymers, copolymers or esters, and the like or combinations thereof. Plasticizers or pigments as discussed above may optionally be used with the film forming agents.

The compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient. In a further embodiment, the first type of particles comprising one or more direct thrombin inhibitors may optionally further comprise at least one pharmaceutically acceptable excipient. In another embodiment, the second type of particles comprising at least one organic acid, may optionally further comprise at least one pharmaceutically acceptable excipient. In yet another embodiment, at least two types of particles that

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are present in the pharmaceutical composition optionally further comprise at least one pharmaceutically acceptable excipient.

The pharmaceutically acceptable excipients that may be incorporated in the composition of the present invention include, but are not limited to, binders, disintegrants, diluents, surfactants, glidants, lubricants, and the like or combinations thereof. Disintegrants that may be employed include, but are not limited to, natural, modified or pregelatinized starch, crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose, crospovidone, calcium silicate and the like or combinations thereof. Examples of suitable binders include, but are not limited to, starch, pregelatinized starch, polyvinyl pyrrolidone, copovidone, cellulose derivatives, such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium carboxy methyl cellulose and the like or combinations thereof. Examples of suitable diluents include, but are not limited to, starch, microcrystalline cellulose, lactose, xylitol, mannitol, maltose, polyols, fructose, guar gum, sorbitol, magnesium hydroxide, dicalcium phosphate, and the like or any combinations thereof. Examples of the lubricant include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, talc, and sodium stearyl fumarate. The tablet compositions of the invention may also include a glidant such as, but not limited to, colloidal silica, silica gel, precipitated silica, or combinations thereof. Examples of surfactants include, but are not limited to, sodium docusate, glyceryl monooleate, polyethylene alkyl ether, polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, sorbic acid, sorbitan fatty acid ester, and mixtures thereof.

The compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, with first type of particles comprising one or more direct thrombin inhibitors and second type of particles comprising at least one organic acid. The particles present in the compositions of the present invention may be in the form of, but not limited to, powder, granules, pellets, beads, minitablets or the like. The granules may be

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prepared by methods such as, but not limited to, wet granulation, melt granulation, dry granulation or roll compaction or the like. In an aspect of the present invention, pellets may be prepared using extrusion spheronization. In another aspect of the present invention, direct thrombin inhibitor present in the first set of particles or at least one organic acid present in the second set of particles can be loaded on an inert carrier. The inert carrier can be selected from, but not limited to, beads, pellets, spheres or similar particles that do not contain an active ingredient. Non-limiting examples of inert carrier include microcrystalline cellulose, sugar or silicon dioxide. In yet another embodiment, the particles of the present invention, in the powder form, may be incorporated in the compositions of the present invention.

The compositions of the present invention comprise from about 5% to about 100% by weight of the mixture of at least two types of particles. Ratio of the first and second types of particles is from about 1:99 to about 99:1.

The term "composition" or "formulation" or "dosage form" has been employed interchangeably for the purpose of the present invention and mean that it is a pharmaceutical composition which is suitable for administration to a patient. In one embodiment the compositions of the present invention can be in the form of capsules, tablets, minitablets, stick formulation, dispersible tablets, dry suspension for reconstitution, powder or granule for solution or suspension, granules, and the like or any combinations thereof. Depending of the final dosage form the compositions of the present invention may comprise appropriate pharmaceutically acceptable excipients such as those mentioned above or some additional ones such as, but not limited to, sweeteners, flavors, colorants and the like or combinations thereof. Further it is contemplated within the scope of the invention that the dosage form can be encapsulated or coated. In one embodiment, the composition of the present invention is in the form of a capsule. Capsules include, for example, hard capsules of gelatine or hydroxypropylmethylcellulose and the like. In a further embodiment, the compositions of the present invention may be manufactured using conventional techniques known in the art.

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In one embodiment the process of preparing the compositions of the present invention comprises the steps of

(i) blending one or more direct thrombin inhibitor and at least one pharmaceutically acceptable excipient such as diluent;

(ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the organic acid granules with a protective coating layer;

(vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) lubricating the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In another embodiment the process of preparing the compositions of the present invention comprises the steps of

(i) blending one or more direct thrombin inhibitor and at least one pharmaceutically acceptable excipient such as diluent;

(ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the granules of active agent with a protective coating layer;

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(vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) lubricating the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In yet another embodiment the process of preparing the compositions of the present invention comprises the steps of

(i) blending one or more direct thrombin inhibitor and at least one pharmaceutically acceptable excipient such as diluent;

(ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent or binder;

(iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

(v) coating the organic acid pellets of step (iv) with a protective coating layer;

(vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) lubricating the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In a further embodiment is provided the use of pharmaceutical composition of direct thrombin inhibitor for the manufacture of a medicament for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Further, the present invention provides a method of for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous

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thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the subject in need thereof pharmaceutical compositions of direct thrombin inhibitors of the present invention.

In another embodiment of the present invention the direct thrombin inhibitors may be combined with other active agents or pharmaceutically acceptable salts thereof including, but not limited to, atorvastatin, dipyridamole, mopidamole and the like or combinations thereof.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. The invention is further illustrated by the following examples, which are for illustrative purposes and should not be construed as limiting the scope of the invention in any way.

Examples

Example 1: Oral capsule formulation of dabigatran etexilate mesylate

A) Preparation of coated tartaric acid pellets

(a) Preparation of tartaric acid pellets

Table 1: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid	80
Microcrystalline cellulose	30
Hydroxypropyl cellulose	10
Isopropyl alcohol*	q.s
Total	**120**

*not present in the final product

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Procedure: Tartaric acid and microcrystalline cellulose were blended and to this blend was added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass was extruded, spheronized, dried and screened to give pellets. These pellets were then coated with a protective coating layer as follows to give coated tartaric acid pellets.

(b) Preparation of coated tartaric acid pellets

Table 2: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid pellets	120
Hydroxypropyl methylcellulose	10
Talc	6
Isopropyl alcohol*	q.s
Total	**136**

*not present in the final product

Procedure: Tartaric acid pellets prepared as above were coated with dispersion of hydroxypropyl cellulose and talc in isopropyl alcohol. The coated pellets were then dried to give coated tartaric acid pellets.

B) Preparation of dabigatran etexilate mesylate granules

Table 3: Composition of dabigatran etexilate mesylate granules

Ingredients	mg/unit
Dabigatran etexilate mesylate equivalent to 110 mg of dabigatran etexilate	126.83
Microcrystalline cellulose	40.17
Lactose anhydrous	30
Crospovidone	4

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Hydroxypropyl cellulose	4
Isopropyl alcohol*	q.s
Total	**205**

*not present in the final product

Procedure: Dabigatran etexilate mesylate, microcrystalline cellulose, lactose anhydrous and crospovidone were blended. The blend was granulated using solution of hydroxypropyl cellulose in isopropyl alcohol. The granules were sized and screened to form dabigatran etexilate mesylate granules.

C) Preparation of oral capsule formulation of dabigatran etexilate mesylate

Table 4: Composition of capsule formulation of dabigatran etexilate mesylate

Ingredients	mg/unit
Dabigatran etexilate mesylate granules	205
Coated tartaric acid pellets	136
Sodium stearyl fumarate	4
Total	**345**

Procedure: Dabigatran etexilate mesylate granules prepared as per composition of Table 3 above and coated tartaric acid pellets prepared as per Table 2 above were blended. Blend was lubricated with sodium stearyl fumarate and filled into capsules by means of a capsule filling machine.

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Example 2: Oral capsule formulation of dabigatran etexilate mesylate

A) Preparation of tartaric acid pellets

Table 5: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid	60
Microcrystalline cellulose	18
Hydroxypropyl cellulose	4
Isopropyl alcohol*	q.s
Total	**82**

*not present in the final product

Procedure: Tartaric acid and microcrystalline cellulose were blended and to this blend was added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass was extruded, spheronized, dried and screened to give pellets.

B) Preparation of dabigatran etexilate mesylate coated granules

(a) Preparation of dabigatran etexilate mesylate granules

Table 6: Composition of dabigatran etexilate mesylate granules

Ingredients	mg/unit
Dabigatran etexilate mesylate equivalent to 110 mg of dabigatran etexilate	86.48
Microcrystalline cellulose	32.52
Lactose anhydrous	25
Crospovidone	3
Hydroxypropyl cellulose	3
Isopropyl alcohol*	q.s
Total	**150**

*not present in the final product

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Procedure: Dabigatran etexilate mesylate, microcrystalline cellulose, lactose anhydrous and crospovidone were blended. The blend was granulated using solution of hydroxypropyl cellulose in isopropyl alcohol. The granules were sized and screened to form dabigatran etexilate mesylate granules.

(b) Preparation of dabigatran etexilate mesylate coated granules

Table 7: Composition of dabigatran etexilate mesylate coated granules

Ingredients	mg/unit
Dabigatran etexilate mesylate granules	150
Polyvinyl pyrrolidone	22
Talc	3
Isopropyl alcohol	q.s.
Total	**175**

*not present in the final product

Procedure: Dabigatran etexilate mesylate granules prepared as per the process mentioned above were coated with a coating dispersion of polyvinyl pyrrolidone and talc in isopropyl alcohol to form coated dabigatran etexilate mesylate granules.

C) Preparation of oral capsule formulation of dabigatran etexilate mesylate

Table 8: Composition of capsule formulation of dabigatran etexilate mesylate

Ingredients	mg/unit
Coated dabigatran etexilate mesylate granules	175
Tartaric acid pellets	82
Sodium stearyl fumarate	3
Total	**260**

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Procedure: Dabigatran etexilate mesylate granules prepared as per Table 7 above and coated tartaric acid pellets prepared as per table 5 above were blended. Blend was lubricated with sodium stearyl fumarate and filled into capsules by means of a capsule filling machine.

Dated this 21st day of February 2012

Pratibha S. Pilgaonkar
Chief Executive Officer
Rubicon Research Pvt. Ltd

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(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

(57) Abstract: Compositions comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, use of said compositions in the reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or in the prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery and processes for the preparation of said compositions.

Claims

1. A composition comprising a mixture of at least two types of particles wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid.

2. A composition according to claim 1 wherein at least one type of particles are coated with a protective coating layer.

3. A composition according to any one of claims 1 and 2 additionally comprising at least one pharmaceutically acceptable excipient.

4. A composition according to any preceeding claim wherein said first type of particles is free from acids.

5. A composition according to any preceding claim wherein said second type of particles is free from dabigatran etexilate.

6. A composition according to any preceeding claim comprising from 0.01 wt % to 90 wt % of dabigatran etexilate (expressed as dabigatran etexilate mesylate).

7. A composition according to any preceeding claim wherein at least 90% by weight of the organic acid present in the composition is contained in said second type of particles and the rest (if any) of the organic acid forms part of the pharmaceutically acceptable excipients.

8. A composition according to any preceeding claim wherein said first type of particles is coated with a protective coating layer.

9. A composition according to any preceeding claim wherein said second type of particles is coated with a protective coating layer.

10. A composition according to any preceeding claim comprising from 2 wt % to 95 wt % of said at least one pharmaceutically acceptable organic acid.

11. A composition according to any preceeding claim wherein at least 90% by weight, of the organic acid present in the composition is contained in said second type of particles, the rest (if any) of the organic acid forming part of said excipients.

12. A unit dosage form prepared from a composition according to any preceeding claim which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

13. Composition according to any one of claims 1 to 11 or a unit dose according to claim 12 for use in the reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or in the prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

14. Use of a composition according to any one of claims 1 to 11 or a unit dose according to claim 12 for the preparation of a medicament to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or to prevent venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery

15. A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the subject in need thereof a composition according to any one of claims 1 to 11 or a unit dose according to claim 12.

16. A process for the preparation of a composition according to any one of claims 3 to 11 comprising the step of mixing said first type of particles and said second type of particles with a at least one at least one pharmaceutically acceptable excipient.

17. The process of claim 16 wherein said first type of particles are prepared by granulation.

18. The process according to claim 17 comprising the steps of:
    (i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;

(ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the organic acid granules with a protective coating layer;

(vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) adding a lubricant to the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

19. The process according to claim 17 comprising the steps of:

(i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;

(ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the granules of dabigatran etexilate with a protective coating layer;

(vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) adding a lubricant to the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

20. A process according to claim 17 comprising the steps of:

(i) blending dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof and at least one pharmaceutically acceptable excipient;

(ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

(iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

(v) coating the organic acid pellets of step (iv) with a protective coating layer;

(vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) adding a lubricant to the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Field of Invention

The present invention relates to oral pharmaceutical compositions comprising dabigatran etexilate or pharmaceutically acceptable salts thereof.

Background of the Invention

Atrial fibrillation is the most common cardiac arrhythmia which is characterized by abnormal heart rhythm. It is considered to be a common cause of irregular heart beat and can cause stroke and other systemic embolic events, eventually leading to death. It has been seen that the incidence of atrial fibrillation increases with age and nearly 6% of individuals over the age of 65 are affected while the prevalence is about 8% in individuals over the age of 80. The lack of organized cardiac contractions in atrial fibrillation generally results in some stagnant blood in the left atrium or left atrial appendage. This lack of movement of blood leads to thrombus formation or blood clotting. Patients with atrial fibrillation are therefore at greater risk of developing clots which increases the risk of stroke and other systemic embolic events. Since the consequence of stroke or systemic embolism is devastating, a primary aim of therapy for atrial fibrillation is to reduce the risk of arterial thrombus formation and thromboembolism. Anticoagulants such as warfarin are mainly used in case of atrial fibrillation along with other medications such as beta blockers and calcium channel blockers or some noninvasive rhythm control methods. Though anticoagulation therapy with warfarin has been shown to significantly reduce the incidence of stroke or systemic embolism, its use is found to be cumbersome due to multiple diet and drug interactions, chances of hemorrhage which are difficult to manage, requirement of frequent laboratory monitoring etc. Use of a newer safe and effective anticoagulant is therefore necessary.

Direct thrombin inhibitors, is another class of anticoagulants that act by directly inhibiting the enzyme thrombin and are expected to replace heparin (and derivatives) and warfarin in various clinical scenarios. Thrombin, a serine protease protein formed by proteolytic cleavage of prothrombin, converts soluble fibrinogen into insoluble strands of fibrin and further catalyzes many other coagulation-related reactions. Direct thrombin inhibitors inhibit thrombin including fibrin-bound thrombin, thereby delimiting thrombus growth, provide predictable anticoagulant responses because they are not

bound to plasma proteins and have no drug-drug interactions. Depending on their interaction with the thrombin molecule, there are bivalent as well as univalent types of direct thrombin inhibitors, with some being in clinical use, while others undergoing clinical development.

Dabigatran is a potent, reversible, univalent direct thrombin inhibitor. It reduces the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It is also useful in primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. Dabigatran was first disclosed in WO98/37075, which claimed compounds with a thrombin-inhibiting effect and the effect of prolonging the thrombin time, under the name 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino) phenyl] aminomethyl] benzimidazol-5-ylcarboxylic acid-N-(2-pyridyl)-N-(2 ethoxycarbonylethyl)amides.

Dabigatran is currently available as dabigatran etexilate mesylate (DEM) under the brand name Pradaxa® from Boehringer Ingelheim as immediate release oral capsules of 75 mg and 110 mg (in Europe) and 75 mg and 150 mg strengths (in the United States) to be administered twice daily. DEM is a salt form of the prodrug dabigatran etexilate which after oral administration is absorbed and converted to dabigatran by esterase-catalysed hydrolysis in the liver. DEM is a yellow-white to yellow non-hygroscopic powder that exists in two anhydrous polymorphic forms, Form I and II, which are described in WO 2005/028468. The aqueous solubility of DEM is strongly pH dependent with rather high solubility in acidic media and very poor solubility in neutral and basic media while solubility in water is 1.8mg/mL. The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately about 3-7% and elimination half life is 12-17 hours. DEM is BCS Class II drug, indicating poor aqueous solubility but good membrane permeability. DEM is stable in the solid state and not sensitive to light irradiation but it predominantly undergoes degradation by hydrolytic pathways in the presence of moisture. It is also acid sensitive.

Due to these physicochemical and biopharmaceutical properties of DEM, some attempts have been made to provide compositions of DEM that are stable and/or provide desirable *in vitro* release and bioavailability.

U.S Patent Application 2006/0183779A1 describes pharmaceutical compositions of DEM for oral administration in the form of pellets comprising (a) substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1g/250ml at 20°C such as tartaric acid; and (b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material. The separating agent layer or insulating layer separates the acid core from the active substance containing layer. The layer of active substance may in turn be enclosed in a coating which increases the abrasion resistance and shelf life of the pellets. Such layered pellets are later filled into hard capsules. However, the process of preparing layered pellets is cumbersome, time consuming and uneconomical.

U.S Patent Application 2005/0038077 discloses a tablet comprising dabigatran etexilate or pharmaceutically acceptable salt thereof; one or more pharmaceutically acceptable organic acids with a solubility in water of > 1g/250ml at 20°C and a pharmaceutically acceptable excipient or filler. However due to the presence of an organic acid in close contact with the active in a tablet composition without any special steps taken to separate the two from each other, can make the active highly susceptible to hydrolysis in the presence of humidity.

The above attempts only provided compositions of DEM, which are either tedious or technologically demanding to prepare or are unlikely to remain stable over the shelf life of the product. Need therefore exists to prepare alternate compositions of dabigatran etexilate that are stable, easy or convenient to prepare, provide the desired *in vitro* release and bioavailability.

The present inventors after rigorous experimentation provide oral compositions of dabigatran etexilate comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein a) the first type of particles comprise the active agent; b) the second type of particles comprise at least one pharmaceutically acceptable organic acid; and c) optionally at least one type of particles are coated with a protective coating layer. Such compositions are chemically and polymorphically stable, provide desired in-vitro and in-vivo performance and can be prepared by simple, non-tedious and cost-effective process.In particular, the

compositions of the present invention provide a quick dissolution particularly at earlier time points as compared to formulation having one type of particles/pellets. Such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster Tmax (~ 45 minutes – 1 hour), (b) significant bioactivation is involved and (c) negligible and variable absorption at higher pH.

Detailed Description of the Invention

The present invention provides, in one of its aspects, pharmaceutical compositions, preferably for oral administration, comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid.

In a particular embodiment, the present invention provides pharmaceutical compositions, preferably for oral administration, comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein a) the first type of particles comprise dabigatran etexilate in the form of free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof; b) the second type of particles comprise at least one pharmaceutically acceptable organic acid; and c) optionally at least one type of particles are coated with a protective coating layer.

The compositions of the present invention are stable, easy to prepare, and provide the desired in-vitro release of the active.

The first type of particles present in the composition of the present invention, comprise dabigatran etexilate. Dabigatran etexilate may be used in the compositions of the present invention as the free base (3-[(2-{4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]methyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino-propionic acid ethyl ester) or in the form of pharmaceutically acceptable salts,, polymorphs, solvates, hydrates thereof. For the sake of conciseness, the term

dabigatran etexilate is employed in this specification to designate any of the above-mentioned forms except when the term is further qualified (i.e. dabigatran etexilate mesylate). Whenever it is necessary to designate the free base of dabigatran etexilate the term "dabigatran etexilate (free base)" is employed.

The term "pharmaceutically acceptable salt" refers to those salts which are, according to medical judgement, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like. Pharmaceutically acceptable salts are well known in the art.

In one embodiment the amount of dabigatran etexilate (expressed as dabigatran etexilate mesylate) in the composition can vary from about 0.01 weight % to about 90 weight %, based on the total weight of the composition. In another embodiment the amount of dabigatran etexilate in the composition can vary from about 0.02 weight % to about 85 weight %, based on the total weight of the composition. In still another embodiment, the amount of dabigatran etexilate in the composition can vary from about 0.05 weight % to about 80 weight %, based on the total weight of the composition.

In one embodiment the compositions of the present invention may be in the form of unit dose forms comprising from 50 mg to 200 mg of dabigatran etexilate mesylate, preferably from 75 mg to 150 mg, more preferably 75 mg, 110 mg or 150 mg.

In one embodiment of the present invention dabigatran etexilate is used in the form of the mesylate salt, i.e. dabigatran etexilate mesylate.

In a particular embodiment of the present invention dabigatran etexilate is used in the form of polymorphic form I of dabigatran etexilate mesylate (as described in WO 2005/028468).

In another particular embodiment of the present invention dabigatran etexilate is used in the form of polymorphic form II of dabigatran etexilate mesylate (as described in WO 2005/028468).

The oral pharmaceutical composition of the present invention comprises a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable

excipient, with a first type of particles comprising dabigatran etexilate and second type of particles comprising at least one pharmaceutically acceptable organic acid.

In a preferred embodiment of the present invention the first type of particles comprising dabigatran etexilate is free from organic and inorganic acids.

In a preferred embodiment of the present invention the first type of particles comprising dabigatran etexilate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof also comprise at least one pharmaceutical excipient.

In a most preferred embodiment of the present invention, the said first type of particles comprising dabigatran etexilate mesylate in the form of the free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof also comprise one or more excipients selected from the group consisting of binders, diluents and/or lubricants.

In a particular embodiment said first type of particles comprise at least one binder, preferably microcrystalline cellulose.

In another particular embodiment, said first type of particles comprises at least one disintegrant, preferably selected from sodium croscarmellose or crospovidone.

In another particular embodiment, said first type of particles comprise at least one diluent, preferably selected from mannitol or lactose.

In another particular embodiment, said first type of particles comprise at least one binder, preferably microcrystalline cellulose, a disintegrant, preferably selected from sodium croscarmellose or crospovidone and a diluent, preferably selected from mannitol or lactose.

In another preferred embodiment of the present invention the second type of particles comprising at least one pharmaceutically acceptable organic acid is free from dabigatran etexilate.

In a most preferred embodiment of the present invention the first type of particles comprising dabigatran etexilate is free from acids and the second type of particles comprising at least one pharmaceutically acceptable organic acid is free from dabigatran etexilate.

In another preferred embodiment of the present invention the second type of particles comprise tartaric acid, preferably in the form of pellets with a particle size between 100 and 900 microns, more preferably between 400 and 700 microns.

An acid is a substance that releases hydrogen ions and decreases the pH of an aqueous solution.

Organic acids that may be employed in the present composition include, but are not limited to, tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, aspartic acid and the like or combinations thereof including the hydrates and acid salts thereof.

In one embodiment the organic acid is present in the composition of the present invention in an amount of about 2% by weight to about 95% by weight of the composition. In another embodiment the organic acid is present in the composition of the present invention in an amount of about 5% by weight to about 90% by weight of the composition. In a further embodiment the organic acid is present in the composition of the present invention in an amount of about 10% by weight to about 85% by weight of the composition.

In one embodiment at least 90% by weight, preferably at least 95% by weight, more preferably at least 99% by weight and still more preferably 100% by weight of the organic acid present in the composition is contained in the second type of particles which comprise at least one pharmaceutically acceptable organic acid, the rest (if any) of the organic acid being added as part of the excipients.

Further the oral pharmaceutical compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein optionally at least one type of particles are coated with a protective coating layer. In one embodiment, the first type of particles is coated with a

protective coating layer. In another embodiment, the second type of particles is coated with a protective coating layer. In yet another embodiment, the first and the second type of particles are coated with a protective coating layer.

The term "protective coating layer" as used herein is intended to mean a layer of a polymeric or a non-polymeric material disposed on the surface of a particle core in order to avoid direct contact of the particle core with its environment.

In one embodiment, protective coating layer is formed of a polymeric or a non-polymeric pharmaceutically acceptable agent or any combination thereof.

The polymeric pharmaceutically acceptable agents used for the protective coating layer include, but are not limited to, cellulose derivatives, vinyl derivatives, polymers and copolymers, gums, acrylic or methacrylic acid polymers, copolymers, esters or derivatives thereof, and the like or combinations thereof. Cellulose derivatives that may be employed, include, but are not limited to, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, ethylcellulose, hydroxypropyl ethylcellulose, carboxymethylethyl cellulose, carboxy ethylcellulose, carboxymethyl hydroxyethylcellulose, hydroxyethylmethyl carboxymethyl cellulose, hydroxyethyl methyl cellulose, carboxymethyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, carboxymethyl sulfoethyl cellulose, sodium carboxymethyl cellulose, and the like or combinations thereof. Vinyl derivatives, polymers and copolymers thereof that may be employed include, but are not limited to copolymers of vinyl pyrrolidone, copolymers of polyvinyl alcohol (Kollicoat IR), polyvinylpyrrolidone or combinations thereof. Gums that may be employed include, but are not limited to, gum arabic, alginates, guar gum, locust bean gum, carrageenan, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, karaya, and the like, or combinations. Acrylic or methacrylic acid polymers, copolymers, esters or derivatives thereof, that may be employed include, but are not limited to, a) copolymer formed from monomers selected from methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters b) copolymer formed from monomers selected from butyl methacrylate, (2-dimethylaminoethyl)methacrylate and methyl methacrylate c) copolymer formed from monomers selected from ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride or d) copolymers of acrylate and

methacrylates with/without quarternary ammonium group in combination with sodium carboxymethylcellulose, e.g. those available from Röhm GmbH under the trademark Eudragit ® like Eudragit EPO (dimethylaminoethyl methacrylate copolymer; basic butylated methacrylate copolymer), Eudragit RL and RS (trimethylammonioethyl methacrylate copolymer), Eudragit NE30D and Eudragit NE40D (ethylacrylate methymethacrylate copolymer), Eudragit RD 100 (ammoniomethacrylate copolymer with sodium carboxymethylcellulose); or the like or any combinations thereof.

The non-polymeric pharmaceutically acceptable agents used for the protective coating layer include, but are not limited to C8-C22 fatty acids, C8-C22 fatty alcohols, fats, in particular mono-, di- or triesters of glycerol and C8-C22 fatty acids, waxes, and the like, or combinations thereof. Fatty acids that may be employed include, but are not limited to, decenoic acid, docosanoic acid, stearic acid, palmitic acid, lauric acid, myristic acid, hydrogenated palm kernel oil, hydrogenated peanut oil, hydrogenated palm oil, hydrogenated rapeseed oil, hydrogenated rice bran oil, hydrogenated soybean oil, hydrogenated sunflower oil, hydrogenated castor oil, hydrogenated cottonseed oil, and the like, and mixtures thereof. Long chain monohydric alcohols that may be employed include, but are not limited to, cetyl alcohol, stearyl alcohol and mixtures thereof. Waxes that may be employed include, but are not limited to, spermaceti wax, carnauba wax, Japan wax, bayberry wax, flax wax, beeswax, Chinese wax, shellac wax, lanolin wax, sugarcane wax, candelilla wax, paraffin wax, microcrystalline wax, petrolatum wax, carbowax, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, glyceryl dipalmitate, glyceryl tripalmitate, glyceryl monopalmitate, glyceryl dilaurate, glyceryl trilaurate, glyceryl monolaurate, glyceryl trimyristate, glyceryl monodecenoate, glyceryl didecenoate, glyceryl tridecenoate, glyceryl behenate and the like, or mixtures thereof.

In a further embodiment, in addition to polymeric or non-polymeric pharmaceutically acceptable agent or any combination thereof, the protective coating layer may optionally further comprise one or more pharmaceutically acceptable excipients such as, but not limited to, plasticizer, anti-tacking agent, pigment, and the like, or combinations thereof. A plasticizer that may be employed includes, but is not limited to, triethyl citrate, acetyl triethyl citrate, propylene glycol, polyethylene glycol, acetyl tributyl citrate, acetylated monoglycerides, glycerin, triacetin, phthalate esters (*e.g.*, diethyl phthalate, dibutyl phthalate), castor oil, sorbitol and dibutyl seccate or a combination thereof. An anti-tacking agent that may be employed includes, but is not limited to, talc,

or glyceryl monostearate. A pigment such as, but not limited to, titanium dioxide, iron oxide, or a mixture thereof may be employed.

The protective coating layer may be optionally applied onto at least one type of particles of the present invention. For example, the protective coating layer is applied onto the first type of particles which comprise dabigatran etexilate in the form of free base or in the form of pharmaceutically acceptable salts, polymorphs, solvates or hydrates thereof.

In a preferred embodiment of the present invention the protective coating layer is coated onto the second type of particles which comprise at least one pharmaceutically acceptable organic acid. In a particular embodiment said coating layer comprises hydroxypropylmethyl cellulose and talc.

In another embodiment, both particles are coated with the said protective coating layer.

The protective coating layer may be optionally applied onto at least a type of particles of the present invention in any suitable equipment where coating can be achieved, such as, but not limited to, coating pan, conventional film coating apparatus or a fluidized bed apparatus, or the like. Furthermore, in one embodiment, the protective coating layer can be applied from an aqueous or organic solution or dispersion. In another embodiment, the particles being coated with the protective coating layer may be coated to a weight gain of about 2% to about 50% by weight.

In one embodiment, in order to reduce any damage to the protective coating layer during transfer into capsules, the particles coated with the protective coating layer may be further seal coated with conventional pharmaceutically acceptable film forming agents which may optionally be combined with plasticizers or pigments. Suitable film forming agents include, but are not limited to, hydroxypropyl cellulose, hydroxypropyl methylcellulose, acrylic and methacrylic acid polymers, copolymers or esters, and the like or combinations thereof. Plasticizers or pigments as discussed above may optionally be used with the film forming agents.

The compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient. In a further

embodiment, the first type of particles comprising dabigatran etexilate may optionally further comprise at least one pharmaceutically acceptable excipient. In another embodiment, the second type of particles comprising at least one organic acid, may optionally further comprise at least one pharmaceutically acceptable excipient. In yet another embodiment, at least two types of particles that are present in the pharmaceutical composition optionally further comprise at least one pharmaceutically acceptable excipient.

The pharmaceutically acceptable excipients that may be incorporated in the composition of the present invention include, but are not limited to, binders, disintegrants, diluents, surfactants, glidants, lubricants, and the like or combinations thereof.

The term "disintegrant" as used herein is intended to mean a compound used in solid dosage formulations to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, natural, modified or pregelatinized starch, modified starches (such as sodium starch glycolate) and partially pregelatinized starches (such as Starch 1500), polyvinylpyrrolidone, crospovidone, croscarmellose sodium, calcium silicate clays, such as bentonite, microcrystalline cellulose, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, alginates, ion exange resins (such as Polacrilin potassium, Polacrilex) Neusilins, low substituted hydroxypropyl cellulose and the like, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in granulations. Examples of suitable binders include, but are not limited to celluloses such as microcrystalline cellulose, modified celluloses (such as low substituted hydroxypropyl cellulose, hydroxypropyl cellulose (or HPC), hydroxypropyl methylcellulose (or HPMC or hypromellose), hydroxyethylcellulose, hydroxyethyl methylcellulose, ethyl cellulose, cellulose gum, xanthan gum, sugars (such as sucrose, glucose, amilose, maltodextrin, dextrose and the like), starches such as corn or potato starch partially pregelatinized starches (such as Starch 1500), polyvinyl acetate (Kollicoat SR), polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat IR), copovidone, cross-linked polyvinylpyrrolidone, acrylic acid polymer

(Carbopol), poloxamer, polycarbophil, polyethylene oxide, polyethylene glycol, and the like, combinations thereof and other material known to those of ordinary skill in the art.

The term "diluent" or "filler" as used herein is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of solid dosage formulations. Examples of suitable diluents include, but are not limited to microcrystalline cellulose, coprocessed microcrystalline celluloses (such as Avicel CI-611, Avicel RC-581, Avicel RC591, Avicel CE, Avicel DG, Avicel HFE), lactose, sucrose, xylitol, mannitol, maltose, polyols, fructose, guar gum, sorbitol, magnesium hydroxide, dibasic calcium phosphate, kaolin, calcium sulphate, carrageenan, chitosan, pectinic acid, sodium alginate, magnesium aluminium silicate, calcium carbonate and the like, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "lubricant" as used herein is intended to mean substances used in solid dosage formulations to reduce friction during compression of the solid dosage. Such compounds include, but are not limited to, magnesium stearate, calcium stearate, zinc stearate, stearic acid, talc, mineral oil and sodium stearyl fumarate, combinations thereof and other such materials known to those of ordinary skill in the art.

The tablet compositions of the invention may also include a glidant. The term "glidant" as used herein is intended to mean agents used in solid dosage formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, but not limited to, colloidal silica, silica gel, precipitated silica, calcium silicate, magnesium silicate, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "surfactant" as used herein is intended to mean substances used to reduce the surface tension of the aqueous solutions comprising them. Examples of surfactants include, but are not limited to, sodium docusate, glyceryl monooleate, polyethylene alkyl ether, polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, sorbic acid, sorbitan fatty acid ester, mixtures thereof and other such materials known to those of ordinary skill in the art.

The compositions of the present invention comprise a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, with first type of particles comprising dabigatran etexilate and second type of particles comprising at least one organic acid.

The term "particle" as used herein is intended to mean any solid or semi-solid portion of a substance or a composition having defined physical boundaries. Examples of particles particles include, but are not limited to, powder, granules, pellets, beads, minitablets or the like. The granules may be prepared by methods such as, but not limited to, wet granulation, melt granulation, dry granulation or roll compaction or the like. In an embodiment of the present invention, pellets may be prepared using extrusion spheronization. In another embodiment of the present invention, dabigatran etexilate present in the first set of particles or at least one organic acid present in the second set of particles can be loaded on an inert carrier. The inert carrier can be selected from, but not limited to, beads, pellets, spheres or similar particles that do not contain an active ingredient. Non-limiting examples of inert carrier include microcrystalline cellulose, sugar or silicon dioxide. In yet another embodiment, the particles of the present invention, in the powder form, may be incorporated in the compositions of the present invention.

In an embodiment of the present invention said first type of particles has a particle size comprised between 50 and 1000 microns and said second type of particles have a particle size comprised between 100 and 1000 microns.

The compositions of the present invention comprise from about 5% to about 100% by weight of the mixture of at least two types of particles. Ratio of the first and second types of particles is from about 1:99 to about 99:1.

The term "composition" or "formulation" has been employed interchangeably for the purpose of the present invention.

The term "dosage form" is as used herein is intended to mean a pharmaceutical composition which is suitable for administration to a patient. In one embodiment the compositions of the present invention can be in the form of capsules, tablets, minitablets, stick formulation, dispersible tablets, dry suspension for reconstitution,

powder or granule for solution or suspension, granules, and the like or any combinations thereof. Depending of the final dosage form the compositions of the present invention may comprise appropriate pharmaceutically acceptable excipients such as those mentioned above or some additional ones such as, but not limited to, sweeteners, flavors, colorants and the like or combinations thereof. Further it is contemplated within the scope of the invention that the dosage form can be encapsulated or coated. In one embodiment, the composition of the present invention is in the form of a capsule. Capsules include, for example, hard capsules of gelatine or hydroxypropylmethylcellulose and the like. In a further embodiment, the compositions of the present invention may be manufactured using conventional techniques known in the art.

The term "unit dosage form" refers to a physically discrete unit suitable as a unitary dosage for a human patient such as a capsule, a tablet or a vial.
In another aspect the present invention provides a unit dosage form prepared from the above mentioned compositions comprising two types of particles.

The compositions of the present invention provide flexibility of blending at least two types of particles to attain different release patterns. In one embodiment, the compositions of the present invention provide tailored in-vitro profiles and corresponding in-vivo profiles. In a further embodiment, the compositions of the present invention can provide tailored profiles wherein dissolution of the compositions of the present invention can be faster at initial time points when compared to formulations having only single type of particles comprising both dabigatran etexilate or pharmaceutically acceptable salts thereof and organic acid. Without being bound to any theory it is believed that such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster Tmax (~ 45 minutes – 1 hour), (b) significant bioactivation is involved for action of dabigatran and (c) negligible and variable absorption is observed at higher pH.

In another aspect the present invention provides a process for the preparation of a composition comprising the two types of particles described above comprising the step of mixing said first type of particles and said second type of particles with a at least one

pharmaceutically acceptable excipient. In a particular embodiment of the present invention said first type of particles are prepared by granulation.

In one embodiment the process of preparing the compositions of the present invention comprises the steps of

(i) blending dabigatran etexilate and at least one pharmaceutically acceptable excipient such as diluent;

(ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the organic acid granules with a protective coating layer;

(vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) lubricating the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In another embodiment the process of preparing the compositions of the present invention comprises the steps of

(i) blending dabigatran etexilate and at least one pharmaceutically acceptable excipient such as diluent;

(ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent;

(iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

(v) coating the granules of active agent with a protective coating layer;

(vi) blending the granules of step (iv) with the coated granules of step (v) to form a mixture of at least two types of granules;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) lubricating the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In yet another embodiment the process of preparing the compositions of the present invention comprises the steps of

(i) blending dabigatran etexilate and at least one pharmaceutically acceptable excipient such as diluent;

(ii) granulating the blend of step (i) with a binder solution to form granules of the active agent;

(iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient such as diluent or binder;

(iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

(v) coating the organic acid pellets of step (iv) with a protective coating layer;

(vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

(vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

(viii) lubricating the blend of step (vii);

(ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

In a further aspect the present invention provides the use of the pharmaceutical composition of dabigatran etexilate of the present invention for the manufacture of a medicament for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

In still another aspect the present invention provides a method of for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and/or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, comprising administering to the subject in need thereof pharmaceutical compositions of dabigatran etexilate of the present invention.

In another embodiment of the present invention the dabigatran etexilate may be combined with other active agents or pharmaceutically acceptable salts thereof including, but not limited to, atorvastatin, dipyridamole, mopidamole and the like or combinations thereof.

The invention is further illustrated by the following examples, which are for illustrative purposes and should not be construed as limiting the scope of the invention in any way.

Examples

Example 1: Oral capsule formulation of dabigatran etexilate mesylate

A) Preparation of coated tartaric acid pellets

(a) Preparation of tartaric acid pellets

Table 1: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid	80
Microcrystalline cellulose	30
Hydroxypropyl cellulose	10
Isopropyl alcohol*	q.s
Total	**120**

*not present in the final product

Procedure: Tartaric acid and microcrystalline cellulose were blended and to this blend was added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass was extruded, spheronized, dried and screened to give pellets. These pellets were then coated with a protective coating layer as follows to give coated tartaric acid pellets.

(b) Preparation of coated tartaric acid pellets

Table 2: Composition of tartaric acid pellets

Ingredients	mg/unit

Tartaric acid pellets	120
Hydroxypropyl methylcellulose	10
Talc	6
Isopropyl alcohol*	q.s
Total	**136**

*not present in the final product

Procedure: Tartaric acid pellets prepared as above were coated with dispersion of hydroxypropyl cellulose and talc in isopropyl alcohol. The coated pellets were then dried to give coated tartaric acid pellets.

B) Preparation of dabigatran etexilate mesylate granules

Table 3: Composition of dabigatran etexilate mesylate granules

Ingredients	mg/unit
Dabigatran etexilate mesylate equivalent to 110 mg of dabigatran etexilate	126.83
Microcrystalline cellulose	40.17
Lactose anhydrous	30
Crospovidone	4
Hydroxypropyl cellulose	4
Isopropyl alcohol*	q.s
Total	**205**

*not present in the final product

Procedure: Dabigatran etexilate mesylate, microcrystalline cellulose, lactose anhydrous and crospovidone were blended. The blend was granulated using solution of hydroxypropyl cellulose in isopropyl alcohol. The granules were sized and screened to form dabigatran etexilate mesylate granules.

C) Preparation of oral capsule formulation of dabigatran etexilate mesylate

Table 4: Composition of capsule formulation of dabigatran etexilate mesylate

Ingredients	mg/unit

Dabigatran etexilate mesylate granules	205
Coated tartaric acid pellets	136
Sodium stearyl fumarate	4
Total	**345**

Procedure: Dabigatran etexilate mesylate granules prepared as per composition of Table 3 above and coated tartaric acid pellets prepared as per Table 2 above were blended. Blend was lubricated with sodium stearyl fumarate and filled into capsules by means of a capsule filling machine.

Example 2: Oral capsule formulation of dabigatran etexilate mesylate

A) Preparation of tartaric acid pellets

Table 5: Composition of tartaric acid pellets

Ingredients	mg/unit
Tartaric acid	60
Microcrystalline cellulose	18
Hydroxypropyl cellulose	4
Isopropyl alcohol*	q.s
Total	**82**

*not present in the final product

Procedure: Tartaric acid and microcrystalline cellulose were blended and to this blend was added solution of hydroxypropyl cellulose in isopropyl alcohol to get a wet mass. This wet mass was extruded, spheronized, dried and screened to give pellets. These pellets were then coated using with a protective coating layer as follows to give coated tartaric acid pellets.

B) Preparation of dabigatran etexilate mesylate coated granules

(a) Preparation of dabigatran etexilate mesylate granules

Table 6: Composition of dabigatran etexilate mesylate granules

Ingredients	mg/unit

Dabigatran etexilate mesylate equivalent to 110 mg of dabigatran etexilate	86.48
Microcrystalline cellulose	32.52
Lactose anhydrous	25
Crospovidone	3
Hydroxypropyl cellulose	3
Isopropyl alcohol*	q.s
Total	**150**

*not present in the final product

Procedure: Dabigatran etexilate mesylate, microcrystalline cellulose, lactose anhydrous and crospovidone were blended. The blend was granulated using solution of hydroxypropyl cellulose in isopropyl alcohol. The granules were sized and screened to form dabigatran etexilate mesylate granules.

(b) Preparation of dabigatran etexilate mesylate coated granules

Table 7: Composition of dabigatran etexilate mesylate coated granules

Ingredients	**mg/unit**
Dabigatran etexilate mesylate granules	150
Polyvinyl pyrrolidone	22
Talc	3
Isopropyl alcohol	q.s.
Total	**175**

*not present in the final product

Procedure: Dabigatran etexilate mesylate granules prepared as per the process mentioned above were coated with a coating dispersion of polyvinyl pyrrolidone and talc in isopropyl alcohol to form coated dabigatran etexilate mesylate granules.

C) Preparation of oral capsule formulation of dabigatran etexilate mesylate

Table 8: Composition of capsule formulation of dabigatran etexilate mesylate

Ingredients	**mg/unit**

Coated dabigatran etexilate mesylate granules	175
Tartaric acid pellets	82
Sodium stearyl fumarate	3
Total	**260**

Procedure: Dabigatran etexilate mesylate granules prepared as per Table 7 above and coated tartaric acid pellets prepared as per table 5 above were blended. Blend was lubricated with sodium stearyl fumarate and filled into capsules by means of a capsule filling machine.

Example 3: Comparative evaluation of two formulation approaches for dabigatran etexilate mesylate

The two formulation approaches for dabigatran etexilate mesylate as shown below were evaluated:

(i) First approach being that of the present invention having two types of particles/pellets (one of dabigatran etexilate mesylate and the other of organic acid) and

(ii) Second approach having one type of particles/pellets having both dabigatran etexilate mesylate and organic acid. This formulation was prepared according to the teachings of US 2006/074056 and, in particular, Example 1. Formulation (B)

(A) Preparation of formulation A having two types of particles/pellets (i.e. Dabigatran etexilate mesylate granules and seal coated tartaric acid pellets)

Table 17: Composition of Dabigatran etexilate mesylate granules

Ingredients	**mg/capsule**
Intragranular	
Dabigatran etexilate mesylate equivalent to 150 mg dabigatran etexilate	172.95
IPA	q.s
Extragranular	

Microcrystalline cellulose	67.05
Croscarmellose Sodium	50
Total weight of the Dabigatran etexilate mesylate granules	290

Table 18: Composition of seal coated tartaric acid pellets

Ingredients	**mg/capsule**
Tartaric acid (TAP® 600)	196.34
Seal coating of Tartaric acid pellets	
Hydroxypropylmethyl cellulose	5.62
Lactose	5.62
Talc	8.42
Isopropyl alcohol- water	q.s
Total weight of seal coated pellets	216

Procedure:

(i) Preparation of Dabigatran etexilate mesylate granules portion

Loaded weighed quantity of dabigatran etexilate mesylate in the granulator and granulated it using isopropyl alcohol. The granules were further dried in fluidized bed drier. The granules were then sized, sifted and blended with microcrystalline cellulose, croscarmellose sodium in a suitable blender to give dabigatran etexilate mesylate granules portion.

(ii) Preparation of seal coated tartaric acid pellets

Hydroxypropyl cellulose was added to a suitable quantity of isopropyl alcohol water mixture under continuous stirring to obtain a clear solution. Lactose was added to this solution and mixed, followed by addition of talc and stirring. The suspension thus formed was filtered through a suitable sieve and sprayed under continuous stirring on tartaric acid pellets using a fluidized bed coater with Wurster column to achieve desired weight gain. The coated tartaric acid pellets were then dried.

The lubricated seal coated tartaric acid pellets and dabigatran etexilate mesylate granules were filled in capsules using the automatic capsule filling machine in HPMC size 0 capsules.

(C) Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A above) and formulation having one type of particles/pellets (Formulation B above)

Dissolution profiles of the formulations in 0.01N HCl pH 2 media at 100 rpm USP type I (basket) are as depicted under A and B below:

Time (minutes)	% release	
	Formulation A (two types of particles/pellets)	Formulation B (one type of particles/pellets)
10	65.1	19.2
15	79.2	57
20	86.7	86.1
30	92	97
45	95.5	97.6
60	96.8	98.5

Comparative evaluation of dissolution profiles of formulation of the present invention having two types of particles/pellets (Formulation A above) and formulation having one type of particles/pellets (Formulation B above) indicates that formulations of the present invention having two types of particles/pellets can provide faster dissolution particularly at earlier time points as compared to formulation having one type of particles/pellets. Such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster Tmax (~ 45 minutes – 1 hour), (b) significant bioactivation is involved and (c) negligible and variable absorption at higher pH.