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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/241,793	04/27/2021	Pratibha S. PILGAONKAR	70204.0018USC1	1465
23552 7590 09/12/2023 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
			09/12/2023	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



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APPLICATION NO.	ISSUE DATE	PATENT NO.
17/241,793	12-Sep-2023	11752142

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

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at <https://patentcenter.uspto.gov>

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit <https://www.uspto.gov/electronicgrants>



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/241,793	09/12/2023	11752142	70204.0018USC1	1465

23552 7590 08/23/2023
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at <https://patentcenter.uspto.gov/>. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at <https://certifiedcopycenter.uspto.gov/index.html>. The Certified Copy Center may be reached at (800)972-6382.

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 0 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 Center (<https://patentcenter.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 Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional inventors):

Pratibha S. PILGAONKAR, Mumbai, INDIA;
Maharukh T. RUSTOMJEE, Mumbai, INDIA;
Anilkumar S. GANDHI, Mumbai, INDIA;

APPLICANT(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional applicants):

Breckenridge Pharmaceutical, Inc., Berlin, CT;

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	17241793
Filing Date	2021-04-27
First Named Inventor	Pilgaonkar
Art Unit	
Examiner Name	
Attorney Docket Number	16326.0018USC1

6	20060074056	2006-04-06	Vaisburg, et al.
7	20050038077	2005-02-17	Kohlrausch
8	20080069891	2008-03-20	Habib

If you wish to add additional U.S. Published Application citation information please click the Add button.

Add

FOREIGN PATENT DOCUMENTS

Remove

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ² i	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1	2005028468	WO		2005-03-31	Boehringer Ingelheim PH		
	2	2012001156	WO		2012-01-05	Krka Tovarna Zdravil		
	3	9837075	WO		1998-08-27	Boehringer Ingelheim PH		
	4	0012064	WO		2000-03-09	Chen		
	5	101632668	CN		01/2010 1028-01-27	Brauns		
	6	1366760	EP		2002-02-12	Sugimoto		

Change(s) applied
to document,
/C.S./
6/28/2023



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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
17/241,793

RECEIPT DATE / TIME
07/21/2023 03:15:17 PM ET

ATTORNEY DOCKET #
70204.0018USC1

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1465

FILED BY Lisa Kenney

PATENT CENTER # 62484308

AUTHORIZED BY Erich Gess

CUSTOMER # 23552

FILING DATE 04/27/2021

CORRESPONDENCE ADDRESS -

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

Payment Information

PAYMENT METHOD
CARD / 4565

PAYMENT TRANSACTION ID
E20237KF16555648

PAYMENT AUTHORIZED BY
Lisa Kenney

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1501	UTILITY ISSUE FEE	1200.00	1	1200.00
TOTAL AMOUNT:				\$1,200.00

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 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.



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07/21/2023 03:15:17 PM ET

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CUSTOMER # 23552

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Erich Gess

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
70204-0018USC1-Issue-Fee-Transmittal.PDF	1	Issue Fee Payment (PTO-85B)	1259 KB

Warning: The attached file contains comments or annotations. Comments are not recommended and may cause processing problems with the document.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
70204-0018USC1-Issue-Fee-Transmittal.PDF	755665EA2C9AEFC567580F2610A5D53828EE227B02A42AC7A 1BE7B5E3BCECBDA49117DE4CDD223C535B3340B29870B38D

D9C95EED E0C66B47C60771DD8C09B92

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.

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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.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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

2352 7590 06/22/2023
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.
17/241,793	04/27/2021	Pratibha S. PILGAONKAR	70204.0018USC1	1465

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	09/22/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
BECKHARDT, LYNDESEY 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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 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 E. Joseph Gess

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

Breckenridge Pharmaceutical, Inc.

(B) RESIDENCE: (CITY AND STATE OR COUNTRY)

Berlin, Connecticut

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)

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

☒ Electronic Payment via Patent Center or 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 /E. Joseph Gess/

Date 21 July 2023

Typed or printed name E. Joseph Gess

Registration No. 28510



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/241,793

RECEIPT DATE / TIME
07/17/2023 11:57:12 AM ET

ATTORNEY DOCKET #
70204.0018USC1

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1465

FILED BY Lisa Kenney

PATENT CENTER # 62450456

FILING DATE 04/27/2021

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Erich Gess

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-07-17_70204-0018USC1-Substance-Interview.pdf	1	Applicant summary of interview with examiner	70 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-07-17_70204-0018USC1-Substance-Interview.pdf	75688FCBFF3555AE29D6EB8D4D58F9B7FB231B08EF3172E939633E01995DEA90E2FE1FE48609068C5BB130D7939CF48CF950BC53A716D3A5A27EF949EA00493C

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New International Application Filed with the USPTO as a Receiving Office

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S/N 17/241,793

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	17/241,793	Group Art Unit:	1613
Filed:	April 27, 2021	Docket No.:	70204.0018USC1
Customer No.	23552	Confirmation No.	1465
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

Applicant thanks Examiner Beckhardt for the telephonic interview conducted 24 May 2023 with Applicant's representative.

Applicant notes that the Examiner's Interview Summary was included with the Notice of Allowance dated 22 June 2023 after submission of Applicant's Supplemental Response filed 26 May 2023.

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

Respectfully submitted,

Date: 17 July 2023

/E. Joseph Gess/
E. Joseph Gess
Reg. No. 28510

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
703.684.2511



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NOTICE OF ALLOWANCE AND FEE(S) DUE

23552 7590 06/22/2023
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
BECKHARDT, LYNDSEY MARIE	
ART UNIT	PAPER NUMBER

1613

DATE MAILED: 06/22/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/241,793	04/27/2021	Pratibha S. PILGAONKAR	70204.0018USC1	1465

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	09/22/2023

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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.

PART B - FEE(S) TRANSMITTAL

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

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

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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)

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

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☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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(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)

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(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)

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

☐ Electronic Payment via Patent Center or 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. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/241,793	04/27/2021	Pratibha S. PILGAONKAR	70204.0018USC1	1465
23552 7590 06/22/2023 MERCHANT & GOULD P.C. P.O. BOX 2903 MINNEAPOLIS, MN 55402-0903				
EXAMINER BECKHARDT, LYNDSEY MARIE				
ART UNIT			PAPER NUMBER	
1613				
DATE MAILED: 06/22/2023				

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.

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. 17/241,793	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 arguments and amendments filed 05/26/2023.
☐ 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 1-15 and 17-21. 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. 14/379,613.
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 <u>03/28/2023</u> . 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. ☒ Interview Summary (PTO-413), Paper No./Mail Date. <u>20230530</u> .	5. ☐ Examiner's Amendment/Comment 6. ☒ Examiner's Statement of Reasons for Allowance 7. ☐ Other _____.
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/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613
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Notice of Allowability

Claims 1-15 and 17-21 are allowed.

Notice of Pre-AIA or AIA Status

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

Information Disclosure Statement

Applicant's Informational Disclosure Statement, filed on 03/28/2023 has been considered. Please refer to Applicant's copy of the 1449 submitted herein.

Terminal Disclaimer

The terminal disclaimer filed on 05/26/2023 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **11,013,729** has been reviewed and is accepted. The terminal disclaimer has been recorded.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: Applicant has amended instant claim 8 and newly added claim 19 to remove the term prevent, thus overcoming the enablement rejection. The data presented by Applicant in the IDS dated 03/28/2023 supports the treatment and reduction of VTE through the use of dabigatran etexilate.

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 1-15 and 17-21 are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDEY MARIE BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached Monday-Thursday 9am to 2pm.

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 published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197

Application/Control Number: 17/241,793
Art Unit: 1613

Page 4

(toll-free). If you would like assistance from a USPTO Customer Service

Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LYNDSEY M BECKHARDT/
Examiner, Art Unit 1613

/ANDREW S ROSENTHAL/
Primary Examiner, Art Unit 1613

<i>Applicant-Initiated Interview Summary</i>	Application No. 17/241,793	Applicant(s) PILGAONKAR et al.		
	Examiner LYNDSEY M BECKHARDT	Art Unit 1613	AI/A (First Inventor to File) Status No	Page 1 of 1

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

Date of Interview: 24 May 2023

Issues Discussed:

35 U.S.C. 112

Examiner and Applicant discussed the enablement rejection over prevent in claim 8 and in the newly added claim 19. Examiner stated that the European Medicine Agency contains the term prevent, however does not present data. Examiner stated the CHMP NPL provided had data regarding the use of dabigatran, however the data provided does not support prevent. The data provided supports reduction and treatment, however there are still instances of VTE and thus do not support prevent (page 18-page 19). Applicant stated they will discuss with their client and provide a supplemental response if the proposed amendments to remove prevent are acceptable. No agreement was reached.

Non-statutory Double Patenting

Examiner stated the arguments response filed 04/03/2023 states that a terminal disclaimer was filed, however no terminal disclaimer can be located. Applicant stated they will file the terminal disclaimer.

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

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.

Search Notes 	Application/Control No. 17/241,793	Applicant(s)/Patent Under Reexamination PILGAONKAR et al.
	Examiner LYNDSEY M BECKHARDT	Art Unit 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	10/12/2022	LMB
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	05/30/2023	LMB

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* 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	10/12/2022	LMB
Google (keyword) see attached	10/12/2022	LMB
Search (keyword, Inventor, Assignee) see attached	05/30/2023	LMB
Google (keyword) see attached	05/30/2023	LMB
Reviewed Parent Application 14/379,613 history	05/30/2023	LMB

/LMB/	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613
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<i>Search Notes</i> 	Application/Control No. 17/241,793	Applicant(s)/Patent Under Reexamination PILGAONKAR et al.
	Examiner LYNDSEY M BECKHARDT	Art Unit 1613

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	Search (keyword.clm.) see attached	05/30/2023	LMB

/LMB/	/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613
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Issue Classification 	Application/Control No. 17/241,793	Applicant(s)/Patent Under Reexamination PILGAONKAR et al.
	Examiner LYNDSEY M BECKHARDT	Art Unit 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 (Assistant Examiner)	30 May 2023 (Date)	Total Claims Allowed: 20	
/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613 (Primary Examiner)	09 June 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No.: 20230530

Issue Classification 	Application/Control No. 17/241,793	Applicant(s)/Patent Under Reexamination PILGAONKAR et al.
	Examiner LYNDSEY M BECKHARDT	Art Unit 1613

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K31/4439		31	4439
A61K9/14		9	14

NON-CLAIMED			

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

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

/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613 (Assistant Examiner)	30 May 2023 (Date)	Total Claims Allowed: 20	
/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613 (Primary Examiner)	09 June 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification 	Application/Control No. 17/241,793	Applicant(s)/Patent Under Reexamination PILGAONKAR et al.
	Examiner LYNDSEY M BECKHARDT	Art Unit 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	1	10	10	16	19										
2	2	11	11	19	20										
3	3	12	12	20	21										
4	4	13	13												
5	5	14	14												
6	6	15	15												
7	7		16												
8	8	17	17												
9	9	18	18												

/LYNDSEY M BECKHARDT/ Examiner, Art Unit 1613 (Assistant Examiner)	30 May 2023 (Date)	Total Claims Allowed: 20	
/ANDREW S ROSENTHAL/ Primary Examiner, Art Unit 1613 (Primary Examiner)	09 June 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No.: 20230530

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L7	96	((("PILGAONKAR") near3 ("Pratibha")) OR ((("RUSTOMJEE") near3 ("Maharukh")) OR ((("GANDHI") near3 ("Anilkumar")))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/23 02:14 PM
L8	4	L7 AND dabigatran	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/23 02:15 PM
L9	1	("11013729").pn.	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/23 02:33 PM
L10	457	dabigatran SAME thromboembolic	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/23 02:33 PM
L11	96	((("PILGAONKAR") near3 ("Pratibha")) OR ((("RUSTOMJEE") near3 ("Maharukh")) OR ((("GANDHI") near3 ("Anilkumar")))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/23 02:33 PM
L12	1	"17241793"	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/23 02:33 PM
L13	51074	(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).cpc.	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/23 02:33 PM
L14	8	"20060183779"	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/23 02:33 PM
L15	96	((("PILGAONKAR") near3 ("Pratibha")) OR ((("RUSTOMJEE") near3 ("Maharukh")) OR ((("GANDHI") near3 ("Anilkumar")))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/23 02:33 PM
L16	4	L7 AND dabigatran	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/23 02:33 PM
L17	1	("11013729").pn.	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L18	458	dabigatran SAME thromboembolic	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L19	96	((("PILGAONKAR") near3 ("Pratibha")) OR ((("RUSTOMJEE") near3	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/30 09:47 AM

L20	1	("Maharukh")) OR (("GANDHI") near3 ("Anilkumar"))).INV. "17241793"	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L21	51108	(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).cpc.	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L22	9	"20060183779"	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L23	96	((("PILGAONKAR") near3 ("Pratibha")) OR (("RUSTOMJEE") near3 ("Maharukh")) OR (("GANDHI") near3 ("Anilkumar"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/30 09:47 AM
L24	4	L7 AND dabigatran	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/30 09:47 AM
L25	1	("11013729").pn.	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L26	458	dabigatran SAME thromboembolic	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L27	96	((("PILGAONKAR") near3 ("Pratibha")) OR (("RUSTOMJEE") near3 ("Maharukh")) OR (("GANDHI") near3 ("Anilkumar"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/30 09:47 AM
L28	1	"17241793"	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L29	51108	(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).cpc.	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L30	9	"20060183779"	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L31	96	((("PILGAONKAR") near3 ("Pratibha")) OR (("RUSTOMJEE") near3 ("Maharukh")) OR	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/30 09:47 AM

L32	4	((("GANDHI") near3 ("Anilkumar"))).INV. L7 AND dabigatran	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2023/05/30 09:47 AM
L33	1	"17241793"	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L34	51108	(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).cpc.	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:47 AM
L35	1384	L34 AND dabigatran	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:48 AM
L36	981	L34 AND dabigatran AND (organic acid OR tartaric)	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 09:48 AM
L37	69	dabigatran AND (organic acid OR tartaric).clm.	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 10:15 AM
L38	33	dabigatran.clm. AND (organic acid OR tartaric).clm.	(US-PGPUB; USPAT)	ADJ	ON	ON	2023/05/30 10:15 AM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-22)

Approved for use through 05/31/2024. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	17241793
	Filing Date	2021-04-27
	First Named Inventor	Pratibha S. PILGAONKAR
	Art Unit	1613
	Examiner Name	BECKHARDT, LYNDSEY MARIE
	Attorney Docket Number	70204.0018USC1

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Examiner Initials*	Cite No	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, pages(s), volume-issue number(s), publisher, city and/or country where published.						T ⁵

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	17241793
	Filing Date	2021-04-27
	First Named Inventor	Pratibha S. PILGAONKAR
	Art Unit	1613
	Examiner Name	BECKHARDT, LYNDESEY MARIE
	Attorney Docket Number	70204.0018USC1

1	European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), European Public Assessment Report for Pradaxa (dabigatran etexilate), published 23 April 2008, pp. 1-36
2	European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), Post Authorisation Summary of Positive Opinion for Pradaxa (dabigatran etexilate mesilate), published 14 April 2011, pp. 1-2

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/LYNDESEY M BECKHARDT/	Date Considered	05/30/2023
--------------------	------------------------	-----------------	------------

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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.

Web Search History

date, time	web site	search string
5/30/2023 10:42:31 AM	Google	dabigatran etexilate
5/30/2023 10:42:34 AM	Google	dabigatran etexilate particle
5/30/2023 10:42:40 AM	Google	dabigatran etexilate a thrombin inhbitor
5/30/2023 10:42:47 AM	Google	dabigatran etexilate stroke and embolism
5/30/2023 10:43:01 AM	Google	system embolism risk of stroke venous thromboembolic
5/30/2023 10:43:21 AM	Google	system embolism risk of stroke venous thromboembolic and dabigatran

Bibliographic Data

Application No: 17/241,793

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.
04/27/2021	424	1613	70204.0018USC1
RULE			

APPLICANTS

Breckenridge Pharmaceutical, Inc., Berlin, CT, UNITED STATES

INVENTORS

Pratibha S. PILGAONKAR, Mumbai, INDIA

Maharukh T. RUSTOMJEE, Mumbai, INDIA

Anilkumar S. GANDHI, Mumbai, INDIA

CONTINUING DATA

This application is a CON of 14379613 08/19/2014 PAT 11013729

14379613 is a 371 of PCT/EP2013/053426 02/21/2013

FOREIGN APPLICATIONS

INDIA IN461/MUM/2012 02/21/2012

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05/04/2021

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INDIA

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MERCHANT & GOULD P.C.

P.O. BOX 2903

MINNEAPOLIS, MN 55402-0903

UNITED STATES

FILING FEE RECEIVED

\$1,820

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 17/241,793		Filing Date 04/27/2021		☐ 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), (l), 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 \$100 =		
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =		*			x \$480 =		
☐ 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	05/26/2023	CLAIMS REMAINING AFTER AMENDMENT			HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0			x \$100 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0			x \$480 =	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		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.								SLIE	
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".								/KIMBERLY R WHITE/	
*** 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.

S/N 17/241,793

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	17/241,793	Group Art Unit:	1613
Filed:	April 27, 2021	Docket No.:	70204.0018USC1
Customer No.	23552	Confirmation No.	1465
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

SUPPLEMENTAL RESPONSE

U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commissioner for Patents

Further to the response filed 3 April 2023 to the Office Action dated 28 October 2022, and the interview conducted on 25 May 2023, Applicant submits herewith the following supplemental amendment and response.

Amendments to the Claims begin on page 2.

Remarks begin on page 6.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation comprising administering to the patient in need thereof 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.
2. (Original) The method of claim 1, wherein the composition is administered as a unit dosage form comprising from 50 mg to 200 mg of dabigatran etexilate mesylate.
3. (Original) The method of claim 2, wherein the unit dosage form is a capsule.
4. (Original) The method of claim 1, wherein the composition further comprises at least one pharmaceutically acceptable excipient.
5. (Original) The method of claim 1, wherein the composition comprises from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.
6. (Original) The method of claim 1, wherein the composition comprises from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

7. (Original) The method of claim 4, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

8. (Currently Amended) A method for treating ~~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 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.

9. (Original) The method of claim 8, wherein the composition is administered as a unit dosage form comprising from 50 mg to 200 mg of dabigatran etexilate mesylate.

10. (Original) The method of claim 9, wherein the unit dosage form is a capsule.

11. (Original) The method of claim 8, wherein the composition further comprises at least one pharmaceutically acceptable excipient.

12. (Original) The method of claim 8, wherein the composition comprises from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.

13. (Original) The method of claim 8, wherein the composition comprises from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

14. (Original) The method of claim 11, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

15. (Original) The method of claim 8, wherein the venous thromboembolic events are deep venous thrombosis (DVT) and pulmonary embolism (PE).

16. (Cancelled)

17. (Previously Presented) The method of claim 19, wherein the capsule contains from 50 mg to 200 mg of dabigatran etexilate mesylate.

18. (Original) The method of claim 19 [[16]], wherein the first type of particles of the capsule comprise at least one pharmaceutically acceptable excipient.

19. (Currently Amended) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation or for treating ~~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 capsule 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 tartaric acid; and

b) the second type of particles comprise tartaric acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

20. (Previously Presented) The method of claim 19, wherein the second type of particles of the capsule comprise at least one pharmaceutically acceptable excipient.

21. (Previously Presented) The method of claim 19, wherein the capsule comprises from 2 wt % to 95 wt % of the tartaric acid.

REMARKS

Claims 1-16, 17, 18, and new claims 19-21 are pending, with claims 1, 8, and 19 being independent. Without conceding the propriety of the enablement rejection, claims 8 and 19 have been amended for additional clarity. Support for the claim amendments can be found throughout the application, including in the original claims. Therefore, no new matter has been added.

Applicant thanks the Examiner for the helpful interview conducted on 25 May 2023 with Applicant's representative. As discussed during the interview, Applicant is amending claims 8 and 19 to reflect the information in the European Medicines Agency's approval of dabigatran in Europe.

Applicant has amended claims 8 and 19 to recite treating venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Applicant intends this "treating" to include the indications as approved by the European Medicines Agency in 2008 and 2011. During the interview, the Examiner agreed that the European Medicines Agency information established enablement for the indications as set forth therein. As such, it is Applicant's position that the present claims reciting "treating venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery" includes the indications as approved by the European Medicines Agency in 2008 and 2011.

As discussed during this interview, it is our understanding that with these claim amendments the claims should be in condition for allowance.

With regard to the double patenting rejection, Applicant has submitted a terminal disclaimer, as discussed at the interview.

If there are any questions relating to this response or the application, Applicant requests that the Examiner telephone the undersigned attorney. The Examiner is authorized to charge any additional fees or refund any overpayments to Deposit Account No. 13-2725 (Docket No. 70204.0018USC1).

Respectfully submitted,

Date: 26 May 2023

/E. Joseph Gess/
E. Joseph Gess
Registration No. 28510

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402
Telephone No. 703.684.2511
Facsimile No. 612.332.9081



AMENDMENTS TO THE CLAIMS

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b) the second type of particles comprise tartaric acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

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21. (Previously Presented) The method of claim 19, wherein the capsule comprises from 2 wt % to 95 wt % of the tartaric acid.

REMARKS

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Respectfully submitted,

Date: 26 May 2023

/E. Joseph Gess/
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Registration No. 28510

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402
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Facsimile No. 612.332.9081





UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/241,793

RECEIPT DATE / TIME
05/26/2023 02:28:46 PM ET

ATTORNEY DOCKET #
70204.0018USC1

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1465

FILED BY Lisa Kenney

PATENT CENTER # 62164194

FILING DATE 04/27/2021

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Erich Gess

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-05-26-70204_0018USC1-Supplemental_Response.PDF	7	Supplemental Response or Supplemental Amendment	98 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-05-26-70204_0018USC1-Supplemental_Response.PDF	4DC3673589AC93045AD1D53871136C6C939A64093AF13E6CD5AC1B35EF5733527BB7C7FDB33AF5E46C54B2B9BC89C5AAD8178BDD0D3C6519162AE85358CD672E

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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 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: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed		PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce	
Electronic Petition Request	TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT		
Application Number	17241793		
Filing Date	27-Apr-2021		
First Named Inventor	Pratibha PILGAONKAR		
Attorney Docket Number	70204.0018USC1		
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
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Owner		Percent Interest	
Breckenridge Pharmaceutical, Inc.		100%	
<p>The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)</p> <p>11013729</p> <p>as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.</p> <p>In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:</p> <ul style="list-style-type: none"> - expires for failure to pay a maintenance fee; - is held unenforceable; - is found invalid by a court of competent jurisdiction; - is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321; - has all claims canceled by a reexamination certificate; - is reissued; or - is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer. <p>☐ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.</p>			

☒ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
<p>THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES</p> <p>I certify, in accordance with 37 CFR 1.4(d)(4) that I am:</p> <p>☒ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application</p> <p style="margin-left: 40px;">Registration Number <u>28510</u></p> <p>☐ A sole inventor</p> <p>☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application</p> <p>☐ A joint inventor; all of whom are signing this request</p>	
Signature	/E. Joseph Gess/
Name	E. Joseph Gess

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
 Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 17241793

Filing Date: 27-Apr-2021

Applicant/Patent under Reexamination: PILGAONKAR

Electronic Terminal Disclaimer filed on May 26, 2023

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt	
EFS ID:	48063215
Application Number:	17241793
International Application Number:	
Confirmation Number:	1465
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:	70204.0018USC1
Receipt Date:	26-MAY-2023
Filing Date:	27-APR-2021
Time Stamp:	11:49:50
Application Type:	Utility under 35 USC 111(a)

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	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	39663	no	2
			33c284027cb1bd2daf38435dfd6f18b3d4ae66dd		
Warnings:					

Information:	
Total Files Size (in bytes):	39663
<p>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.</p> <p><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.</p> <p><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.</p> <p><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.</p>	

TERMINAL DISCLAIMER TO OBTAIN A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 70204.0018USC1
<p>In re Application of: Pilgaonkar et al.</p> <p>Application No.: 17/241,793</p> <p>Filed: April 27, 2021</p> <p>For: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE</p> <p>The applicant, <u>Breckenridge Pharmaceutical, Inc.</u>, owner of <u>100</u> percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent No. <u>11,013,729</u> as the term of said prior patent is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.</p> <p>In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:</p> <ul style="list-style-type: none">expires for failure to pay a maintenance fee;is held unenforceable;is found invalid by a court of competent jurisdiction;is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;has all claims canceled by a reexamination certificate;is reissued; oris in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer. <p>Check either box 1 or 2 below, if appropriate.</p> <p>1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.</p> <p>I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.</p> <p>2. ☒ The undersigned is an attorney or agent of record. Reg. No. <u>28510</u></p> <div style="margin-top: 20px;"><div style="display: flex; justify-content: space-between;"><div style="width: 60%; text-align: center;"><u>/E. Joseph Gess/</u> Signature</div><div style="width: 35%; text-align: center;"><u>May 25, 2023</u> Date</div></div><div style="display: flex; justify-content: center; margin-top: 10px;"><u>E. Joseph Gess</u> Typed or printed name</div><div style="display: flex; justify-content: space-between; margin-top: 20px;"><div style="width: 40%; text-align: center;"><u>Partner</u> Title</div><div style="width: 55%; text-align: center;"><u>703-684-2511</u> Telephone Number</div></div></div> <p>☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.</p> <p style="text-align: center; font-weight: bold;">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.</p>	

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UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
17/241,793

RECEIPT DATE / TIME
05/25/2023 11:29:17 AM ET

ATTORNEY DOCKET #
70204.0018USC1

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1465

FILED BY Lisa Kenney

PATENT CENTER # 62152714

AUTHORIZED BY Erich Gess

CUSTOMER # 23552

FILING DATE 04/27/2021

CORRESPONDENCE
ADDRESS -

FIRST NAMED
INVENTOR Pratibha S. PILGAONKAR

Payment Information

PAYMENT METHOD
CARD / 4565

PAYMENT TRANSACTION ID
E202350B35096469

PAYMENT AUTHORIZED BY
Lisa Kenney

PRE-AUTHORIZED ACCOUNT
132725

PRE-AUTHORIZED CATEGORY
37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
TOTAL AMOUNT:				\$170.00

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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 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.



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PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/241,793

RECEIPT DATE / TIME
05/25/2023 11:29:17 AM ET

ATTORNEY DOCKET #
70204.0018USC1

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CONFIRMATION # 1465

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PATENT CENTER # 62152714

FILING DATE 04/27/2021

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Erich Gess

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
70204-0018USC1-Communication-TD.PDF	1	Miscellaneous Incoming Letter	80 KB
70204-0018USC1__TD__aia0026.PDF	2	Terminal Disclaimer Filed	231 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
70204-0018USC1-Communication-TD.PDF	90281FFE2D642A821C798E2C11CA0A6D2F91713A31B7DC4CE BC56440CF7056D8FBC063B84ADF396DE2491E4E42E06A4733

FC9D4E4F65969306C3C7AC778413D3

70204-	924CCDB7BF91AF13B38D4374960BFF026B44E52100CA34675
0018USC1_TD_aia0026.PDF	00219502213B7F4535F0815651EDAD44EAA01CFECF193A0B79
	9AD26033EF5C2260D38429FCA3554

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S/N 17/241,793

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	17/241,793	Group Art Unit:	1613
Filed:	April 27, 2021	Docket No.:	70204.0018USC1
Customer No.	23552	Confirmation No.	1465
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

COMMUNICATION: SUBMISSION OF TERMINAL DISCLAIMER

U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commissioner for Patents

Further to the Response filed 3 April 2023, Applicant submits herewith a Terminal Disclaimer in view of U.S. Patent No. 11,013,729 (the '729 patent). Applicant intended to file the Terminal Disclaimer with the Response; however, it was inadvertently omitted.

If there are any questions regarding this submission, Applicant requests that the Examiner telephone the below-signed attorney.

The Examiner is authorized to charge any additional fees or refund any overpayments to Deposit Account No. 13-2725 (Docket No. 70204.0018USC1).

Respectfully submitted,

Date: 25 May 2023

/E. Joseph Gess/
E. Joseph Gess
Registration No. 28510

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402
Telephone No. 703.684.2511
Facsimile No. 612.332.9081



S/N 17/241,793

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	17/241,793	Group Art Unit:	1613
Filed:	April 27, 2021	Docket No.:	70204.0018USC1
Customer No.	23552	Confirmation No.	1465
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 October 28, 2022, Applicant submits herewith the following amendment and response, petition for three month extension of time, and the attached Request for Interview.

Amendments to the Claims begin on page 2.

Remarks begin on page 6.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation comprising administering to the patient in need thereof 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.
2. (Original) The method of claim 1, wherein the composition is administered as a unit dosage form comprising from 50 mg to 200 mg of dabigatran etexilate mesylate.
3. (Original) The method of claim 2, wherein the unit dosage form is a capsule.
4. (Original) The method of claim 1, wherein the composition further comprises at least one pharmaceutically acceptable excipient.
5. (Original) The method of claim 1, wherein the composition comprises from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.
6. (Original) The method of claim 1, wherein the composition comprises from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

7. (Original) The method of claim 4, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

8. (Currently Amended) A method for treating 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 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.

9. (Original) The method of claim 8, wherein the composition is administered as a unit dosage form comprising from 50 mg to 200 mg of dabigatran etexilate mesylate.

10. (Original) The method of claim 9, wherein the unit dosage form is a capsule.

11. (Original) The method of claim 8, wherein the composition further comprises at least one pharmaceutically acceptable excipient.

12. (Original) The method of claim 8, wherein the composition comprises from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.

13. (Original) The method of claim 8, wherein the composition comprises from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

14. (Original) The method of claim 11, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

15. (Original) The method of claim 8, wherein the venous thromboembolic events are deep venous thrombosis (DVT) and pulmonary embolism (PE).

16. (Cancelled)

17. (Currently Amended) The method of claim 19 [[16]], wherein the capsule contains from 50 mg to 200 mg of dabigatran etexilate mesylate.

18. (Original) The method of claim 19 [[16]], wherein the first type of particles of the capsule comprise at least one pharmaceutically acceptable excipient.

19. (New) A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation or for treating 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 capsule 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 tartaric acid; and

b) the second type of particles comprise tartaric acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

20. (New) The method of claim 19, wherein the second type of particles of the capsule comprise at least one pharmaceutically acceptable excipient.

21. (New) The method of claim 19, wherein the capsule comprises from 2 wt % to 95 wt % of the tartaric acid.

REMARKS

Claims 1-16, 17, 18, and new claims 19-21 are pending, with claims 1, 8, and 19 being independent. By the present amendment, claims 8, 17, and 18 have been amended to focus on particularly preferred embodiments and new claims 19-21 have been added for the same reason. Support for the claim 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 and submits herewith a Request for Interview.

Priority

The Examiner indicated that the application should be designated as a divisional because no method of use claims were allowed in the parent application (US 14/379,613). Applicant notes that there was a restriction requirement in the parent case; however, in the Notice of Allowance dated 26 April 2021, the Examiner indicated that the restriction requirement was withdrawn. (page 2).

Accordingly, Applicant filed the present application as a continuation application and respectfully maintain it as a continuation application. If the Examiner disagrees, Applicant requests that the Examiner contact Applicant's representative to discuss so that allowance can be expedited.

Rejections under 35 U.S.C. § 112

Claims 8-18 are rejected under 35 U.S.C. § 112(a) for alleged lack of enablement. Applicant respectfully traverses this rejection in view of the amended claims.

Applicant notes that the Examiner indicates that the specification is enabling for treating venous thromboembolic events in adult patients who have undergone elective hip replacement surgery and reducing the risk of stroke and systemic embolism in patient with non-valvular arial

fibrillation. However, the Examiner alleges that the specification is not enabling for *preventing* venous thromboembolic events (emphasis added).

The specification describes and discusses the dabigatran (Pradaxa[®]) product. As described in the Background section, dabigatran (Pradaxa[®]) is a potent, reversible, univalent direct thrombin inhibitor. Also as described, dabigatran (Pradaxa[®]) was known to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and was approved for that indication. Further as described, dabigatran (Pradaxa[®]) was known to be useful in primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, and also had been approved for that indication. As evidence of this knowledge that dabigatran (Pradaxa[®]) was approved for these indications prior to the earliest priority date, Applicant submitted two published documents from the European Medicines Agency (the European equivalent of the FDA) in an IDS and attached these documents again to this response for ready reference.

The first document is the European Medicines Agency Initial Marketing-authorization for Pradaxa from April 2008 – this document is entitled European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), European Public Assessment Report for Pradaxa (dabigatran etexilate), published 23 April 2008. This document confirms that the European Medicines Agency approved Pradaxa (i.e., dabigatran etexilate (DE)) for preventing venous thromboembolism (VTE) after elective total hip replacement (THR) and total knee replacement (TKR) in 2008. Applicant references page 33, where under the section entitled **Efficacy**, it is stated:

The clinical efficacy of DE in VTE prevention after
elective THR or TKR has been demonstrated in four multi-centre,
double blind, double-dummy, randomised, parallel group,
controlled clinical studies.

The second document from the European Medicines Agency is the Post Authorisation Summary of Positive Opinion for Pradaxa (dabigatran etexilate mesilate) published 14 April 2011. This document indicates that the Committee for Medicinal Products for Human Use (CHMP) had adopted a new indication for Pradaxa (dabigatran) of prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation. The document also confirms the previously

approved indication and states that the full indications for Pradaxa (dabigatran) as of 14 April 2011 were as follows (emphasis added):

For 75 mg strength

Primary **prevention** of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

For 110 and 150 mg strengths

Primary **prevention** of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

- Previous stroke, transient ischemic attack, or systemic embolism (SSE)
- Left ventricular ejection fraction < 40 %
- Symptomatic heart failure, $\geq$ New York Heart Association (NYHA) Class 2
- Age $\geq$ 75 years
- Age $\geq$ 65 years associated with one of the following:
diabetes mellitus, coronary artery disease, or hypertension

Based on the common knowledge of the approved indications for Pradaxa (dabigatran) by the European Medicines Agency as of 2008 and 2011, the specification of the present application disclosed and described that in another aspect the present invention provides 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 pharmaceutical compositions of dabigatran etexilate of the present invention (page 17 of the specification).

As the Examiner acknowledged in the Notice of Allowance in the parent application (US 14/379,613, now issued US 11,013,729) the allowable subject matter was the novel pharmaceutical compositions of dabigatran and claims directed to this novel subject matter. Methods of treatment reciting use of these novel compositions of dabigatran, also should be allowable.

Accordingly, it is respectfully submitted that the novel compositions of dabigatran were enabled at least for all of the approved indications of dabigatran as of the priority date for the application. As such, one ordinary skill in the art readily would have been enabled to practice all of the approved indications, including the indication of *preventing* venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, as recognized by the European Medicines Agency as of 2008.

For at least these reasons, Applicant respectfully requests that the rejection under 35 U.S.C. § 112 for alleged lack of enablement be withdrawn.

Double Patenting

Claims 1-18 are rejected for non-statutory double patenting in view of claims 1-18 of U.S. Patent No. 11,013,729 (the '729 patent) in view of Loke and Huisman. As noted above, the present application claims priority to the '729 patent. Without conceding the propriety of the rejections, Applicant submits herewith a terminal disclaimer to address the double patenting rejection. Applicant notes that the filing of a terminal disclaimer is not to be construed as an admission of the propriety of the rejection on obviousness double patenting. *The Quad Environmental Technologies Corp. v. the Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991).

Conclusion

In view of the foregoing remarks, amendments, and the terminal disclaimer, 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 formally requests an opportunity to discuss the presently claimed invention with the Examiner. As such, Applicant includes herewith a formal Request for Interview.

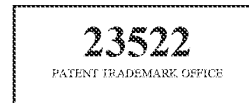
The Examiner is authorized to charge any additional fees or refund any overpayments to Deposit Account No. 13-2725 (Docket No. 70204.0018USC1).

Respectfully submitted,

Date: 3 April 2023

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European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/174363/2008

**CHMP ASSESSMENT REPORT
FOR
Pradaxa**

International Nonproprietary Name:
dabigatran etexilate

Procedure No. EMEA/H/C/829

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ACS	Acute Coronary Syndrome
AE	Adverse event
aPTT	activated Partial Thromboplastin Time
AUC	area under the curve
b.i.d.; bid (in tables)	Twice daily dosing
BP	Blood Pressure
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
C _{max}	Maximum concentration in plasma
CL _{CR}	Creatinine clearance
CNS	Central nervous system
CRBE	Clinically Relevant Bleeding Events
CT	Computed tomography (also known as: CAT scan)
CTR	Clinical Trial Report
CV	Coefficient of variation
CUS	Compression ultrasound
dabig etex	Dabigatran etexilate
dabig etex 150	Dabigatran etexilate 150 mg
dabig etex 220	Dabigatran etexilate 220 mg
DAB	dabigatran
DE	Dabigatran etexilate
DEM	dabigatran etexilate mesilate
DSC	Differential scanning calorimetry
DTI	Direct Thrombin Inhibitor
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECT	Ecarin Clotting Time
E _{max}	maximum effect
EMA	The European Agency for the Evaluation of Medicinal Products
Enox (in tables)	Enoxaparin
etex	Etexilate
EU	[the] European Union
FAS	Full analysis set
FAS-m	FAS-major; Full analysis set -major
FUM	Follow-up Measure
GC	Gas chromatography
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HIT	heparin-induced thrombocytopenia
HPLC	High performance liquid chromatography
INR	International Normalized Ratio
i.v.	intravenous
LMWH	Low molecular weight heparin
MBE	Major bleeding event
MID	Minimum Important Difference
mL	Milliliter
MOS	major orthopedic surgery
n	Number
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drugs

p.o. (po, in tables)	<i>per os</i> , oral administration
PD	Pharmacodynamics
PE	Pulmonary embolism
PhEur	European Pharmacopoeia
PK	Pharmacokinetic
PT	prothrombin time
q.d. (qd, in tables)	Once daily dosing
s.c.	Subcutaneous
tDVT	Total deep venous thrombosis
THR	total hip replacement
TKR	total knee replacement
TT	thrombin time
UH	unfractionated heparin
U.S.	United States of America
VKAs	vitamin K antagonists
VTE	Venous thromboembolism

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 01 February 2007 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pradaxa, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 June 2006. The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier:
composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The applicant applied for the following indication: "Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery".

Licensing status:

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Steffen Thirstrup Co-Rapporteur: Pierre Demolis

1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 1 February 2007.
- The procedure started on 21 February 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 May 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 May 2007.
- During the meeting 18-21 June 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 June 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 6 September 2007.
- The final Integrated inspection report of the inspection carried out in the investigator sites was issued on 19 September 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 October 2007.
- During the CHMP meeting 12-15 November 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.

- During the meeting 21-24 January 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Pradaxa on 24 January 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 January 2008.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 18 March 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

The need to prevent venous thromboembolism (VTE) in patients undergoing total knee [TKR] or hip replacement [THR] surgery is well established. In the absence of VTE prophylaxis, the absolute risk of VTE ranges from 40-60%; hence, prophylaxis should be administered during the period of highest risk. Heparin and especially the low molecular weight heparins (LMWH) are the most commonly used anticoagulants for the prevention of VTE after major orthopedic surgery (MOS). More recently, fondaparinux has been also recommended. Additionally, vitamin K antagonists (VKAs) are also frequently used in some countries. These drug classes are highly effective therapeutic agents. However, heparin and its derivatives, as well as fondaparinux, must be administered parentally, making self administration both challenging and less desirable. Moreover, unfractionated heparin and, to a lesser extent, the LMWH can cause heparin-induced thrombocytopenia (HIT), a rare but potentially life-threatening adverse event. Warfarin and other VKAs are given orally; however, their use is associated with numerous limitations. These include a high potential for food-drug interactions and drug-drug interactions, which necessitates the need for frequent monitoring of INR and occasional dose adjustments. In addition, VKAs have a slow onset and offset of action, which may limit their effectiveness as prophylactic agents for the prevention of VTE, since the peri-operative period is when the risk of thrombosis formation is greatest. Consequently, bridging therapy with a parenteral agent may be necessary at the initiation of therapy. Given the limitations and inconveniences of currently available agents, many patients do not receive satisfactory anticoagulant therapy or stop it too early. There is a significant need for a fixed dose anticoagulant that is at least as effective as available anticoagulants, which can be given orally, and is free from the challenges of VKAs.

Dabigatran etexilate (DE) is a potent, synthetic, non-peptide competitive, rapidly acting oral direct thrombin inhibitor (oral DTI). DE is the oral pro-drug of the active moiety dabigatran (DAB) and does not possess anticoagulant activity. The pro-drug dabigatran etexilate is used in its salt form dabigatran etexilate mesilate (DEM). That specifically and reversibly inhibits thrombin, the final enzyme in the coagulation cascade. The granted indication is primary prevention of VTE in patients undergoing elective MOS [(THR or TKR)]. The recommended dose is 220mg once daily taken as 2 capsules of 110mg. For patients with moderate renal impairment or aged above 75 years, the recommended dose is 150mg once daily taken as 2 capsules of 75mg. The treatment should be initiated orally within 1-4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days in knee surgery and 28-35 days in hip surgery. The Phase III DE programme for the primary prevention of VTE consisted of three studies: two European (EU) studies, considered as pivotal, and a supportive North American study. These studies were designed to be as similar as possible. However, the significant differences in practice patterns, registered doses of comparator drugs and differing recommendations for the duration of prophylactic therapy for different types of surgery (hip vs. knee) necessitated some differences in the Phase III study designs, which are discussed in the relevant sections of this document.

A recommended primary endpoint in therapeutic confirmatory trials as written in the CHMP Guideline (CPMP/EWP/ 707/98) is a composite endpoint consisting of clinically relevant and objectively documented events including venographically documented proximal DVT, symptomatic and well-documented non-fatal pulmonary embolism (PE) and VTE related death or death due to any cause. However, despite the total DE development program including over 8000 patients, the individual studies were not thought to be sufficiently powered to reliably assess efficacy for the composite endpoint including proximal DVT, symptomatic VTE and VTE related death (= major VTE and VTE related death).

A meta- analysis was pre-specified in order to evaluate the effects of DE on the composite endpoint specified in the CHMP Guideline (CPMP/EWP/ 707/98). This approach could justify the deviation from the CHMP Guideline if the results of the individual pivotal trials show non-inferiority compared to enoxaparin. This could not be shown in supportive US study. That is why the meta-analysis was considered of exploratory, not of the confirmatory nature.

The introduction of UH and later LMWH as standard prophylactics has reduced the frequency of major VTE and VTE related mortality significantly. Therefore large study populations are needed in order to show non-inferiority. Therefore, a “new” surrogate end-point was proposed which occurs with a higher frequency in order to keep the study population at a reasonable size. Total VTE and all-cause mortality was used during the treatment period as such “new” surrogate marker. Major VTE and VTE related mortality was chosen as one of the secondary endpoints. The MAA for DE was submitted prior to the revision of the CHMP Guideline (CPMP/EWP/ 707/98/Rev 1).

2.2 Quality aspects

Introduction

Dabigatran etexilate has been developed as an orally active anticoagulant for the prevention of venous thromboembolic events in patients who have undergone elective total hip or knee replacement surgery. It is available as 110 mg and 75 mg hard capsules for oral administration presented in aluminium / aluminium blisters or in polypropylene bottles with desiccant.

The recommended dose is 220 mg once daily taken as 2 capsules of 110 mg. For patients with moderate renal impairment the recommended dose of dabigatran etexilate is 150 mg once daily, taken as 2 capsules of 75 mg.

The maximum daily dose for dabigatran etexilate mesilate (DEM) is 300 mg.

Active Substance

The chemical name (IUPAC) of dabigatran etexilate mesilate is ethyl N-{{[2-({[4-((E)-amino {{[(hexyloxy) carbonyl] imino} methyl) phenyl] amino} methyl)-1-methyl-1H-benzimidazol-5-yl] carbonyl} -Npyridin-2-yl-β-alaninate methanesulfonate corresponding to the molecular formula $C_{35}H_{45}N_7O_8S$. The molecular mass is 723.86 for the salt and 627.75 for the free base.

Dabigatran etexilate is the pro-drug of the active substance, dabigatran which corresponds to the molecular formula $C_{25}H_{25}N_7O_3$ and molecular mass 471.5.

DEM is a yellow-white to yellow non-hygroscopic powder. The partition coefficient of the neutral form (free base) is $\log P = 3.8$, $pK_{a1} = 4.0 \pm 0.1$ $pK_{a2} = 6.7 \pm 0.1$. Solubility is strongly pH dependent with increased solubility at acidic pH. The solubility in water is 1.8 mg/ml. DEM is freely soluble in methanol, soluble in ethanol, sparingly soluble in isopropanol, very slightly soluble in acetone and practically insoluble in ethyl acetate.

It has no chiral centers and therefore does not form enantiomers. Geometric isomers (tautomers) are possible.

DEM exhibits polymorphism. Two forms, modification I and II are known. The drug substance is modification I in the anhydrous form and is routinely produced by the commercial method of synthesis. A hydrated form with a stoichiometry close to a hemihydrate also exists.

• Manufacture

The active substance is synthesised in 3 steps and a number of recrystallisation steps on intermediates and the final substance. Protection from humidity is implied during manufacturing and storage to prevent hydrolysis of the pro-drug forming moieties and polymorphic form transformations. Extensive experimental work and scientific evaluation of the potential carryover of these impurities and their derivatives during further process steps were carried out. These experiments prove that the proposed acceptance criteria for the identified impurities in each isolated intermediate are appropriate and ensure that these impurities (as well as their potential derivatives) are removed by extraction and purification procedures of the synthesis process to remain within the levels specified for the drug substance.

Data showing that alkyl methane sulfonates compounds are not formed during drug substance production have been presented which justify why quality controls in the last step of the synthesis are not necessary.

Appropriate controls in the last step of the synthesis are carried out to ensure the formation of the desired crystalline modification I.

- **Specification**

The specifications for the control of the drug substance includes tests for appearance (visual), identification (IR), colour and clarity of solution (PhEur), purity and polymorphism (DSC), impurities (HPLC), residual solvents (GC), heavy metals (PhEur), water content (PhEur), sulphated ash (PhEur), assay (HPLC and titration), particle size (Laser-beam diffraction).

The specifications have been established based on analytical release data, stability studies and pharmaceutical development studies. In particular, the limits for organic impurities are based on the batch data for 38 representative clinical batches made according to the commercial synthesis process and on the primary stability data. All results meet the proposed regulatory specifications

The proposed specifications for impurities in the active substance are for some specified impurities above the qualification threshold of the ICH guideline *Impurities in new drug substances*, however toxicological qualification has been presented in Module 4 of the application.

The specification limits for two specific impurities of concern may also be considered to be fully qualified, because they are intermediates/metabolites of the active substance and are present in vivo.

- **Stability**

Stability data were presented for three full-scale production batches of dabigatran etexilate mesilate synthesized according to the proposed commercial process at the commercial site of manufacture. These batches were stored for 12 months under long-term storage conditions (25°C/60% RH) and for 6 months under accelerated conditions (40°C/75% RH).

Additional supportive stability data were available for a pilot scale batch stored for 36 months at long-term conditions (25°C/60% RH). This batch was also synthesized according to the proposed commercial process.

Primary stability studies were conducted in accordance with the ICH Q1A(R2) guideline.

All stability testing was performed according to the regulatory analytical procedures and the data evaluated according to the current specification for the drug substance.

After 12 months storage at 25°C/60% RH, the three primary stability batches did not show unexpected degree of decomposition, which in any case was in line with the supportive stability data available for the drug substance over 36 months at 25°C/60% RH.

The retest period is justified based on the stability results available for 24 months of storage.

Stress stability studies of the drug substance were performed on two batches to elucidate the major degradation pathways. DEM was exposed to various stress conditions (Solid state: elevated temperature, humidity and light irradiation and in aqueous solutions: different pH values, elevated temperature and exposure to oxidizing conditions).

In the solid state, DEM is very stable. After storage for 4 weeks at 70 °C in a closed container, not more than 0.50 % total degradation was observed. The degradation rate of the drug substance is markedly accelerated by the presence of moisture. This behaviour provides the rationale for the selection of a container/closure system that protects the drug substance against exposure to moisture. In aqueous solution at 40 °C, dabigatran etexilate mesilate undergoes considerable hydrolytic degradation.

The results of the stress stability studies show that dabigatran etexilate mesilate predominately undergoes degradation by hydrolytic pathways.

DEM is not sensitive to light irradiation in the solid state.

Medicinal Product

- **Pharmaceutical Development**

Based on these physicochemical and biopharmaceutical properties of dabigatran etexilate mesilate, and the clinical requirements for a reliable drug release a multilayer pellet was selected. Active ingredient layered organic acid containing pellets filled into hard capsules were developed as dosage form. Other formulation approaches were evaluated during early development, but were inferior to the selected formulation in terms of drug load, stability and *in vivo* performance.

DEM has low solubility in water and high intrinsic passive permeability, and is considered a Class II compound according to the biopharmaceutical classification system.

The active substance is susceptible to hydrolysis in presence of humidity under acidic conditions, which is why a manufacturing process limiting water and acidic conditions is chosen. Drug substance particle size limits are established to ensure consistent drug product manufacturability.

All of the selected excipients, including HPMC capsule shell, are commonly used in oral commercial pharmaceutical dosage forms and are compendial materials. The selection of excipients and their corresponding levels was based on *in vitro* dissolution, stability, and *in vivo* bioavailability studies using various prototype formulations.

The compatibility tests results indicate that all tested active-excipient mixtures are sufficiently stable for selection as an excipient in the intended commercial formulation

HPMC capsule shells were selected because DAB is sensitive to hydrolysis and because of the minimum brittleness of the capsule material, when desiccants used in primary packaging. Dissolution profiles of gelatine and HPMC capsules demonstrate that the release from the HPMC capsules is delayed from about 25% in 15 min but that no difference is observed at 30min. This difference has no impact on *in vivo* release. This was confirmed by a relative bioavailability study performed on 150mg strength capsules of HPMC and gelatine.

In the drug product, alkyl methanesulfonates were controlled during development, as these alkyl methane sulfonates might be formed during manufacture and storage of dabigatran etexilate capsules.

The analysis was performed with dabigatran etexilate pellets final stage, either prior to encapsulation or with the final drug product, dabigatran etexilate capsules.

Batch analysis results confirm that alkyl methane sulfonates that could potentially be formed during manufacturing are not formed at detectable levels during the manufacturing of the finished product.

The manufacturing process has been validated during the manufacture of the drug product intermediates and for three batches of 75mg capsules and three batches of 110mg capsules at the production site. Retrospective validation data have been provided for the manufacture of the intermediate products. Holding times of the drug product intermediates have been established.

- **Adventitious Agents**

None of the excipient used is of animal or human origin.

- **Manufacture of the Product**

The commercial manufacturing process of dabigatran etexilate capsules 75 mg / capsule and 110 mg / capsule includes the following operations:

- manufacture of drug product intermediates
- final blending resulting in dabigatran etexilate pellets final stage
- encapsulation
- packaging of capsules into blisters or bottles

A standard process is used to produce the pellets to be filled in the HPMC capsules.

The same manufacturing process has been utilised for the primary stability batches and the Phase III clinical batches for dabigatran etexilate capsules which were all manufactured at full commercial batch size with respect to the dabigatran etexilate pellets final stage.

The data gathered during process validation and the provided batch analyses demonstrates that the manufacturing process is robust and consistently yields drug product, which meets the predetermined quality characteristics. The chosen in-process controls have been shown to be suitable for monitoring the manufacturing process.

- **Product Specification**

The specification for batch release and shelf-life include the following tests: appearance (visual), loss on drying for pellets (gravimetry), loss on drying for capsule shell (gravimetry), identification (at release only) (HPLC, UV), active ingredient content (HPLC), degradation products (HPLC), uniformity of dosage units (at release only) (PhEur), dissolution (PhEur), microbiological purity (PhEur)

Residual solvents are controlled in the intermediate product, dabigatran etexilate pellets final stage, according to the requirements of ICH Q3C(R3).

Batch analysis results of nine batches plus results from three other batches (used for clinical trials) were presented. Supportive batch analysis data for batches manufactured during the different stages of development are also provided. The results comply with the specification and confirm consistency of the product.

- **Stability of the Product**

Three pilot scale batches of each strength have been stored at 25°C/60% RH for 12 months and at 40°C/75% RH for 6 months in the proposed market packaging. Batches were of same formulation as proposed for commercial batches, except that the capsules were not imprinted.

Parameters investigated: Appearance, Loss on drying (pellets and shell), degradation products, assay, dissolution, microbial contamination.

No significant changes have been observed after storage at either condition in *PP container*. However, in *alu/alu blister* an increase in all degradation products are observed, most markedly for BIBR1154 at both accelerated and long term conditions. This behaviour is due to the drying capacity of the desiccant in the PP container. Statistical evaluation of BIBR1154, total degradation products and assay, has been presented for the 3 primary stability batches of each strength. Results reveal no marked trend, therefore the proposed shelf life is considered acceptable.

Supportive stability results from one pilot scale 150mg capsule batch were also provided, stored in Alu/alu-blisters (with equivalent protective properties as the proposed blister) for 36 months at 25°C/60% RH and 30°C/70%RH, and for 6 months at 40°C/75%RH. No significant changes were observed for any of the tested parameters (appearance, loss on drying, dissolution, degradation and assay) and the proposed shelf life specifications were met after 36 months storage under long-term conditions.

Stability results on formation of methane sulfonic acid alkyl esters impurities in the drug product were presented. These results show there is no risk of the formation of these substances at release and at stability conditions/period of 6 months at 40°C/75%RH and 12 months at 30°C/70%RH.

Stability results on formation of polymorphic form II during storage is presented in separate report. No further conversion to Form II is observed even if high amounts of Form II was present from t=0. Form II is limited in the drug substance.

In-use stability: The in-use study was carried out on one batch of each strength in proposed PP container. Results support the proposed in-use shelf life for capsules stored in the polypropylene bottle container system with desiccant. Batches used had first been stored for 12 months at 25°C/60%RH, and then simulated use was carried out by periodically opening and closing (twice a day) and removing capsules from the bottle (but still stored at 25°C/60%RH). Testing points were after 0, 14 and 30 days. No change in degradation products is observed.

The in-use study supports the proposed in-use shelf life for capsules stored in the polypropylene bottle container system with desiccant.

Photostability: Light stability study of filled capsules revealed no relevant changes (appearance, dissolution, assay and related substances), which is why no further investigation in primary packaging was carried out which is in agreement with the ICH Q1B guideline.

Stress testing: after one day stored open at 40°C/75%RH loss on drying of pellets and of capsule shell increased for the two strengths, as did the hydrolysis degradation products. After 85 days at 60°C (uncontrolled humidity) no significant changes were observed apart from declining loss on drying results and an increase change in total degradation products. These results were however expected as the finished product is sensitive to moisture.

Based on the stability data obtained and their statistical evaluation the proposed shelf-life and storage condition are accepted, as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Pradaxa hard capsules is adequately established. In general, sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug substance and drug product has been presented. There are no major deviations from EU and ICH requirements. The results of tests carried out indicate satisfactory consistency and uniformity of all the important product quality characteristics. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant submitted a Letter of Undertaking dated on 22 January 2008 and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

It can be safely concluded that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-clinical aspects

Introduction

Pradaxa contains 75 mg or 110 mg of DE, the oral pro-drug of the active moiety dabigatran (DAB). The pro-drug DE is present in its salt form dabigatran etexilate mesilate (DEM). The marketing authorization application dossier for Pradaxa contains data from the preclinical studies performed with DEM.

Pharmacology

- **Primary pharmacodynamics**

DAB is a novel, synthetic, non-peptide competitive, rapidly acting and reversible inhibitor of thrombin. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. DAB also inhibits free thrombin, fibrin-bound thrombin and thrombin induced platelet aggregation. DAB is a specific inhibitor of thrombin that demonstrates anticoagulant and antithrombotic activity both *in vitro* and *in vivo*. *In vivo* it has a relatively wide safety window between antithrombotic efficacy and bleeding side effects. In addition according to general/safety pharmacological profiling, it has no proarrhythmic potential based on *in vitro* and *in vivo* assays and is generally well tolerated. DAB is a synthetic non-peptide compound, which acts as a competitive inhibitor at the active site of thrombin. It inhibits human thrombin with a K_i of 4.5 nM. In contrast to heparin, which acts by augmenting the activity of anti-thrombin, DTIs also inhibit fibrin-bound thrombin, as is observed in a blood clot. DAB is poorly absorbed following oral dosing thus it is orally administered in the form of the pro-drug DEM. Administration of i.v. DAB and p.o. DEM, produces a dose- and time-dependent prolongation of coagulation time in various species. The effect of i.v. pre-treatment with DAB on venous clot formation was investigated in a rat and a rabbit model of venous thrombosis. A 50% reduction in clot size (ED_{50}) was observed following i.v. administration of 33 µg/kg and 66 µg/kg DAB in the rat and rabbit, respectively. DAB did not inhibit platelet aggregation in human plasma following the introduction of various platelet activating factors.

- **Secondary pharmacodynamics**

DAB exhibited low affinity ($K_i > 3.5$ µM) towards the serine proteases factor Xa, factor XIa, factor VIIa/tissue factor complex, plasma kallikrein, plasmin, urokinase, tissue-type plasminogen activator, activated protein C, granulocyte elastase and C1 esterase. DAB inhibited trypsin with a K_i of 50.3 nM, however the digestive enzyme trypsin does not normally occur in the blood and is not involved in haemostasis. The lack of a broader receptor screen was considered acceptable based on the large battery of safety pharmacology and toxicological studies performed.

- Safety pharmacology programme

Safety pharmacology studies applying i.v. administration of DAB or p.o. administration of DEM revealed no special hazard for acute effects on the function of the cardiovascular system, central nervous system, respiratory system, and renal and gastrointestinal system.

- Pharmacodynamic drug interactions

No non-clinical pharmacodynamic (PD) drug interaction studies were performed that was considered acceptable by the CHMP.

Pharmacokinetics

Absorption

DEM was identified as a medium-affinity substrate for the efflux transporter P-glycoprotein in the human colon carcinoma derived cell line Caco-2. Moreover, DEM inhibited the apical-to-basolateral transport of the P-glycoprotein substrate digoxin in a concentration-dependent manner with an IC₅₀ of 25 µM (50-fold clinical C_{max}). A clinical study confirmed that no pharmacokinetic (PK) interactions occur when DEM is co-administered with digoxin. Following single administration, the oral bioavailability of [¹⁴C]-DEM was 16% in rat, 5% in rabbit, 8% in Rhesus monkey and 7% in man. The clearance was 4.5 to 6-fold higher in rat, rabbit and monkey when compared to man and consequently the half-life was lower in these species. T_{max} was obtained 0.5 h following p.o. dosing in mouse and rat, at 1.3 h in rabbit and monkey and at 1.5 h in man. No gender differences were observed with respect to absorption following repeated dosing of mice, rats and monkeys. No consistent trend towards lower plasma exposure levels with repeated dosing was observed in the species tested.

Distribution

DEM related radioactivity distributed into most tissues 30 minutes following oral dosing in rats whereas only very limited levels of radioactivity were detected in the CNS. Besides the gastrointestinal tract, DEM related radioactivity was predominantly detected in liver, urinary tract, artery wall and adrenal medulla. Minor levels of radioactivity were detected in skin and bone marrow. 24 hours following oral dosing, traces of radioactivity were only detected in the liver. DEM and DAB displayed no affinity for melanin containing tissues. The distribution of [¹⁴C]-DAB from plasma into blood cells was negligible. Only very low levels of radioactivity were detected in foetal tissues following p.o. dosing to rats thus DEM exhibits low placental transfer. The plasma protein binding of [¹⁴C]-DAB was low in plasma of mice (22-26%), rat (29-33%), rabbits (32%), Rhesus monkeys (38 - 39%) and humans (29-30%).

Metabolism

The metabolism of DEM was investigated in mice, rats, rabbits and Rhesus monkeys. Following DEM administration, the two intermediate pro-drugs BIBR 1087 SE (most predominant) and BIBR 951 CL are formed. This intermediate BIBR 951 CL is pharmacologically active however due to the intermediate nature of BIBR 1087 SE and BIBR 951 CL, they constitute only trace amounts in human plasma samples. Subsequently, these pro-drugs are converted into DAB. Only traces of BIBR 1087 SE undergo further oxidative metabolism. Cytochrome P450 (CYP450) enzymes did not contribute to the metabolism of DEM, DAB nor of the two intermediate pro-drugs BIBR 1087 SE and BIBR 951 CL. Instead, the metabolism of DEM is catalysed by esterases, such as soluble esterases and also microsomal carboxylesterases. More than 20 metabolites were detected in the investigated animal species but DAB was the predominant compound in all samples of matrices investigated. The chemical structure of DAB contains a carboxylic acid functional group which is metabolically converted to the 1-*O*-acyl glucuronide. Due to non-enzymatic isomerization of the 1-*O*-acyl glucuronide, several positional isomers are formed. The 1-*O*-acyl glucuronide as well as its isomers prolonged the APTT to the same extent as the parent compound DAB. All acyl glucuronides present in man are also generated in significant amounts in the main animal species (rats and Rhesus monkeys) used in preclinical studies thus they are considered qualified. There were no human-specific metabolites.

Excretion

Following p.o. administration of [¹⁴C]-DEM, excretion of radioactivity is predominantly via faeces in mice, rats, rabbits and Rhesus monkeys (87-93%). DAB is secreted into the bile. However,

enterohepatic circulation of DAB occurs only to a very limited extent (0.4% of the administered radioactivity within 6 hrs) due to the fact that DAB cannot readily be reabsorbed by the gut. The excretion of radioactivity into milk was in the range of 0.08 to 0.13% of the dose administered to the dams.

Pharmacokinetic drug interaction

DEM and DAB neither induced the activity of major CYP450 enzymes in primary human hepatocytes nor in vivo in rat liver microsomes. However, the potential for induction of CYP2C9, 2C19 and 2C8 enzymes have not been investigated. DEM, DAB, BIBR 951 CL and BIBR 1087 SE had no effect on the activity of major CYP450 enzymes at clinically relevant concentrations. DEM absorption is not significantly affected by P-glycoprotein-mediated efflux. Altogether, the risk for CYP450 and P-glycoprotein mediated PK drug interactions following DEM administration are considered very limited.

Toxicology

- Single dose toxicity

Single-dose p.o. administration of DEM did not give rise mortalities in mice and rats at doses up to 2000 mg/kg and up to 600 mg/kg in Rhesus monkeys.

- Repeat dose toxicity (with toxicokinetics)

The pivotal studies consisted of 26-week studies performed in rats and monkeys and a 52-week study conducted in monkeys. The toxicity observed in the repeat-dose toxicity studies conducted in mice, rats, dogs and Rhesus monkeys was associated to the exaggerated pharmacological activity of DEM. The clinical and biochemical findings consisted of bruising, pallor, decreased activity, swelling of limbs and tail (in rodents) or lips and cheeks (monkeys), blood in faeces, mildly increased fibrinogen levels, increased aPTT, PT and TT values and regenerative anaemia. Histopathological findings in rats consisted predominantly of signs of recurrent haemorrhage in thymus, heart and pancreas. These organs were possibly particularly susceptible to haemorrhage due to the mechanical forces exerted on these tissues during gavage. In monkeys, the site of haemorrhage varied from the urinary bladder, subcutaneous tissue on the head, thymus, uterus, vagina, and to the skin. All treatment-related findings were reversible. Mortalities due to excessive bleeding possibly induced by the exertion of mechanical forces during gavaging were observed at 300 mg/kg in rats. Similarly, a single female monkey administered 200 mg/kg died due to excessive menstrual bleeding. Subsequently, the female monkeys were not dosed during the menstrual period. Altogether, the major safety concern with DEM is the risk for bleeding effects in humans. No signs of hepatotoxicity were observed in the repeat-dose toxicity studies conducted with DEM.

- Genotoxicity

The pro-drug DEM and the active moiety DAB were non-genotoxic in Ames tests, in the *in vitro* mouse lymphoma L5178Y *tk*^{+/+} assay and in the *in vivo* rat bone marrow micronucleus assay.

- Carcinogenicity

No carcinogenicity studies have been submitted since DEM will not be regularly administered over a substantial part of patient's lifetime. Moreover, there are no causes for concern suggesting a carcinogenic potential for DEM.

- Reproduction Toxicity

Male fertility was not adversely affected in rats following p.o. treatment with doses of up to 200 mg/kg DEM. A decrease in implantations was observed in females with a NOAEL of 15 mg/kg which approximately corresponds to clinical exposure levels. Moreover, the incidence of early resorptions was increased at 200 mg/kg. At maternotoxic and lethal doses (200 mg/kg), a decrease in viable foetuses was observed along with an increase in early, late and total resorptions in the rat embryo-foetal study. Moreover, the foetal weight was decreased in the 200 mg/kg group. A slightly increased incidence of variations was observed in high-dose foetuses. The NOAEL for foetal effects was 70 mg/kg, which gives rise to a safety margin of around 5. In a dose-range finding study, embryo-lethality (increased resorption rate) was observed in pregnant rabbits administered 200 mg/kg.

However, in the pivotal embryo-foetal study, treatment of rabbit with up to 200 mg/kg DEM had no effect on corpora lutea, implantations, viable foetuses, resorptions or resorption rate. The increased incidence of foetal variations was not increased. The NOAEL for foetal effects was 200 mg/kg, which gives rise to an AUC-based safety margin of 2. Maternal toxicity was observed at doses ≥ 30 mg/kg in the rat pre- and post-natal study and maternal mortality caused by bleeding to death during resorption of the embryos and parturition was observed at 70 mg/kg. The post-implantation loss and the number of dead offspring were significantly increased in the 70 mg/kg group. However, treatment had no negative effects on body weight, developmental landmarks, CNS parameters and on fertility of the pups. Consequently, pre-parturition, the NOAEL for foetal mortality was 30 mg/kg whereas post-parturition, the NOAEL for developmental effects in the offspring was 70 mg/kg. These values correspond to AUC-based safety margins of 1.6 and 3.9, respectively. Since the milk excretion of DAB only constitutes less than 0.13% of the dose administered to the rat dams, the lack of post-natal developmental effects are not unexpected. Small weights of the testes, epididymides, seminal vesicles and prostate gland were observed in monkeys treated with DAB for 52 weeks, but also in untreated control animals, and therefore no relationship to treatment is established

- Other toxicity studies

DEM was well-tolerated by rabbit skin and eyes and did not have a skin sensitisation potential in rabbits. Even though a weak phototoxic signal was detected in the 3T3 NRU assay, a review of the extensive safety database for DEM showed no evidence of a phototoxic potential in patients. The impurities and degradation products BIBR 951, BIBR 1087, BIBR 1150, BIBR 1154, BIBR 1155 and CDBA 513 are considered qualified up to the specified limits. The potential presence of the genotoxic impurities methyl mesylate, ethyl mesylate, isopropyl mesilate and n-hexyl mesilate at a level up to 1 ppm each does not represent a significant safety risk. It is unlikely that DAB use will result in an environmental risk.

Ecotoxicity/environmental risk assessment

The PEC_{sw} for DAB was calculated for total Europe as well as for the country with the highest expected market penetration (France). The F_{pen} values were based on current sales forecasts which might be estimated based on the expected number of patients. The resulting PEC_{sw} values were 0.0036 $\mu\text{g/L}$ and 0.0057 $\mu\text{g/L}$ for EU and France, respectively. These values were below the Phase II trigger value but Phase II assessment was performed. Log K_{ow} for DAB was below 4.5 thus a screening for persistence, bioaccumulation and toxicity was not needed. The adsorption/desorption coefficient K_{OC} was 5758 L/kg (OECD 106) thus an assessment of the drug substance in the terrestrial compartment was not required. It was expected that DAB will disappear rapidly from aerobic aquatic systems mainly via binding to sediment and formation of several minor metabolites (OECD 308). The level of ^{14}C -DAB in the sediment reached a plateau between days 3 and 14 with a maximal detected value of 5.7%. However, due to the structural resemblance to not ready biodegradable substances, a tier B study on transformation in aquatic sediment systems was performed (OECD 308). The calculated $PEC/PNEC$ ratios were all below 1. In summary, due to the low risk further testing in for effects on the aquatic environment, microorganisms and the terrestrial compartment were not required. In addition, due to the low K_{ow} a bioaccumulation study was not needed. $PEC_{sediment}$ values were obtained for EU (0.453 $\mu\text{g/kg}$) and the "worst-case scenario" France (0.718 $\mu\text{g/kg}$). Since the $PEC/PNEC$ ratio for the sediment was clearly below 1, it was concluded that with the present use pattern, DAB constitutes an insignificant risk for the sediment compartment. In conclusion, it is unlikely that DAB use will result in an environmental risk.

Discussion on the non-clinical aspects

DAB is a synthetic non-peptide compound, which acts as a competitive inhibitor at the active site of thrombin. DAB is poorly absorbed following oral dosing. Thus it is orally administered in the form of the pro-drug: DEM. Administration of i.v. DAB and p.o. DEM, produces a dose- and time-dependent prolongation of coagulation time in various species. Safety pharmacology studies revealed that treatment with DEM caused an increase in respiratory rate and minute volume and an inhibition of gastric emptying. However, no adverse events have been reported clinically that could be associated to these effects.

Following single administration, the oral bioavailability of DEM was 12% in rat, 5.4% in rabbit, 7.7% in Rhesus monkey and 7.2% in man. The clearance was 4.5 to 6-fold higher in rat, rabbit and monkey when compared to man and consequently the half-life was lower in these species. A less than dose-proportional increase in the exposure parameters C_{max} and AUC were generally observed in mice and monkeys following repeated dosing. DAB plasma exposure in rats and rabbits was generally dose proportional with no consistent effect of gender or repeated dosing. DEM related radioactivity was distributed into most tissues with very limited levels in the CNS. The metabolism of DEM was investigated in mice, rats, rabbits and Rhesus monkeys. Following its administration, the two intermediate pro-drugs were formed. These intermediate pro-drugs are pharmacologically active however they constitute only trace amounts in human plasma samples. Subsequently, they were converted into DAB. The metabolism of DEM is catalysed by esterases and the metabolites are excreted predominantly via faeces in mice, rats, rabbits and Rhesus monkeys. DAB is secreted into the bile. However, enterohepatic circulation of DAB occurs only to a very limited extent.

Single-dose oral administration of DEM did not give rise mortalities in mice and rats at doses up to 2000 mg/kg and up to 600 mg/kg in Rhesus monkeys. The toxicity observed in the repeat-dose toxicity studies conducted in mice, rats, dogs and Rhesus monkeys was associated with exaggerated pharmacological activity of DEM. The findings made in rats consisted predominantly of recurrent haemorrhage, fibrosis, fibrin deposition and haemosiderosis in the thymus, heart and pancreas. In monkeys, the site of haemorrhage varied from the urinary bladder, subcutaneous tissue on the head, thymus, uterus, vagina, and to the skin. In both rats and monkeys, haemorrhage was observed without safety margins to the clinical DAB plasma AUC level. Altogether, the major safety concern with DEM is the risk for bleeding effects in humans. No signs of hepatotoxicity were observed with DE which was of particular concern because it was observed with other DTIs. The pro-drug DEM and DAB were non-genotoxic. No carcinogenicity studies have been submitted since DEM will not be regularly administered over a substantial part of the patient's lifetime. Male fertility was not adversely affected in rats but reduced weights and atrophy of the testis, the epididymides, the seminal vesicles and prostate were observed in DAB-treated monkeys. Although these effects might in part be due to seasonal sexual inactivity at the time of the necropsy, a relationship to treatment cannot be excluded. An effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (5-fold the plasma exposure level in patients). At doses that were toxic to the mothers (5 to 10-fold the plasma exposure level in patients), a decrease in foetal body weight and viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

2.4 Clinical aspects

Introduction

DE is the orally bioavailable prodrug of DAB, a novel, non-peptidic, reversible inhibitor of thrombin. The primary objective of this application is to review data demonstrating the efficacy of DE 150 mg and 220 mg once daily dosing (q.d.) for the prevention of VTE following MOS. Evidence to support the claimed indication consists of data from two large EU Phase III therapeutic confirmatory clinical trials. These trials were performed in patients undergoing either elective TKR surgery (study 1160.25) or elective THR surgery (1160.48). These studies compared two doses of DE (150 mg and 220 mg, given orally as capsules once daily) against the standard comparator drug, enoxaparin (40 mg, given once daily subcutaneously). Consistent with medical practice and labelling in the EU, the initial dose of enoxaparin was given prior to surgery. In addition, Phase III TKR study (study 1160.24) was performed in parallel in North America using a higher daily dose of the same comparator, enoxaparin (given subcutaneously 30 mg injection twice daily), consistent with labelling in the US. Prior to the Phase III programme, dose-ranging studies were performed in patients undergoing joint replacement. The doses and administration schedule used in Phase III were developed based on the PK database collected during the Phase II programme.

Table 1: Overview of controlled clinical studies pertinent to the claimed indication

Study ID (Phase)	Study design	Key endpoints	Treatment groups	Number of patients randomised
Pivotal 1160.25 (III)	Randomised, double-blind, parallel group	Total VTE ^a and all-cause mortality Major VTE ^b and VTE related mortality	DE 220 mg qd DE 150 mg qd Enoxaparin 40 mg qd	n = 693 n = 708 n = 699 N = 2101
1160.48 (III)	Randomised, double-blind, parallel group	Total VTE ^a and all-cause mortality Major VTE ^b and VTE related mortality	DE 220 mg qd DE 150 mg qd Enoxaparin 40 mg qd	n = 1157 n = 1174 n = 1162 N = 3494
Supportive 1160.24 (III)	Randomised, double-blind, parallel group	Total VTE ^a and all-cause mortality Major VTE ^b and VTE related mortality	DE 220 mg qd DE 150 mg qd Enoxaparin 30 mg bid	n = 862 n = 877 n = 876 N = 2615
Dose- ranging 1160.19 (II)	Randomised, double-blind, parallel group	Total VTE ^a	DE 300 mg qd DE 225 mg bid DE 150 mg bid DE 50 mg bid Enoxaparin 40mg qd	n = 392 n = 398 n = 393 n = 393 n = 393

^a Total VTE includes at least one of the following: confirmed PE, confirmed symptomatic DVT, or DVT detected by venography

^b Major VTE includes at least one of the following: confirmed PE, confirmed symptomatic proximal DVT, or proximal DVT detected by venography

GCP

The main dose response study and the phase III studies were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

A total of 31 studies enrolling approximately 3100 subjects have been conducted with DAB to evaluate dose-response, PK/PD relationship, mode of action and potential for drug-drug interactions. DE is an oral prodrug. This prodrug is present in a salt form (methane sulfonate or mesilate). It contains the active moiety DAB and an ethyl-ester group. After oral administration, DE is rapidly and completely converted to DAB, which is the active form in plasma. The cleavage of the prodrug DE by esterase-catalysed hydrolysis to the active principle DAB is the predominant metabolic reaction. The absolute bioavailability of DAB following oral administration of DE was approximately 6.5 %. After oral administration of DE in healthy volunteers, the PK profile of DAB in plasma is characterized by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration.

• Absorption

A study evaluating post-operative absorption of DE, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations were

reached at 6 hours following administration in a postoperative period due to contributing factors such as anesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. It was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration. Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours.

- **Distribution**

Low (34-35 %) concentration independent binding of DAB to human plasma proteins was observed. The volume of distribution of DAB of 60 – 70 L exceeded the volume of total body water indicating moderate tissue distribution of DAB. C_{max} and the area under the plasma concentration-time curve were dose proportional. Plasma concentrations of DAB showed a biexponential decline with a mean terminal half-life of 12 - 14 hours in healthy volunteers and 14 – 17 hours in patients undergoing major orthopaedic surgery. The half-life was independent of dose.

- **Metabolism and elimination**

Metabolism and excretion of DAB were studied following a single intravenous dose of radiolabeled DAB in healthy male subjects. After an intravenous dose, the DAB-derived radioactivity was eliminated primarily in the urine (85 %). Faecal excretion accounted for 6 % of the administered dose. Recovery of the total radioactivity ranged from 88 - 94 % of the administered dose by 168 hours post dose. DAB is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10 % of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. DAB is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 ml/min corresponding to the glomerular filtration rate.

- **Dose proportionality and time dependencies**

DAB C_{max} and AUC increased linearly with dose from 10 to 400 mg. Repeat dose study was performed with t.i.d. dosing (50 to 400 mg). Steady-state was achieved on day 2 of administration. DAB displayed moderate accumulation. The accumulation ratios for AUC_{ss} and C_{max ss} were about 1.6 – 2.5. No PK study was performed with the posology recommended in the SPC i.e. 220 mg q.d.. Variability: in healthy volunteers and in patients, the interindividual variability of C_{max} and AUC expressed as CV was high i.e. approximately 80%. In healthy volunteers the intraindividual variability was close to 30%.

- **Special populations**

Renal insufficiency

The exposure (AUC) of DAB after the oral administration of DE is approximately 2.7 fold higher in volunteers with moderate renal insufficiency (CrCL between 30 – 50 ml/min) than in those without renal insufficiency. In a small number of volunteers with severe renal insufficiency (CrCL 10 - 30 ml/min), the exposure (AUC) to DAB was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency. An observational cohort study will be conducted to evaluate efficacy and safety of DAB in patients with moderate renal impairment as part of the FUMs. This will better describe the benefit/risk profile of the 150 mg dose of DAB in patients with moderate renal impairment.

Elderly patients

Specific PK studies with elderly subjects showed an increase of 40 to 60 % in the AUC and of more than 25 % in C_{max} compared to young subjects. Population-based PK studies have evaluated the PKs of DAB after repeated doses in patients (up to 88 years). The observed increase of DAB exposure correlated with the age-related reduction in creatinine clearance.

Hepatic insufficiency

No change in DAB exposure was seen in 12 subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls.

Body weight

Population PK studies have evaluated the PKs of DAB in patients of 48 to 120 kg body weight. Body weight had a minor effect on the plasma clearance of dabigatran resulting in higher exposure in patients with low body weight.

Gender

Active substance exposure in female patients is about 40 % to 50 % higher than in male patients and no dose adjustment is recommended.

Ethnic origin

The PKs of DAB was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the PKs of DAB in a clinically relevant manner. No PK data in black patients are available.

- **Pharmacokinetic interaction studies**

In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of CYT P450. This has been confirmed by in vivo studies with healthy volunteers, who did not show any interaction between this treatment and the following active substances: atorvastatin (CYP3A4), digoxin (P-glycoprotein transporter interaction) and diclofenac (CYP2C9). DAB exposure in healthy subjects was increased by 60 % in the presence of amiodarone. A drug-drug interaction study with steady state concentrations of a specific P-gp inhibitor (clarithromycin) will be performed as part of the FUM.

Pharmacodynamics

- **Mechanism of action**

DE is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, DE is rapidly absorbed and converted to DAB by esterase-catalysed hydrolysis in plasma and in the liver. DAB is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. DAB also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. There is a clear correlation between plasma DAB concentration and degree of anticoagulant effect. DAB is a reversible inhibitor of thrombin of relatively low affinity (4.5 nM) compared to heparin and heparin. However, no data have been presented on the interest of inhibiting bound thrombin, contrary to what was usually presented for previously developed DTI. These previous DTI were characterized by a higher affinity for thrombin.

- **Primary and Secondary pharmacology**

As for all other DTI developed until now the effects of DAB were assessed using coagulation tests which are known to be non adapted for accurate and sensitive evaluation of DTI: activated partial thromboplastin time (aPTT), prothrombin time (PT), expressed as International Normalized Ratio (INR), thrombin time (TT), and one test which is better adapted but not of current practice in clinical laboratories: ecarin clotting time (ECT).

The maximum effect (Emax) of DAB on PD parameters occurred at the same time as Cmax, indicating that thrombin inhibition by DAB is a direct effect, linked to the DAB plasma concentration. INR, TT and ECT increased in direct proportion to the plasma concentration of DAB, whereas aPTT prolongation was linearly related to the square root of the DAB plasma concentration. PK/PD analyses confirmed marked differences between the various assays used in terms of sensitivity and precision with varying DAB plasma concentrations.

A curvilinear relationship was shown between DAB plasma concentrations and aPTT. It is the reason for which the measurement of aPTT may provide a qualitative indication of anticoagulant activity, but it may not be suitable for the precise quantification of anticoagulant effect.

The data suggest a linear relationship between plasma concentration and INR (<2.0); however, this assay lacked sensitivity within the clinically-relevant DAB plasma concentration range and showed high variability. Therefore, INR is not considered a suitable tool for monitoring the anticoagulant effects of DE.

The TT assay exhibited a linear relationship with plasma concentration with a high level of sensitivity. TT might be too sensitive to DAB plasma concentrations in the clinically relevant plasma concentration range. At DAB concentrations greater than 600 ng/mL, the TT frequently exceeded the maximum measurement time of the coagulometer. TT assay is only presented as a sensitive method for determining if any DAB is present. Additionally, since the reagents used for determining TT at different laboratories are not standardized, the clinical utility of this test during DAB dosing was questioned. Nevertheless, it should be mentioned that an adaptation of the test to allow sensitivity and an effort of standardization among the clinical labs should allow seeing a modified TT as an easy and inexpensive test to monitor DAB and will be done as part of the FUM.

The ECT assay displayed a linear relationship with drug plasma concentrations over the full range of concentrations, and did not plateau at higher concentrations. Furthermore, ECT was more sensitive to DAB than, for example, aPTT, as evidenced by an 8-fold maximum ECT prolongation, compared with a 2.5-fold maximum aPTT prolongation at the 400 mg multiple doses of DE. ECT is also a more precise parameter than aPTT. Overall, the ECT may provide a more accurate measurement of DAB anticoagulation than the other PD parameters. However, it should be mentioned that the ECT assay is not regularly used in clinical lab and has never been the object of any tentative of standardization. Therefore, its routine use cannot be recommended. But again this test could be standardized among clinical lab and as such be used in routine even if more expensive than a TT.

To conclude, at the today's standards of the clinical lab there is no assay sufficiently sensitive and standardized to assess routinely the anticoagulant status of patients following DAB administration. But this situation could be improved if an assay allowing DAB plasma concentration monitoring when thought necessary would be developed. A cross-validation of chronometric TT measurements at local laboratories will be performed as part of the FUM. Commercially available TT test kits developed for measurement of TT following administration of DTIs (i.e. hirudin) will be validated for measurement of TT of DAB.

Clinical efficacy

There were 4 multi-center, double blind, double-dummy, randomised, parallel group, controlled clinical studies submitted pertinent to the claimed indication. In all studies, enoxaparin, a recognized and widely used LMWH for this indication, was used as an active control.

- **Dose response study**

In the phase II dose ranging study 1160.19 there were 5 parallel groups: DE 300 mg q.d., DE 225 mg b.i.d., DE 150 mg b.i.d., DE 50 mg b.i.d. and enoxaparin 40mg q.d.. DE was administered orally, enoxaparin subcutaneously. As in the 2 pivotal studies, DE was administered 1-4 hours post surgery and enoxaparin was administered on the evening before surgery. Patients undergoing THR and TKR were included, which is acceptable for a dose-finding study, however, stratification according to the type of surgery would have been preferred. The primary endpoint was rate of VTE events which included DVT (proximal and distal) as detected by routine bilateral venography on Day 8 $\pm$ 2, plus symptomatic DVT occurring during the treatment period and confirmed by venography, or PE confirmed by objective testing (chest X-ray, ventilation/perfusion scintigraphy, pulmonary angiography, spiral CT). This endpoint is acceptable for a therapeutic exploratory trial and in accordance with the 'Guideline on clinical investigation of medicinal products for prophylaxis of high intra- and post-operative venous thromboembolic risk' (CPMP/EWP/707/98 Rev. 1).

A total of 1973 patients were randomised, of these, 1921 patients were treated and operated (1306 THR, 615 TKR).

Different analyses sets were defined: the Safety Population (all randomised patients who were treated and who had any available data), the Full Analysis Set (FAS) (which consisted of all randomised patients who had at least one s.c. injection and one oral dose of study medication, with confirmed VTE data available after surgery) and the Per Protocol data Set (PPS) (FAS minus patients with major protocol deviations). The FAS was used for the analysis of efficacy variables. Treatment duration was 5-10 days, which was not according to the newest standards for THR but acceptable for the time (2002/2003) the study was conducted.

The results of the primary endpoint showed a dose-dependent effect of treatment with DE on the VTE rate. The VTE rate for each treatment group (50 mg b.i.d., 150 mg b.i.d., 300 mg q.d. and 225 mg b.i.d.) was 28.5%, 17.4%, 16.6%, and 13.1%, respectively, and 24.0 % for enoxaparin. Treatment with 50 mg dab b.i.d. was not significantly different from 40 mg enoxaparin q.d. with respect to VTE

rate ($p=0.2446$). Patients treated with 150 mg and 225 mg DAB b.i.d. had statistically significantly less VTE events than patients in the active control group enoxaparin ($p=0.0401$ and $p=0.0007$, respectively). No significant difference in VTE rate was observed for b.i.d. or q.d. dosing for a daily dose of 300mg of DE. Subgroup analyses showed that patients >70 years, females, and patients with BMI ≥ 35 kg/m², as well as patients undergoing TKR and those with intake of the drug >4 h after surgery had a higher VTE rate.

In approximately 350 patients from dedicated Scandinavian centres a PK/PD sub-study was conducted. Plasma concentration-time profiles of DAB were obtained after administration of the first dose of DE on the day of surgery and on Day 4 or 5 of treatment. The number of sub-study patients per dose group was similar. Steady state trough plasma concentrations of DAB measured from Day 4 onwards were obtained from all patients. Linear PK data were observed. In general very high coefficients of variation were observed for all PK parameters. Oral absorption on the day of surgery was delayed by approximately 2 hours compared to steady state and the drug exposure after the first dose varied extremely. The majority of the data for PK evaluation are derived from non-general anaesthesia. The exposure in steady state was comparable for the 150mg b.i.d. and the 300mg q.d. dosing. Lower creatinine clearance increased drug concentrations; this appeared to be more distinct in female patients. Furthermore, a higher exposure to the drug was observed in females compared to males, potentially due to lower average creatinine clearance in females. The prolongation of ECT was linearly related to DAB plasma concentrations. The major bleeding rates in all dose regimens but the 50 mg b.i.d. regimen were higher than for enoxaparin. Therefore, none of these doses was finally chosen for the phase III studies but it was concluded that therapeutic doses must lie between 100 and 300mg daily.

- Main studies

Three phase III studies were conducted. They are summarised in the table below. All were randomised, double-blind, parallel group. All phase III studies were non-inferiority studies and their margin justified according to guidelines. There was one pivotal study (1160.25) conducted in patients with primary elective TKR surgery and one pivotal study (1160.48) in patients with primary elective THR surgery (both conducted predominantly in Europe) as well as one supportive study (1160.24) (conducted in North America) in patients with TKR. The latter study applied the North American dosing recommendations for enoxaparin which differ from the European ones, randomised patients post surgery and administered DE with a delay compared to the other phase III studies and what is proposed in the SPC.

Study ID (Phase)	Study design	Type of surgery	Key endpoints	Treatment groups	Number of patients randomised
Pivotal 1160.25 (RE-MODEL)	Randomised, double-blind, parallel group	Total knee replacement	1°Total VTE ^a and all-cause mortality 2°Major VTE ^b and VTE related mortality	Dabigatran etexilate 220 mg q.d. Dabigatran etexilate 150 mg q.d. Enoxaparin 40 mg q.d.	n = 693 n = 708 n = 699 N = 2101
1160.48 (RE-NOVATE)	Randomised, double-blind, parallel group	Total hip replacement	1°Total VTE ^a and all-cause mortality 2°Major VTE ^b and VTE related mortality	Dabigatran etexilate 220 mg q.d. Dabigatran etexilate 150 mg q.d. Enoxaparin 40 mg q.d.	n = 1157 n = 1174 n = 1162 N = 3494
Supportive 1160.24 (RE-MOBILIZE)	Randomised, double-blind, parallel group	Total knee replacement	1°Total VTE ^a and all-cause mortality 2°Major VTE ^b and VTE related mortality	Dabigatran etexilate 220 mg q.d. Dabigatran etexilate 150 mg q.d. Enoxaparin 30 mg b.i.d.	n = 862 n = 877 n = 876 N = 2615

^a primary endpoint: Total VTE includes at least one of the following: confirmed PE, confirmed symptomatic DVT, or DVT detected by venography

^b secondary endpoint: Major VTE includes at least one of the following: confirmed PE, confirmed symptomatic proximal DVT, or proximal DVT detected by venography

METHODS

Studies 1160.25 and 1160.48

Study Participants

There were 2101 patients randomised in study 1160.25 and 3494 patients in study 1160.48. In- and exclusion criteria were consistent across the phase III studies. The baseline characteristics of patients were well matched. Surgery was performed in general anaesthesia in 37.9% of patients in study 1160.25 and in 30.5% of patients in study 1160.48. Also patients with risk factors have been entered into the studies: in studies 1160.25 and 1160.48, 19.6% and 14.1% of patients, respectively were >75 years of age, 26.5% and 18.5% of patients, respectively, had a weight >90 kg, 45% and 28% of patients, respectively, had a BMI >30kg/m². Approximately one third of patient in each of the two studies had mild renal insufficiency based on calculated creatinine clearance and 5.4% of patients in study 1160.25 and 6.6% of patients in study 1160.48 had moderate renal insufficiency with creatinine clearance 30 -50 ml/min. However, a large portion of patients, more than 70% in study 1160.25, and 63% in study 1160.48 were never-smokers and more than 90 % were abstinent at the time of surgery. This fact does not corresponded with the "real world" and raises concerns regarding selection of population and introduction of bias. It is a well known fact that smokers have higher morbidity and mortality and when the primary endpoint include all cause mortality this introduces bias. In addition, a rather limited percentage of patients with concomitant diseases, being consistent with an increased risk for the patients, have been included. This was true and generally more emphasised in study 1160.48, for patients with CAD, CHF, history of VTE, history of malignancy (active malignancy was an exclusion criterion). As concerns concomitant medication, drugs influencing the coagulation system were excluded, including ASA >160 mg/d or NSAIDs with t_{1/2} > 12 h within 7 days prior to surgery.. Overall, NSAIDs were used concomitantly of 55.2% and 63.7% and ASA of 4.1% and 3.3% of patients in studies 1160.48 and 1160.25, respectively.

Treatments

Patients were randomised to DE 220 mg q.d., DE 150 mg q.d. or Enoxaparin 40 mg q.d.. As mentioned previously none of these doses had been tested previously. For the chosen doses a population PK model was used to predict plasma concentration time profiles. Half dose was administered on the day of surgery. Study 1160.48 is one of the first studies where treatment duration of prophylaxis is extended to 28-35 days as recommended in the EMEA Guideline (CPMP/EWP/707/98 Rev.1) for THR surgery. Duration of prophylaxis in study 1160.25 was 6-10 days and thus suboptimal considering that at least 10 days treatment were recommended at the time the study was conducted.

Objectives

The primary objective of these studies was to demonstrate the noninferiority of DE 150 mg and 220 mg once daily dosing (q.d.) per comparison to Enoxaparin 40 mg bid for the prevention of VTE following MOS (separately for THR and TKR). The primary efficacy endpoint of these studies was a composite endpoint of total VTE and all-cause mortality during the treatment period. Total VTE included proximal and distal DVT based on mandatory venography at the end of the treatment period, symptomatic DVT confirmed by venous compression ultrasound, venography or autopsy and objectively confirmed PE. The primary and secondary efficacy endpoints were independently assessed by blinded adjudication committees according to guidelines. The routine venography was to be performed within 24 hours of last oral study medication dose, i.e. Day 28-35 in study 1160.48 and Day 8±2 in 1160.25. This means that venographies were performed on out-patient basis in study 1160.48 (Re-Novate) and study 1160.24 (Re-Mobilize) and just prior to discharge in study 1160.25 (Re-Model). According to a protocol amendment, VTE observed until 3 days after the last administration of trial drug were considered as events occurring "during treatment" and therefore included in the primary efficacy endpoint and secondary endpoints of events occurring during treatment. There were approximately 25% of unevaluable venograms which is comparable with other studies performed in this indication.

Sample size

In study 1160.25, 2101 patients were randomised and in study 1160.48 3494 patients. These were approximately equally distributed on the 3 parallel groups DE 220 mg q.d., DE 150 mg q.d. and enoxaparin 40mg q.d.

Randomisation and blinding (masking)

All phase III studies were randomised and double-blind.

Statistical methods

All phase III studies were non-inferiority studies and their margins were justified according to guidelines.

For evaluation, different analysis sets were defined:

Safety population or Safety Set: All randomized and treated patients. A patient was regarded as treated if he or she received at least 1 dose of trial medication, i.e. DAB, enoxaparin, or placebo.

FAS-op population: All randomized, treated patients who underwent surgery. A patient was regarded as treated if he or she received at least 1 dose of trial medication,

FAS population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram or confirmed symptomatic DVT, PE, or death) during the treatment period.

FAS-major population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram for proximal DVT or confirmed symptomatic DVT, PE, or death) during the treatment period.

FAS-pDVT population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram for proximal DVT or confirmed symptomatic DVT) during the treatment period.

FAS-tDVT population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram for distal and proximal DVT or confirmed symptomatic DVT) during the treatment period.

Per-protocol set or PP or PPS population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram or confirmed symptomatic DVT, PE, or death) during the treatment period without relevant protocol deviations.

According to the statistical plan the primary analysis was based on the FAS, whereas the PPs analysis was foreseen to be used additionally only if this population fell below 90% of the primary efficacy analysis population. In the opinion of the Rapporteur this approach is not completely in accordance with the guideline "statistical principles for clinical trials" (CPMP/ICH/363/96) which states that in a "non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully." The "Points to Consider for switching between Superiority and Non-Inferiority" (CPMP/EWP/482/99) assigns equal importance to the Full Analysis Set and the PP analysis Set. Both the FAS and the PP analysis in the pivotal trials provided similar results.

RESULTS

Outcomes and estimation

Comparative analysis of total VTE and all-cause mortality during treatment period based on the FAS population

	Dabigatran 220 mg N(%)		Dabigatran 150 mg N(%)		Enoxaparin N(%)	
Study	1160.25	1160.48	1160.25	1160.48	1160.25	1160.48
FAS		503 880		526 874		512 897
Incidence, N (%)	183 (36.4)	53 (6.0)	213 (40.5)	75 (8.6)	193 (37.7)	60 (6.7)
95% CI*	(32.2, 40.6)	(4.5, 7.6)	(36.3, 44.7)	(6.7, 10.4)	(33.5, 41.9)	(5.1, 8.3)
Risk difference vs. Enoxaparin (%)*	-1.3	-0.7	2.8	1.9	-	-
95% CI*	(-7.3, 4.6)	(-2.9, 1.6)	(-3.1, 8.7)	(-0.6, 4.4)	-	-
p-value*	0.6648	0.5648	0.3553	0.1339	-	-
Relative risk over Enoxaparin (%) #	0.97	0.90	1.07	1.28	-	-
95% CI	(0.82, 1.13)	(0.63, 1.29)	(0.92, 1.25)	(0.93, 1.78)	-	-
Odds ratio over Enoxaparin @	0.9	0.9	1.1	1.3	-	-
95% CI	(0.7, 1.2)	(0.6, 1.3)	(0.9, 1.4)	(0.9, 1.9)	-	-

* based on normal approximation of independent binomial distribution without stratification

p-value tested the hypothesis of no difference between two treatment groups (superiority test)

based on normal approximation of log relative risk without continuity correction

@ based on logistic regression including the main factor of treatment derived from contrast that compared the two treatments

Summary of individual components contributing to the primary endpoint based on the FAS population

	Dabigatran 220 mg		Dabigatran 150 mg		Enoxaparin	
Study	1160.25	1160.48	1160.25	1160.48	1160.25	1160.48
FAS, N (%)	503 (100.0)	880 (100.0)	526 (100.0)	874 (100.0)	512 (100.0)	897 (100.0)
Total VTE or death N (%) during treatment period #,	183 (36.4)	53 (6.0)	213 (40.5)	75 (8.6)	193 (37.7)	60 (6.7)
asymptomatic DVT	181 (36.0)	40 (4.5)	208 (39.5)	63 (7.2)	184 (35.9)	56 (6.2)
symptomatic DVT	1 (0.2)	5 (0.6)	3 (0.6)	9 (1.0)	8 (1.6)	1 (0.1)
non-fatal PE	0 (0.0)	5 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.3)
death VTE cannot be ruled out	0 (0.0)	1 (0.1)	1 (0.2)	3 (0.3)	1 (0.2)	0 (0.0)
death not associated with VTE	1 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Localisation of DVTs						
distal DVT	169 (33.6)	23 (2.6)	193 (36.7)	37 (4.2)	175 (34.2)	24 (2.7)
proximal DVT¶	13 (2.6)	22 (2.5)	18 (3.4)	35 (4.0)	17 (3.3)	33 (3.7)
during follow-up #@						
Symptomatic DVT, PE, or death (N)	4	1	2	3	2	2

Treatment period: from administration of first dose of study medication and ending 3 days after administration of last dose of study medication. Follow-up is from the end of treatment period to the conclusion of subject participation.

@ Study 1160.25: For Dabigatran 220mg: 1 symptomatic DVT, 2 PE, and 1 death; for Dabigatran 150 mg: 2 symptomatic DVTs, 0 PE, and 0 death; for Enoxaparin: 0 symptomatic DVT, 0 PE, 2 deaths.

@ Study 1160.48: For Dabigatran 220 mg: 1 symptomatic DVT, 0 PE, 0 death, for Dabigatran 150 mg: 1 symptomatic DVT, 0 PE, 2 death, for Enoxaparin: 0 symptomatic DVT, 1 PE, 1 death.

¶ Study 1160.25: Includes patients with confirmed proximal DVT as well as 1 patient with a distal and a proximal DVT.

Note: patients were counted only once in the most severe category in subcategories of DVT, PE and death

Major VTE and VTE-related mortality during the treatment period based on the FAS-major population

	Dabigatran 220 mg		Dabigatran 150 mg		Enoxaparin	
Study	1160.25	1160.48	1160.25	1160.48	1160.25	1160.48
FAS-major, N	506	909	527	888	511	917
Incidence, N (%)	13 (2.6)	28 (3.1)	20 (3.8)	38 (4.3)	18 (3.5)	36 (3.9)
95% CI*	(1.2, 3.9)	(2.0, 4.2)	(2.2, 5.4)	(2.9, 5.6)	(1.9, 5.1)	(2.7, 5.2)
Risk difference vs. Enoxaparin (%)*	-1.0	-0.8	0.3	0.4	-	-
95% CI*	(-3.1, 1.2)	(-2.5, 0.8)	(-2.0, 2.6)	(-1.5, 2.2)	-	-
Relative risk over Enoxaparin#	0.73	0.78	1.08	1.09	-	-
95% CI	(0.36, 1.47)	(0.48, 1.27)	(0.58, 2.01)	(0.70, 1.70)	-	-
Odds ratio over Enoxaparin @	0.7	0.8	1.1	1.1	-	-
95% CI	(0.4, 1.5)	(0.5, 1.3)	(0.6, 2.1)	(0.7, 1.7)	-	-

* Based on normal approximation of independent binomial distribution without stratification, p-value is for testing no difference between two treatment groups.

Based on normal approximation of log relative risk without continuity correction.

@ Based on logistic regression including the main factor of treatment, derived from contrast that compared the two treatments.

In both studies, a clear dose-response for DAB was observed. The results in the DAB 220 mg dose group were consistently numerically slightly better than in the DAB 150 mg group. Statistical analysis of the primary endpoints and the secondary endpoints showed non inferiority compared to Enoxaparin for both high and low dose of DAB. Superiority was not shown (superiority testing was foreseen in the statistical analysis plan in case non-inferiority was confirmed). Mainly distal DVTs account for total VTE in the TKR surgery study 1160.25. In the THR surgery study 1160.48 proximal DVT account for roughly half of the DVTs, independent of the treatment group. The vast majority of DVT in both types of surgery were asymptomatic. The total VTE results for TKR are in the range of those seen with other oral DTI whereas those for THR are considerably lower, probably due to an extended prophylaxis period. The incidence of proximal DVTs was comparable in both types of surgery.

Ancillary analyses

Exploratory subgroup analyses were performed which showed an increased risk in patients with moderate renal insufficiency, patients with general anaesthesia, older patients, females, patients with weight >110 kg (only in study 1160.25) and in patients who received the first oral dose of study medication <4 hours after surgery.

A routine inspection was carried out of study 1160.25 at two sites in South Africa and Hungary. A critical finding was that in approximately one third of patients a starch derivative was used which potentially may affect both the efficacy and the safety of the investigational product. Further analyses have therefore been provided by the Applicant. These findings indicate that in both of the European pivotal studies (1160.25 and 1160.48) the rates of total VTE and all cause mortality are lower in patients who received colloidal starch therapy (roughly one third of patients in study 1160.25 and half of patients in 1160.48) than in those patients who did not. The secondary endpoint major VTE and VTE related mortality confirmed that trend. Bleeding was slightly increased. These results were consistent in both DAB and enoxaparin treatment groups, and DAB results by subgroups are homogeneous with overall results.

- Analysis performed across trials (pooled analyses and meta-analysis)

A meta- analysis was pre-specified in order to evaluate the effects of DE and enoxaparin on the composite endpoint of major VTE and VTE related mortality (proposed primary endpoint in the CHMP guideline CPMP/EWP/ 707/98). A meta- analysis was pre-specified in order to evaluate the effects of DE on the composite endpoint specified in the CHMP Guideline (CPMP/EWP/ 707/98). This approach was only acceptable for justifying the deviation from the CHMP Guideline "if all results of the individual trials point all in the same direction". This was not the case since only the pivotal EU studies showed non inferiority compared to enoxaparin, this could not be shown in supportive US study. Although it was stated that the studies are very similar and only differ due to clinical practice there are major differences in key areas between Europe and US. These comprise types of surgeries (hip/knee), duration of treatment (short/long), selection of patients by time of randomization (pre-/postsurgery), 1st oral dosing time (0-4 h post surgery vs. 6-12 h post surgery), dose regimen (enoxaparin 40mg vs. 30mg b.i.d.), and time span between surgery and venography. It

was also questioned whether data on VTE can be pooled from two different surgical procedures where mechanical properties (etc. use of tourniquet during knee surgery and therefore no blood flow in the lower leg at all) have different impact on the anatomical regions in question. One would expect that this factor had a greater influence on distal DVT than on proximal DVT. In the view of the CHMP these differences makes it highly unlikely that a meta-analysis can be performed in two so different populations. In phase III studies it is rather unusual to perform "no confirmatory statistical hypothesis testing". No Delta value was prespecified. These analyses were not specified in the protocol and therefore not "lege artis" and unacceptable from a statistical point of view. The above mentioned points were serious faults and concerns regarding the way the meta-analysis was performed. That is why the metaanalysis was considered of exploratory, not of confirmatory nature.

- Supportive study

Supportive study (1160.24) differed from the pivotal studies in the timing of the study medication and the dosing of enoxaparin. The enoxaparin dose schedule was 30 mg b.i.d. and the first dose was given 12-25 h post surgery. The first DE dose was administered 6-12h after surgery (instead of 1-4 h after surgery as in the pivotal studies). More importantly, patients were randomised post surgery, provided that haemostasis was present, and it must be assumed that bias was introduced by this method. Those patients with complications during surgery and long surgery time were most likely excluded and those patients would most likely also be at higher risk for VTE. The incidence of the primary endpoint in the DE 220 mg group was 31.1% (95%CI 27.4, 34.8), in the DE 150 mg group 33.7% (30.1, 37.4) and in the enoxaparin group 25.3% (22.0, 28.7). The risk difference vs. enoxaparin for the DE 220 mg group was 5.8 ((0.8, 10.8), and for the DE 150mg group 8.4 (3.4, 13.3). The non-inferiority margin of 9.2% was thus exceeded and non-inferiority not demonstrated.

- Discussion on clinical efficacy

A recommended primary endpoint in therapeutic confirmatory trials as written in the CHMP Guideline (CPMP/EWP/ 707/98) is a composite endpoint consisting of clinically relevant and objectively documented events including venographically documented proximal DVT, symptomatic and well-documented non-fatal pulmonary embolism (PE) and VTE related death or death due to any cause. However, despite the total DE development program including over 8000 patients, the individual studies were not thought to be sufficiently powered to reliably assess efficacy for the composite endpoint including proximal DVT, symptomatic VTE and VTE related death (= major VTE and VTE related death).

A meta- analysis was pre-specified in order to evaluate the effects of DE on the composite endpoint specified in the CHMP Guideline (CPMP/EWP/ 707/98). This approach was only acceptable "if the results of the individual trials point all in the same direction". This was not the case since only the pivotal EU studies showed non inferiority compared to enoxaparin. This could not be shown in supportive US study. That is why the meta-analysis was considered of exploratory, not of the confirmatory nature.

The introduction of UH and later LMWH as standard prophylactics has reduced the frequency of major VTE and VTE related mortality significantly. Therefore large study populations are needed in order to show non-inferiority. Therefore, a "new" surrogate end-point was proposed which occurs with a higher frequency in order to keep the study population at a reasonable size. Total VTE and all-cause mortality was used during the treatment period as such "new" surrogate marker. Major VTE and VTE related mortality was chosen as one of the secondary endpoints. The MAA for DE was submitted prior to the revision of the CHMP Guideline (CPMP/EWP/ 707/98/Rev 1).

Clinical safety

- Patient exposure

A total of 10.084 patients were treated in 4 actively controlled VTE prevention trials with at least one dose of the medicinal product. Of these 5419 were treated with 150 mg or 220 mg daily of DE, while 389 received doses less than 150 mg daily and 1168 received doses in excess of 220 mg daily.

The most commonly reported adverse reactions are bleedings occurring in total in approximately 14 % of patients; the frequency of major bleeds (including wound site bleedings) is less than 2 %.

	Dabigatran etexilate				Enoxaparin	Total
	< 150 mg	150 mg	220 mg	> 220 mg		
Treatment period						
Number of treated patients (N [%])	389 (100.0)	2737 (100.0)	2682 (100.0)	1168 (100.0)	3108 (100.0)	10084 (100.0)
Exposure days (N [%])						
≥1	389 (100.0)	2737 (100.0)	2682 (100.0)	1168 (100.0)	3108 (100.0)	10084 (100.0)
≥18	0	1038 (37.9)	1044 (38.9)	0	1043 (33.6)	3125 (31.0)
≥43	0	67 (2.4)	64 (2.4)	0	63 (2.0)	194 (1.9)
Summary statistics						
Mean	8.0	19.8	20.0	7.8	18.4	17.6
SD	2.0	12.2	12.2	2.1	12.1	12.0
Median	8.0	15.0	15.0	8.0	14.0	13.0
Minimum	1	1	1	1	1	1
Maximum	13	52	69	13	49	69
Total exposure years	8.5	148.5	146.9	25.0	156.5	485.4

• Adverse events

The AEs in the 2 pivotal trials as well as the 4 active controlled VTE prevention studies were largely comparable, also between the treatment groups. The most frequent AEs in the pivotal studies were nausea (21.2% / 20.5% / 25% for DE 150mg /220 mg /enoxaparin), vomiting (16.0% / 16.8% / 16.8%), constipation (11.0% / 11.9% / 12.3%) , deep vein thrombosis (9.3% / 6.4% / 7.3%), insomnia (8.2% / 7.8% / 8.1%), oedema peripheral (7.3% / 6.4% / 5.9%), wound secretion (6.9% / 7.0% / 4.7%). There were no marked differences between DAB and the enoxaparin groups with regards to treatment emergent AEs classified by system organ class for the 2 pivotal studies, neither was any marked dose effect evident. Slight differences in the unfavour of DE were noted for the following AEs: hypokalemia (1.2% in the DAB 150mg group, 1.6% in the DAB 220mg group, 0.9% in the enoxaparin group), oedema peripheral (7.3% in the DAB 150mg group, 6.4% in the DAB 220mg group, 5.9% in the enoxaparin group), and wound secretion (6.9% in the DAB 150mg group, 7.0% in the DAB 220mg group, 4.7% in the enoxaparin group). Furthermore, deep vein thrombosis was more frequent in the DAB 150 mg group (but not in the 220mg group) compared to enoxaparin (9.3% vs. 7.3%). The same pattern was observed when taking the 4 VTE active controlled trials together. Most AEs were mild and moderate in severity. The severe AEs were comparable between treatment groups. In all treatment groups, AEs increased with increased age group, increased with decreasing creatinine clearance, and were more frequent in females.

Bleeding events

Bleeding events were classified as Major Bleeding Events (MBE), Clinically Relevant Bleeding Events (CRBE) and Minor Bleeding Event. The latter were defined as all other bleeding events that did not fulfil the criteria of MBE or CRBE. The clinical safety evaluations by MBE are in accordance with the CHMP/EMA guideline. The evaluation of CRBE has been proposed by the Applicant but has not been validated. Many of the criteria are not well defined and one would expect a large variation between centres causing interpretation to be difficult. Data are presented according to the time of randomization (study 1160.24 post operative randomization and 1160.19, 1160.25, and 1160.48 pre operative randomization). The table below shows frequencies of patients experiencing a bleeding event by category of bleeding severity in the four active-controlled VTE prevention trials.

	Dabigatran etexilate				Enoxaparin
	<150 mg	150 mg	220 mg	>220 mg	
	Number (%)				
Post-operative randomisation ^a					
Treated patients	NA	871 (100.0)	857 (100.0)	NA	868 (100.0)
Most severe bleeding					
Major bleeding	--	5 (0.6)	5 (0.6)	--	12 (1.4)
Clinical relevant bleeding	--	22 (2.5)	23 (2.7)	--	21 (2.4)
Minor bleeding	--	45 (5.2)	46 (5.4)	--	51 (5.9)
No bleeding	--	799 (91.7)	783 (91.4)	--	784 (90.3)
Pre-operative randomisation ^b					
Treated patients	389 (100.0)	1866 (100.0)	1825 (100.0)	1168 (100.0)	2240 (100.0)
Most severe bleeding					
Major bleeding	1 (0.3)	24 (1.3)	33 (1.8)	49 (4.2)	35 (1.6)
Clinical relevant bleeding	9 (2.3)	103 (5.5)	88 (4.8)	48 (4.1)	87 (3.9)
Minor bleeding	16 (4.1)	131 (7.0)	130 (7.1)	91 (7.8)	168 (7.5)
No bleeding	363 (93.3)	1608 (86.2)	1574 (86.2)	980 (83.9)	1950 (87.1)

a Included Trial 1160.24.

b Included Trial 1160.19, 1160.25, and 1160.48.

Note: For Phase III Trials 1160.24, 1160.25, and 1160.48, bleeding events with onset between study drug initiation and 3 days after the last study drug administration were considered treatment emergent. For the Phase II Trial 1160.19, treatment-emergent bleeding events included those with onset up to 1 day after the last dose of study drug.

There was a difference in bleeding frequency observed between pre- and post-operative randomizations. As expected, the orthopaedic surgical site was the most frequently reported site of major bleeding in all of the VTE prevention trials. A clear dose response with respect to bleeding was seen for DAB. For any bleeding event, there was no statistical difference between DE 150 mg and enoxaparin and between DE 220 mg and Enoxaparin. Patients with MBE who required transfusion in the pivotal studies (> 2units or more) were more frequent in DAB 220mg than in enoxaparin and much less in DAB 150mg (1.58% , 1.13% and 0.75% respectively). The use of transfusions in the pivotal studies is difficult to assess since no strict rules on when to transfuse are given. In a clinical setting most transfusions are given based on haemodynamic parameters, but these are missing all together. Discontinuation due to bleeding in the pivotal studies occurred similarly and less frequently in DAB 150mg and enoxaparin than in DAB 220mg (0.05% vs 0.16%). Re-operation due to bleeding was slightly more frequent in DAB 220mg, and similar in DAB 150mg and enoxaparin (0.27% vs 0.21% respectively). A large proportion of patients with mild renal impairment (less with moderate renal impairment) was included in order to provide safety data in this subpopulation. Impaired renal function causes increased blood concentration and a raise in bleeding events. The bleeding frequency decreased with increasing creatinine clearance. Patients >75 years and patients with decreased renal function were especially at higher risk of bleeding.

The use of ASA and derivatives increases bleeding frequency although it remained lower than with the use of Enoxaparin. Very few patients used concomitant ASA or derivatives and the effect on bleeding events can not be evaluated from these studies.

Acute Coronary Syndrome (ACS)

For clinical trials with DAB that were all blinded, ACS events were based on investigator reported SAEs that might represent an ACS event. And for the three ongoing phase III trials, all reported SAEs by the investigator and related to ACS were adjudicated. Similar frequencies of ACS events in orthopaedic surgical clinical trials were observed regarding both adjudicated and non adjudicated events.

- Serious adverse event/deaths/other significant events

In the pivotal VTE primary prevention trials, frequencies of patients who experienced one or more SAEs were similar across treatment groups. Frequencies were 7.2% in the DE 150 mg group, 6.6% in the DE 220 mg group, and 6.8% in the enoxaparin group. The SOC with the most frequently experienced SAEs were injury, poisoning, and procedural complications (1.7% in the dab 150 mg group, 1.6% in the dab 220 mg group, 2.1% in the enoxaparin group); vascular disorders (1.9% / 1.2% / 1.5%); infections and infestations (0.9% / 1.3% / 1.0%); and cardiac disorders (1.1% / 0.6% / 0.7%). For cardiac disorders, no specific SAE was prominent. For injury, poisoning, and procedural complications, the most frequent specific SAE was wound secretion, which was slightly more frequent in the DE 150 mg group (0.5%) and DE 220 mg group (0.4%) than the enoxaparin group (0.2%). For vascular disorders, the most frequent specific SAE by far was DVT, which was 1.4% in the DE 150 mg group, 0.7% in the DE 220 mg group, and 1.0% in the enoxaparin group. In the active-controlled VTE prevention trials (1160.19, 1160.24, 1160.25, and 1160.48) 31 patients (0.3%) died. During the treatment 11 patients died, 5 patients (0.2%) in the DE 150 mg group, 5 patients (0.2%) in the DE 220 mg group, 1 patient (<0.1%) in the enoxaparin group. No patients from the DE <150 mg group and the >220 mg group died during the treatment. During the post treatment period 12 patients died, and during the post study period 8 patients died. In the pivotal and active-controlled VTE prevention trials, most deaths in DE treatment groups had fatal AEs with onsets during the treatment period and most deaths in the enoxaparin group had fatal AEs with onsets during the post-treatment period. The most frequent treatment-emergent SOC was cardiac disorders, and the most frequent treatment-emergent AE was cardiac arrest. None of the treatment-emergent or post-treatment AEs leading to death were considered by investigators to be related to study medication.

The percentage of patients in the pivotal studies with common comorbidities and/or risk factors for VTE was rather low; there were for instance 2.7% and 2.3% of patients in studies 1160.25 and 1160.48, respectively with heart failure, 11.2% and 8.4% with coronary artery disease, 3.7% and 2.9% with a history of VTE. This concern should also be seen in view of the chosen endpoint which includes all-cause mortality.

- Laboratory findings

No clinically significant haematological or other laboratory abnormalities were consistently identified in the trials within the DE clinical development programme. Decrease in haemoglobin and haematocrit were reported in all treatment groups and across all clinical trials and approximately 40% of patients had possible clinically significant abnormalities regarding haematocrit and 35% regarding haemoglobin in both Re-Model and Re-Novate trials. This is what to be expected in patients exposed to MOS.

Liver function

During DAB development, additional LFT surveillance was added to all ongoing and planned DAB clinical trial protocols, in order to detect any potential signal of hepatotoxicity. Special attention was paid to increase of ALT, as increased ALT > 3ULN is considered as a specific indicator of liver injury (hepatocyte necrosis) and increased ALT > 3ULN combined to elevated bilirubin above 2xULN within 30 days (in the absence of biliary obstruction) may indicate severe hepatotoxicity. Elevations of ALT occurred primarily in the period up to 10 days post surgery. When precisely, is not known, since no laboratory testing was done earlier. Disregarding the <150 mg and the >220 mg dosage groups in the shorter term trials, no dose response in LFT elevations was noted for DE.

Shorter term VTE prevention trials (1160.19, 1160.24, 1160.25): Elevations >2ULN, >3ULN and >5ULN were slightly more frequent in the enoxaparin groups. Elevations >10ULN occurred in 3 patients in the dab 150mg group (0.2%), 1 patient in the dab 220 mg group (0.1%) (as well as 1 patient in the >220mg group) and 2 patients in the enoxaparin group (0.1%). The elevations in the DAB 150mg group occurred in the periods 11-19 days (2 patients) and 20-56 days (1 patient). There was 1 ALT elevation >20ULN, this occurred in the dab 150 mg group, in the period 20-56 days. Longer term VTE prevention trial (1160.48): all magnitudes of ALT elevations were either more frequent or identically frequent (only in the >20ULN group) in the enoxaparin group compared to the DE groups. Elevated ALT frequencies were higher in the longer term treatment trial 1160.48 compared to the shorter term duration trials.

In summary, the LFT analyses from the VTE prevention trials do not seem to indicate hepatotoxicity. Only few data were provided in the current application from long term ongoing clinical trial in atrial

fibrillation (PETRO-EX) with DAB. Indeed up to September 2006, only 300 patients were exposed to DAB for at least one year. Increased ALT above 3 ULN was reported in eleven patients mostly with DAB 150mg b.i.d.. The causality of DAB is difficult to establish. In two cases, normalised LFTs were observed while patients remained on treatment, in three cases, a negative rechallenge was reported and in four cases a positive dechallenge was reported. The applicant provided also data from a prespecified, interim analysis of RE-LY, a long-term trial of DE in patients with atrial fibrillation. Patients with active hepatic disease or with persistent ALT, AST or alkaline phosphatase >2xULN were excluded. Patients were scheduled to receive a minimum of 1 year of treatment with either one of two blinded doses of DE (110 mg bid or 150 mg bid) or open label warfarin (target INR 2-3) with the goal of preventing strokes and systemic emboli. The overall absolute frequency of transaminase elevations >3xULN was low, approximately 1% at 6 months for both warfarin and DAB.

- Safety in special populations

Bleeding events are the most relevant safety issue in special populations. The table below presents the frequency of bleeding events stratified after special populations in the active-controlled VTE prevention trials (1160.19, 1160.24, 1160.25, and 1160.48).

	Dabigatran etexilate												Enoxaparin		
	<150 mg			150 mg			220 mg			>220 mg					
	Patients with MBE			Patients with MBE			Patients with MBE			Patients with MBE			Patients with MBE		
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Treated patients	389			2737			2682			1168			3108		
Patient with MBE	389	1	(0.3)	2737	29	(1.1)	2682	38	(1.4)	1168	49	(4.2)	3108	47	(1.5)
Gender															
Male	166	1	(0.6)	1112	16	(1.4)	1119	12	(1.1)	441	16	(3.6)	1234	20	(1.6)
Female	223	0		1625	13	(0.8)	1563	26	(1.7)	727	33	(4.5)	1874	27	(1.4)
Age (years)															
<65	157	0		1193	10	(0.8)	1128	13	(1.2)	464	16	(3.4)	1294	7	(0.5)
65-75	158	1	(0.6)	1116	13	(1.2)	1105	12	(1.1)	483	18	(3.7)	1289	23	(1.8)
>75	74	0		428	6	(1.4)	449	13	(2.9)	221	15	(6.8)	525	17	(3.2)
BMI (kg/m ²)															
Missing	0			1	0		2	0		0			5	0	
<25	117	0		539	9	(1.7)	534	13	(2.4)	330	22	(6.7)	665	16	(2.4)
25-30	170	1	(0.6)	1096	13	(1.2)	1044	17	(1.6)	473	16	(3.4)	1209	17	(1.4)
30-35	73	0		680	3	(0.4)	708	7	(1.0)	258	9	(3.5)	840	10	(1.2)
>35	29	0		421	4	(1.0)	394	1	(0.3)	107	2	(1.9)	389	4	(1.0)
Weight (kg)															
Missing	0			0	0		0			0			1		
<50	2	0		15	0		19	0		18	0		27	1	(3.7)
50-110	380	1	(0.3)	2542	28	1.1	2496	38	1.5	1108	48	4.3	2915	44	1.5
>110	7	0		180	1	0.6	167	0		42	1	2.4	165	2	1.2
Creatinine Clearance (mL/min)															
Missing	5	0		70	1	(1.4)	64	0		16	2	(12.5)	62	0	
<30	1	0		7	0		10	0		6	1	(16.7)	14	1	(7.1)

Dabigatran etexilate																	Enoxaparin		
<150 mg						150 mg			220 mg			>220 mg							
Patients with						Patients with			Patients with			Patients with			Patients with				
MBE						MBE			MBE			MBE							
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%				
30-50	24	0		185	0		199	8	(4.0)	109	8	(7.3)	248	10	(4.0)				
50-80	152	1	(0.7)	1011	14	(1.4)	945	12	(1.3)	446	20	(4.5)	1148	17	(1.5)				
≥80	207	0		1464	14	(1.0)	1464	18	(1.2)	591	18	(3.0)	1636	19	(1.2)				

Note: N = number of treated patients; n = number of patients with MBE events.

The results in the table above remain unchanged even if a patient that were randomized post operative (study 1160.24) is excluded due to the fact that this study introduce bias towards less bleeding events. A clear dose response with respect to bleeding is seen for DAB. Patients >75 years and patients with decreased renal function (well knowing that these factors are related) are especially at risk.

- Safety related to drug-drug interactions and other interactions

Interaction studies have only been performed in adults.

Anticoagulants and platelet aggregation agents: The following treatments are not recommended concomitantly with DE: UHs and heparin derivatives, LMWH, fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that UH can be administered at doses necessary to maintain a patent central venous or arterial catheter.

Interactions linked to DE and DAB metabolic profile: DE and DAB are not metabolised by the CYP450 system and have no *in vitro* effects on human CYP 450 enzymes. Therefore, related medicinal product interactions are not expected with DAB.

NSAIDs: When DE was coadministered with diclofenac, the plasma exposure of both medicinal products remained unchanged indicating a lack of a PK interaction between DE and diclofenac. However, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended.

Transporter interactions: Amiodarone is an inhibitor of the efflux transporter P-glycoprotein and DE a substrate of this transporter. When DE was coadministered with amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The DAB AUC and C_{max} were increased by about 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone. Dosing should be reduced to 150 mg DE daily in patients who received concomitantly DE and amiodarone.

P- glycoprotein inhibitors: Caution should be exercised with strong P- glycoprotein inhibitors like verapamil, clarithromycin, and others. Quinidine is contraindicated.

P- glycoprotein inducers: Potent P- glycoprotein inducers such as rifampicin or St John's wort (*Hypericum perforatum*), may reduce the systemic exposure of DAB. Caution is advised when co-administering these medicinal products.

Digoxin: In a study performed with 24 healthy subjects, when DE was coadministered with digoxin, no changes on digoxin and no clinical relevant changes on DAB exposure have been observed.

Pantoprazole: When DE was coadministered with pantoprazole, a decrease in the DAB area under the plasma concentration - time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors were co-administered with DE in clinical trials and no effects on bleeding or efficacy were observed.

Ranitidine: Ranitidine administration together with DE had no clinically relevant effect on the extent of absorption of DAB.

- Discontinuation due to adverse events

During the two pivotal VTE primary prevention trials alone, frequencies of patients who discontinued study medication because of AEs were similar across the three treatment groups, with

6.1% in the DE 150 mg group, 5.4% in the DE 220 mg group, and 5.3% in the enoxaparin group. The only SOC with specific AEs occurring in $\geq 0.3\%$ of treated patients in any treatment group were cardiac disorders (atrial fibrillation in 0.3% / 0.3% / 0.4% and myocardial infarction in 0.3% / 0.1% / 0.3% in the DAB.150mg/ DAB 220mg/ enoxaparin groups), vascular disorders (DVT 0.6% / 0.3% / 0.4% in the DAB.150mg/ DAB 220mg/ enoxaparin groups), and gastrointestinal disorders (nausea 0.8% / 0.7% / 0.8% and vomiting 0.3% / 0.2% / 0.3% in the DAB.150mg/ DAB 220mg/ enoxaparin groups). The largest difference among treatment groups for any of these SOC was only 0.5% for cardiac disorders, with 1.2% in the DE 150 mg group, 0.7% in the DE 220 mg group, and 1.1% in the enoxaparin group. No specific AE varied by more than 0.3% across treatment groups. The rates of discontinuation due to AEs did not seem to be clearly dose-dependant for the proposed therapeutic DE doses and seem to be similar to the enoxaparin group. It seems, however, that the discontinuation rate due to AEs in the DAB>220 mg group, was higher. It should be remembered, though, that these higher doses were applied only in study 1160.19. The most common reasons for discontinuation due to AEs were nausea, vomiting, injury, poisoning, and procedural complications, and deep vein thrombosis.

- Discussion on clinical safety

The safety data was based on 7942 subjects who received at least one dose of DE, 6976 of these in the VTE prevention trials. The AEs in the 2 pivotal trials as well as the 4 active controlled VTE prevention studies were largely comparable, also between the treatment groups. The most frequent AEs in the pivotal studies were nausea, vomiting, constipation, deep vein thrombosis, insomnia, oedema peripheral, and wound secretion. There were no marked differences between DAB and the enoxaparin groups with regards to treatment emergent AEs classified by system organ class for the 2 pivotal studies, neither was any marked dose effect evident. Slight differences in unfavour of DE were noted for the following AEs: hypokalaemia, oedema peripheral and wound secretion. The most common reasons for discontinuation due to AEs were nausea, vomiting, injury, poisoning, and procedural complications, and deep vein thrombosis.

Bleeding events were classified as Major Bleeding Events (MBE), Clinically Relevant Bleeding Events (CRBE) and Minor Bleeding Event. The latter were defined as all other bleeding events that did not fulfil the criteria of MBE or CRBE. The clinical safety evaluations by MBE are in accordance with the CHMP/EMA guideline. There was a difference in bleeding frequency observed between pre- and post-operative randomizations. As expected, the orthopaedic surgical site was the most frequently reported site of major bleeding in all of the VTE prevention trials. A clear dose response with respect to bleeding was seen for DAB. For any bleeding event, there was no statistical difference between DE 150 mg and enoxaparin and between DE 220 mg and Enoxaparin. The use of ASA and derivatives increases bleeding frequency although it remained lower than with the use of Enoxaparin. Very few patients used concomitant ASA or derivatives and the effect on bleeding events can not be evaluated from these studies. The possibility of drug monitoring would be valuable, especially for these patients at risk and commercially available TT test kits will be developed for measurement of TT following administration of DTIs (FUM). Also, increased risk of bleeding observed with DE therapy in patients with moderate renal impairment or elderly was the reason for deciding that an observational cohort study on the risk of bleeding to be conducted in the postauthorisation phase. In the pivotal VTE primary prevention trials, frequencies of patients who experienced one or more SAEs were similar across treatment groups in the main studies. The most frequently experienced SAEs were injury, poisoning, procedural complications, vascular disorders, infections and infestations, and cardiac disorders.

The percentage of patients in the pivotal studies with common co-morbidities and/or risk factors for VTE was rather low. No clinically significant haematological or other laboratory abnormalities were consistently identified in the trials within the DE clinical development programme.

During DAB development, additional LFT surveillance was added to all ongoing and planned DAB clinical trial protocols, in order to detect any potential signal of hepatotoxicity. The LFT analyses from the VTE prevention trials do not seem to indicate hepatotoxicity.

Bleeding events are the most relevant safety issue in special populations. Patients >75 years and patients with decreased renal function are especially at risk.

Drug interaction studies have only been performed in adults. The following treatments are not recommended concomitantly with DE: UHs and heparin derivatives, LMWHs, fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran,

sulfinpyrazone and vitamin K antagonists. It should be noted that UH can be administered at doses necessary to maintain a patent central venous or arterial catheter.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risk: Bleeding	Routine pharmacovigilance activities will be used to monitor the incidence of bleeding.	An updated RMP including a prescriber guide to educate prescribers regarding methods of coagulation testing for dabigatran and its interpretation. An observational cohort study on the risk of bleedings to be conducted in the more general population of patients with an increased risk of bleeding.
Potential risk: Hepatotoxicity	Routine pharmacovigilance activities will be used to monitor for any signs/symptoms of hepatotoxicity. Data from ongoing and to be initiated controlled clinical trials of dabigatran etexilate will be monitored. In particular, there is one large trial underway from which data has already been provided to the member states. This long term study (RELY study [1160.26]) is evaluating the use of dabigatran etexilate (2 blinded doses) compared to open label warfarin in patients with atrial fibrillation. It has so far randomized 18, 114 patients and has a minimum 12-month follow-up period, which is continuing. The primary endpoint is the composite of stroke and systemic embolism. Criteria for safety include: (1) Bleeding events – major and minor bleeds; (2) Hepatobiliary events including clinically relevant changes in liver function tests and hepatic dysfunction; and (3) Other adverse events.	Contraindication for Hepatic impairment or liver disease expected to have any impact on survival in section 4.3 of the SPC. Special warning: <u>Hepatic impairment</u> in section 4.4 of the SPC. Patients with elevated liver enzymes > 2 ULN were excluded in controlled clinical trials. Therefore the use of Pradaxa is not recommended in this population. ALT should be measured as part of the standard pre-operative evaluation. Increase of hepatic enzymes listed as ADR in section 4.8 Undesirable effects of the SPC.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product were investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Effects observed in the repeat-dose toxicity studies were due to the exaggerated PD effect of DAB. An effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (5-fold the plasma exposure level in patients). At doses that were toxic to the mothers (5 to 10-fold the plasma exposure level in patients), a decrease in foetal body weight and viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients). Carcinogenicity studies have not yet been completed with DAB.

Efficacy

The clinical efficacy of DE in VTE prevention after elective THR or TKR has been demonstrated in four multi-centre, double blind, double-dummy, randomised, parallel group, controlled clinical studies. In all studies, enoxaparin, a recognized and widely used LMWH for this indication, was used as active control. The clinical confirmatory trials were all non-inferiority trials with use of non-inferiority margin in accordance with current CHMP guidance. The chosen endpoint was not in accordance with the current CHMP guidance. The endpoint proposed by the current CHMP guidance was however studied as a secondary endpoint. The proposed therapeutic doses (150 or 220 mg q.d.) were found to be non-inferior to enoxaparin in the pivotal studies.

Safety

The safety data was based on 7942 subjects who received at least one dose of DE, 6976 of these in the VTE prevention trials. The most frequent AEs in the pivotal studies were nausea, vomiting, constipation, deep vein thrombosis, insomnia, oedema peripheral, and wound secretion. There were no marked differences between DAB and the enoxaparin groups with regards to treatment emergent AEs. For any bleeding event, there was no statistical difference between DE 150 mg and enoxaparin and between DE 220 mg and enoxaparin. A clear dose response with respect to bleeding was seen for DAB. From the safety database all the adverse reactions reported in clinical trials have been included in the SPC. Having considered the safety concerns in the RMP, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- **User consultation**

The Applicant performed a readability testing ("user consultation") and a satisfactory report has been provided.

Risk-benefit assessment

- **Benefits**

In the elective THR or TKR more than 50% of the patients develop DVT in the absence of prophylactic therapy. UH and more recently LMWH have been used as anticoagulants to prevent thromboembolic events in these patients. The advantage of LMWH over UH is no need for blood level monitoring. However, the need for parenteral or subcutaneous administration is a clear disadvantage. Currently the only orally administered alternative is vitamin-K-antagonist which has numerous

limitations such as slow onset of action, a narrow therapeutic range, large inter- and intra-individual variability in PK and PD properties as well as many drug-drug interactions all necessitating frequent laboratory monitoring to adjust the dosage. In these settings an oral anticoagulant like DE not needing laboratory monitoring is therefore highly needed.

The clinical efficacy in VTE prevention after elective THR or TKR has been demonstrated in four multi-centre, double blind, double-dummy, randomised, parallel group, controlled clinical studies. In all studies, enoxaparin, a recognized and widely used LMWH for this indication, was used as active control. Two pivotal phase III studies were conducted in Europe, 1 supportive phase II study in US. Differences between European and US studies relate to time of randomization (pre-/postsurgery, respectively), 1st oral dosing time (0-4 h post surgery vs. 6-12 h post surgery, respectively), and dose regimen (enoxaparin 40mg vs. 30mg b.i.d., respectively). The patient population studied may not fully reflect the target population (exclusion of patients on platelet inhibitors such as ASA and patients with risk factors for VTE.). The prolonged duration of treatment for 28-35 days in hip surgery is considered adequate, being in line with recent guidelines. The duration of treatment in the TKR study was thus suboptimal (6-10 days) At the time of initiation of the study 10 days of thromboprophylaxis were recommended, nowadays it is 10-14 days. The clinical confirmatory trials were all non-inferiority trials with use of non-inferiority margin in accordance with current CHMP guidance. The chosen endpoint (all VTE [=proximal and distal DVT+PE] and all-cause mortality) was not in accordance with the current CHMP guidance. The endpoint proposed by the current CHMP guidance (major VTE [proximal DVT+PE] and VTE related mortality) was however studied as a secondary endpoint. The proposed therapeutic doses (150 or 220 mg q.d.) were found to be non-inferior to enoxaparin in terms of efficacy in the pivotal studies. Superiority was not shown (superiority testing was foreseen in the statistical analysis plan in case of non-inferiority was confirmed). In the US supportive study non-inferiority for both DE doses in comparison with enoxaparin was not met. Mainly distal DVTs accounted for total VTE in the study of TKR surgery. In the EU study, there were less distal DVTs in the DAB 220mg group as compared with the enoxaparin group and more in the DAB 150mg group. In the North-American supportive study, there were more distal DVTs in both DAB groups as compared with the enoxaparin group. DVT rates were lower in the US supportive study than in the EU study in TKR surgery. This may be due to the selection of patients because of post-operative randomisation, but it could also be due to the duration of treatment (not sufficiently long in the pivotal study). In THR surgery, about 50% of all DVTs were distal and about 50% were proximal in the DAB groups. There were as many distal DVTs in the DAB 220mg group as in the enoxaparin group but more distal DVTs in the DAB 150mg group, whereas there were less proximal DVTs in the DAB 220mg group as compared with the enoxaparin group and a little more in the DAB 150mg group. The vast majority of DVT in both types of surgery were asymptomatic. Regarding the "Major VTE and VTE related mortality", secondary endpoint in both pivotal studies there were numerical fewer events in the DAB 220mg group compared to the enoxaparin group (2.6% vs 3.5% in TKR, 3.1% vs. 3.9% in THR, with no statistically significant difference) and a higher number of events in the DAB 150mg group (3.8% vs 3.5% in Re-Model, 4.3% vs 3.9% in Re-Novate). The number of symptomatic DVTs, PEs, and deaths during the treatment period was low in all three treatment groups of the phase III studies.

- **Risks**

The safety profile of DAB was similar to the one observed with enoxaparin. The most frequent AEs were related to gastrointestinal disorders, vascular disorders, injury and poisoning and procedural complications. Most AE were mild and moderate in severity. In all treatment groups, AEs increased with increased age group, increased with decreasing creatinine clearance, and were more frequent in females. A dose response with respect to bleeding was seen for DE. For the proposed doses of DE bleeding events seem overall comparable to enoxaparin. The rate of major bleeding events in the trials with pre-operative randomisation (116019, 116025, 116048) was 1.3% (95% CI 0.8; 1.9) in DAB 150mg, 1.8% (95% CI 1.2; 2.5) in DAB 220mg and 1.6% (95% CI 1.1; 2.2) in the enoxaparin groups. Any bleeding event was seen in 13.8% (95% CI 12.3; 15.4) in DAB 150mg, 13.8% (95% CI 12.2; 15.3) in DAB 220mg and 12.9% (95% CI 11.6; 14.3) in enoxaparin groups. Identified risk factors for bleeding were female in general (male patients were at increased risk in Re-Model trial), patients aged over 75 years, patients with moderate renal impairment (creatinine clearance: 50-30ml/min), BMI < 25. As expected the use of ASA and derivatives increases bleeding frequency although it remains lower than with the use of Enoxaparin. Very few patients use concomitant ASA or derivatives and the

effect on bleeding events can not be fully evaluated. The possibility of drug monitoring would be valuable, especially for these patients at risk and commercially available TT test kits will be developed for measurement of TT following administration of DTIs. No objective measures (e.g. Hgb, MAP, CVP, Hct) were used when deciding on whether a patient needed transfusion or not and a non-validated algorithm was used to evaluate bleeding events. These circumstances make it very unlikely that patients across the study sites are classified and treated in the same way when it comes to bleeding. No clinically significant haematological or other laboratory abnormalities were consistently identified in the trials within the DE clinical development programme. Because pre-clinical toxicology studies did not provide any indication of potential hepatic injury, early clinical studies of DE employed only routine surveillance for hepatotoxicity signals. Additional LFT surveillance intended to detect any potential signal of hepatotoxicity was added during all ongoing and planned DE clinical trial protocols. The applicant provided also data from a prespecified, interim analysis of RE-LY, a long-term trial of DE in patients with AF. These data do not seem to indicate hepatotoxicity. DE and DAB are not metabolised by the cytochrome P450 system and have no effects in vitro on human cytochrome P450 enzymes. Therefore, clinically relevant drug-drug interactions are not expected. Towards transport proteins such as P-glycoprotein, an effect of DAB cannot be excluded. Clinical relevant PD interactions must be expected with other drugs acting on the coagulation system and their use is therefore discouraged.

- **Balance**

The use of DE seems to be associated with a clinical efficacy comparable to that seen with the LMWH enoxaparin but with less inconveniency as the therapy can be administered orally instead of by subcutaneous injections. There is a clinical need for this kind of product. The risks are also comparable to that seen with LMWH-therapy. Likewise seems the bleeding risk comparable to that of LMWH therapy, however, with the limitation that the assessment of bleeding was partially based on a non validated algorithm. Hepatotoxicity, which previously was found for another DTI, has not been detected for DAB in the clinical program submitted. Efficacy and safety results in the EU studies show a clear dose-effect of DAB for anticoagulation. The objective of non-inferiority of DAB on total VTE and all-cause mortality was met in comparison with enoxaparin for both dosages 220mg and 150mg. There is a trend to higher efficacy of DAB 220mg compared with enoxaparin, associated with an increased bleeding risk. On the opposite, with DAB 150mg, there is a trend to lower efficacy compared with enoxaparin, associated with a lower bleeding risk, which might be useful for some at risk populations (patients with moderate renal impairment, elderly) which have increased DAB exposure. It is important to underline that the PK characteristics of DAB i.e low bioavailability (6.5%) with a very large interindividual variability, the concentration-effect relationship and the bleeding risks strongly suggest that drug monitoring is needed. Based on the above balance the benefits associated with the proposed use of DE are considered to outweigh the risks.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Pradaxa in the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery was favourable and therefore recommended the granting of the marketing authorisation.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 April 2011
EMA/CHMP/304146/2011
Committee for medicinal products for human use (CHMP)

Summary of opinion¹ (post authorisation)

Pradaxa
dabigatran etexilate mesilate

On 14 April 2011 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product Pradaxa. The marketing authorisation holder for this medicinal product is Boehringer Ingelheim International GmbH. They may request a re-examination of the CHMP opinion, provided that they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The CHMP adopted a *new indication* as follows:

"Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

Previous stroke, transient ischemic attack, or systemic embolism (SEE)

- **Left ventricular ejection fraction < 40 %**
- **Symptomatic heart failure, $\geq$ New York Heart Association (NYHA) Class 2**
- **Age $\geq$ 75 years**
- **Age $\geq$ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension"**

The CHMP adopted a change to a *contraindication* as follows:

"Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus (see section 4.5)"

Detailed conditions for the use of this product will be described in the updated summary of product characteristics (SmPC), which will be published in the revised European public assessment report (EPAR), and will be available in all official European Union languages after the variation to the marketing authorisation has been granted by the European Commission.

¹ Summaries of positive opinion are published without prejudice to the commission decision, which will normally be issued within 44 days (Type II variations) and 67 days (Annex II applications) from adoption of the opinion.



For information, the full indications for Pradaxa will be as follows²:

For 75 mg strength

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

For 110 and 150 mg strengths

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

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

For information, the full contraindication(s) for Pradaxa will be as follows³:

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCL < 30 ml/min)
- Active clinically significant bleeding
- Organic lesion at risk of bleeding
- Spontaneous or pharmacological impairment of haemostasis
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, **cyclosporine, itraconazole and tacrolimus (see section 4.5)**

² The text in bold represents the new or the amended indication.

³ The text in bold represents the new or the amended contraindication.



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/241,793

RECEIPT DATE / TIME
04/03/2023 03:55:05 PM ET

ATTORNEY DOCKET #
70204.0018USC1

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1465

FILED BY Lisa Amos

PATENT CENTER # 61858883

FILING DATE 04/27/2021

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Erich Gess

Documents

TOTAL DOCUMENTS: 5

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-04-03_70204-0018USC1_Request-for-Interview.PDF	1	Letter Requesting Interview with Examiner	79 KB
2023-04-03_EOT_70204-0018USC1.PDF	2	Extension of Time	357 KB
2023-04-03_70204-0018USC1_Response.PDF	48	-	2386 KB
2023-04-03_70204-0018USC1_Response-A....pdf	(1-1) 1	Amendment/Request for Reconsideration-After Non-Final Rejection	85 KB

2023-04-03_70204-0018USC1_Response-CLM.pdf	(2-5)	4	Claims	89 KB
2023-04-03_70204-0018USC1_Response-REM.pdf	(6-48)	43	Applicant Arguments/Remarks Made in an Amendment	2373 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-04-03_70204-0018USC1_Request-for-Interview.PDF	B9B6220C1574739780F6D57E2F4B0E4DFC8A76AB7A0D6D9C545326E137ACE9DBB2166F863BDE39F59BB91175DBB62FEA9D8AB540F08AF013B5CA52E11C769338
2023-04-03_EOT_70204-0018USC1.PDF	6087E71E7F5AFCD8E15A8A503FDBF24E849C9FE88086FE9C3B01CB99C764C3375C7E5BFB13DA4DCD2C71ED8535FEBFC405CC169D61DD3430EB2F282BE20A581C
2023-04-03_70204-0018USC1_Response.PDF	D07FC5656BA38D6B23E1BB00C563FCA8C00A98F537F83D90012E54E20E78E266A525CE8F71405014EB150842F6138DC7D16CDE66EBF7FA6C6F582AE0E1FF1BF9
2023-04-03_70204-0018USC1_Response-A....pdf	75B405701E83F2CE5811D653851A3B2843B827FDAC88349AC17E31231C0E8E31619AAF2517222148888370B2C90BC25A05E6EBDD2942C12EB8D0E13F072985F7
2023-04-03_70204-0018USC1_Response-CLM.pdf	080FD8BE918EB25B9DE66C793A006A9D4CBDDDB9C73F93D4798F9ABB07BA9750BD07F747B9A00377A999FFE840D0A087B4CE33BAA11118D8E7F5B3CCCBA61CFBE
2023-04-03_70204-0018USC1_Response-REM.pdf	5FF2A2BCE1C332CEAF90C5D1FD7D256E4323DEF4C0206BF03DD005A4A813E6DE33482470B92B77C6266C928A5D9206F90FB97098D8D7173EDAED793E63C10E9B

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

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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 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.



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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
17/241,793

RECEIPT DATE / TIME
04/03/2023 03:55:05 PM ET

ATTORNEY DOCKET #
70204.0018USC1

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

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under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1465

FILED BY Lisa Amos

PATENT CENTER # 61858883

AUTHORIZED BY Erich Gess

CUSTOMER # 23552

FILING DATE 04/27/2021

CORRESPONDENCE
ADDRESS -

FIRST NAMED
INVENTOR Pratibha S. PILGAONKAR

Payment Information

PAYMENT METHOD
CARD / 2273

PAYMENT TRANSACTION ID
E202343F58178362

PAYMENT AUTHORIZED BY
Lisa Amos

PRE-AUTHORIZED ACCOUNT
132725

PRE-AUTHORIZED CATEGORY
37 CFR 1.19 (Document supply fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1253	EXTENSION FOR RESPONSE WITHIN THIRD MONTH	1480.00	1	1480.00
TOTAL AMOUNT:				\$1,480.00

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Receipt will establish the filing date of the application

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 70204.0018USC1																																		
Application Number 17/241,793	Filed April 27, 2021																																			
For ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE																																				
Art Unit 1613	Examiner Lyndsey Marie Beckhardt																																			
<p>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.</p> <p>The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):</p> <table style="width: 100%; border-collapse: collapse;"><thead><tr><th></th><th style="text-align: center;"><u>Fee</u></th><th style="text-align: center;"><u>Small Entity Fee</u></th><th style="text-align: center;"><u>Micro Entity Fee</u></th><th></th></tr></thead><tbody><tr><td>☐ One month (37 CFR 1.17(a)(1))</td><td style="text-align: right;">\$220</td><td style="text-align: right;">\$88</td><td style="text-align: right;">\$44</td><td>\$ _____</td></tr><tr><td>☐ Two months (37 CFR 1.17(a)(2))</td><td style="text-align: right;">\$640</td><td style="text-align: right;">\$256</td><td style="text-align: right;">\$128</td><td>\$ _____</td></tr><tr><td>☒ Three months (37 CFR 1.17(a)(3))</td><td style="text-align: right;">\$1,480</td><td style="text-align: right;">\$592</td><td style="text-align: right;">\$296</td><td>\$ 1,480</td></tr><tr><td>☐ Four months (37 CFR 1.17(a)(4))</td><td style="text-align: right;">\$2,320</td><td style="text-align: right;">\$928</td><td style="text-align: right;">\$464</td><td>\$ _____</td></tr><tr><td>☐ Five months (37 CFR 1.17(a)(5))</td><td style="text-align: right;">\$3,160</td><td style="text-align: right;">\$1,264</td><td style="text-align: right;">\$632</td><td>\$ _____</td></tr></tbody></table> <p>☐ Applicant asserts small entity status. See 37 CFR 1.27.</p> <p>☐ 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.</p> <p>☐ A check in the amount of the fee is enclosed.</p> <p>☐ Payment by credit card. Form PTO-2038 is attached.</p> <p>☐ The Director has already been authorized to charge fees in this application to a Deposit Account.</p> <p>☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number <u>132725</u>.</p> <p>☒ Payment made via USPTO's patent electronic filing system (Patent Center or EFS-Web).</p> <p>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.</p> <p>I am the</p> <p>☐ applicant.</p> <p>☒ attorney or agent of record. Registration number <u>28510</u>.</p> <p>☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.</p> <table style="width: 100%; border-collapse: collapse;"><tr><td style="width: 50%; padding: 5px;"><u>/E. Joseph Gess/</u> Signature</td><td style="width: 50%; padding: 5px;"><u>April 3, 2023</u> Date</td></tr><tr><td style="padding: 5px;"><u>E. Joseph Gess</u> Typed or printed name</td><td style="padding: 5px;"><u>703.684.2511</u> Telephone Number</td></tr></table> <p>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*.</p>				<u>Fee</u>	<u>Small Entity Fee</u>	<u>Micro Entity Fee</u>		☐ One month (37 CFR 1.17(a)(1))	\$220	\$88	\$44	\$ _____	☐ Two months (37 CFR 1.17(a)(2))	\$640	\$256	\$128	\$ _____	☒ Three months (37 CFR 1.17(a)(3))	\$1,480	\$592	\$296	\$ 1,480	☐ Four months (37 CFR 1.17(a)(4))	\$2,320	\$928	\$464	\$ _____	☐ Five months (37 CFR 1.17(a)(5))	\$3,160	\$1,264	\$632	\$ _____	<u>/E. Joseph Gess/</u> Signature	<u>April 3, 2023</u> Date	<u>E. Joseph Gess</u> Typed or printed name	<u>703.684.2511</u> Telephone Number
	<u>Fee</u>	<u>Small Entity Fee</u>	<u>Micro Entity Fee</u>																																	
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<u>E. Joseph Gess</u> Typed or printed name	<u>703.684.2511</u> Telephone Number																																			

☒ * Total of 1 forms are submitted.

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S/N 17/241,793

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Pilgaonkar et al.	Examiner:	Lyndsey Marie Beckhardt
Serial No.:	17/241,793	Group Art Unit:	1613
Filed:	April 27, 2021	Docket No.:	70204.0018USC1
Customer No.	23552	Confirmation No.	1465
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

REQUEST FOR INTERVIEW

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

Commissioner:

The Applicant's representative respectfully requests a formal Interview with Examiner
Lyndsey Marie Beckhardt to help advance prosecution of the subject application.

Respectfully submitted,

April 3, 2023

/E. Joseph Gess/
E. Joseph Gess
Registration No. 28,510
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Minneapolis, MN 55402
Telephone No. 703.684.2522
Facsimile No. 612.332.9081



INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	17241793
	Filing Date	2021-04-27
	First Named Inventor	Pratibha S. PILGAONKAR
	Art Unit	1613
	Examiner Name	BECKHARDT, LYNDSEY MARIE
	Attorney Docket Number	70204.0018USC1

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17241793
	Filing Date		2021-04-27
	First Named Inventor	Pratibha S. PILGAONKAR	
	Art Unit	1613	
	Examiner Name	BECKHARDT, LYNDESEY MARIE	
	Attorney Docket Number	70204.0018USC1	

1	European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), European Public Assessment Report for Pradaxa (dabigatran etexilate), published 23 April 2008, pp. 1-36
2	European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), Post Authorisation Summary of Positive Opinion for Pradaxa (dabigatran etexilate mesilate), published 14 April 2011, pp. 1-2

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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		17241793
	Filing Date		2021-04-27
	First Named Inventor	Pratibha S. PILGAONKAR	
	Art Unit	1613	
	Examiner Name	BECKHARDT, LYNDSEY MARIE	
	Attorney Docket Number	70204.0018USC1	

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).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

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	/E. Joseph Gess/	Date (YYYY-MM-DD)	2023-03-28
Name/Print	E. Joseph Gess	Registration Number	28510

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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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 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.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/241,793RECEIPT DATE / TIME
03/28/2023 05:18:01 PM ETATTORNEY DOCKET #
70204.0018USC1**Title of Invention**

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application InformationAPPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1465

FILED BY Lisa Kenney

PATENT CENTER # 61827713

FILING DATE 04/27/2021

CUSTOMER # 23552

FIRST NAMED INVENTOR Pratibha S. PILGAONKAR

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Erich Gess

Documents**TOTAL DOCUMENTS: 3**

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-03-28_70204-0018USC1_IDS.PDF	4	Information Disclosure Statement (IDS) Form (SB08)	1234 KB
NPL_Pradaxa_X-13_SmOP.PDF	2	Non Patent Literature	138 KB
NPL-Pradaxa-INN-dabigatran_etexilate_Published_04-23-2008.PDF	36	Non Patent Literature	2056 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-03-28_70204-0018USC1_IDS.PDF	9DB1B2E3FFEAD3BAF043837A1DF8114C374199B79D86106BAC2114FB1F50C56AF2E9DFECA3A302AE7C64A8A73DAD4A6F8202185BBAC5B3896DD52C3C3628FC14
NPL_Pradaxa_X-13_SmOP.PDF	B90789304F7ADCC5AF5E7760DFE3D8C0051657A536EAF899F24279E629FBFEE47E8B2F01B173EB9467F1E705CB457DCDBC E8D917F98C575D574C66AC44C68EB6
NPL-Pradaxa-INN-dabigatran_etexilate_Published__04-23-2008.PDF	579F78D8522A78AB9E6AB6A93F13DB234E7EC39F9E23E37676131432C97768166083B9B5B39A933260817D8141C36C5E5ADA215C6A044BE2D3F9B45F46F75CB7

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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 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.



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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
17/241,793

RECEIPT DATE / TIME
03/28/2023 05:18:01 PM ET

ATTORNEY DOCKET #
70204.0018USC1

Title of Invention

ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 1465

FILED BY Lisa Kenney

PATENT CENTER # 61827713

AUTHORIZED BY Erich Gess

CUSTOMER # 23552

FILING DATE 04/27/2021

CORRESPONDENCE
ADDRESS -

FIRST NAMED
INVENTOR Pratibha S. PILGAONKAR

Payment Information

PAYMENT METHOD
CARD / 4565

PAYMENT TRANSACTION ID
E20233RH20265238

PAYMENT AUTHORIZED BY
Lisa Kenney

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	260.00	1	260.00
TOTAL AMOUNT:				\$260.00

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New Applications Under 35 U.S.C. 111

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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.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/241,793	04/27/2021	Pratibha S. PILGAONKAR	16326.0018USC1	1465
23552 7590 10/28/2022 MERCHANT & GOULD P.C. P.O. BOX 2903 MINNEAPOLIS, MN 55402-0903			EXAMINER BECKHARDT, LYNDSEY MARIE	
			ART UNIT 1613	PAPER NUMBER
			NOTIFICATION DATE 10/28/2022	DELIVERY MODE 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. 17/241,793		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 04/27/2021.
 ☐ 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) 1-18 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) 1-18 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. 14/379,613.

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)	3) ☐ Interview Summary (PTO-413)
2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)	Paper No(s)/Mail Date ____.
Paper No(s)/Mail Date <u>10/15/2021</u>	4) ☐ Other: ____.

U.S. Patent and Trademark Office

PTOL-326 (Rev. 11-13)

Office Action Summary

Part of Paper No./Mail Date 20221012

DETAILED ACTION

Claims 1-18 are currently pending and under examination.

Notice of Pre-AIA or AIA Status

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

Priority

The instant case is a continuation of 14/379,613, filed 08/19/2014, which is a national stage entry of PCT/EP2013/053426, filed 02/21/2013, which claims priority to foreign application 461/MUM/2012, filed 02/21/2012.

The instant application is filed as a continuation application, however the proper status should be divisional, as no method of use claims were allowed in the parent application.

Information Disclosure Statement

Applicant's Informational Disclosure Statement, filed on 10/15/2021 has been considered. Please refer to Applicant's copy of the 1449 submitted herein.

Claim Rejections - 35 USC § 112 (a)

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—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 or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 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.

Claims 8-18 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for treating venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery and reducing the risk of stroke and systemic embolism in patient with non-valvular atrial fibrillation is not enabling for preventing venous thromboembolic events. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in *Wands* states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The instant claims are drawn to a method for treating or preventing venous thromboembolic events in adult patient who have undergone elective total hip replacement surgery and a method of reducing the risk of stroke and systemic embolism in patient with non-valvular atrial fibrillation or for preventing venous

thromboembolic even in an adult by administering to a patient a mixture of particles containing dabigatran etexilate and a second particle containing an organic acid.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Loke teaches Dabigatran are new oral anticoagulants for thromboprophylaxis after elective orthopaedic surgery. The outcomes for total venous thromboembolism, VTE (deep venous thrombosis, non-fatal pulmonary embolism and all cause mortality) (abstract). Loke studied VTE events demonstrating not all VTE was prevented ((a), (b), Figure 2). Dabigatran was dosed at 150 or 220 mg after hip or knee surgery (118, second column, 4th paragraph).

(5) The relative skill of those in the art:

The skill in the art is high, most likely at the Ph.D./MD level.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The instant specification states the dabigatran etexilate can be used for treating or preventing venous thromboembolic events in adult patient who have undergone elective total hip replacement surgery and a method of reducing the risk of stroke and systemic embolism in patient with non-valvular atrial fibrillation or for preventing venous thromboembolic even in an adult (instant specification page 17, last paragraph) however does not provide any examples or data supporting the prevention of venous thromboembolic events.

(8) The quantity of experimentation necessary:

Neither the instant specification or the prior art demonstrates the prevention of venous thromboembolic events. Thus the level of experimentation to obtain such a result is high.

Considering the state of the art as discussed by the reference above, particularly with regards to the prevention of venous thromboembolic events through the use of dabigatran etexilate is not enabled and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims. The treating of venous thromboembolic events and reducing the risk of stroke and systemic embolism in patient with non-valvular atrial fibrillation is enabled by the instant specification.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory

double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-18 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. **11,013,729** in view of Loke and Huisman. The instant invention and the '729 patent are both directed to a composition comprising a mixture of at least two distinct types of particles wherein the first type of particles comprise dabigatran etexilate in the form of the free base wherein the first type of particles is free from organic acids and inorganic acid and a second type of particles comprising an organic acid and coated with a protective coating layer and free of dabigatran etexilate.

The instant claims differ in that they require a method for reducing the risk of stroke and systemic embolism in patient with non-valvular atrial fibrillation, treating or preventing venous thromboembolic events in adult patient who have undergone elective total hip replacement surgery and reducing the risk of stroke and systemic embolism in patient with non-valvular atrial fibrillation or preventing venous thromboembolic events in adult patient who have undergone elective total hip replacement surgery.

Huisman teaches dabigatran etexilate for stroke or systemic embolism prevention in patients with non-valvular atrial fibrillation through administering dabigatran etexilate (abstract).

Loke teaches Dabigatran for prevention of venous thromboembolism administered orally. The patient population was after elective orthopedic surgery. (abstract). VTE prophylaxis after hip or knee replacement surgery is taught (page 111, second column, last paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use dabigatran etexilate compositions as taught by the '729 patent to be administered for reducing the risk of stroke and system embolism in a patient with non-valvular atrial fibrillation and for treating venous thromboembolic events in adult patient who have undergone elective total hip replacement surgery because Huisman teaches that it is known to use dabigatran etexilate for stroke or systemic embolism prevention in patients with non-valvular atrial fibrillation through administering dabigatran etexilate and Loke teaches dabigatran for prevention of venous thromboembolism administered orally to patient that have undergone hip or knee replacement surgery. Thus it would have been obvious to one of ordinary skill in the art

at the time of the invention to use the composition taught by the '729 patent for its known treatments as taught by Huisman and Loke.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNDESEY MARIE BECKHARDT whose telephone number is (571)270-7676. The examiner can normally be reached Monday-Thursday 9am to 2pm.

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 published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197

Application/Control Number: 17/241,793
Art Unit: 1613

Page 9

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/LYNDSEY M BECKHARDT/
Examiner, Art Unit 1613

<i>Notice of References Cited</i>	Application/Control No. 17/241,793	Applicant(s)/Patent Under Reexamination PILGAONKAR et al.	
	Examiner LYNDSEY M 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					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

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	Loke, Y. K., et al., Journal of Clinical Pharmacy and Therapeutics (2011) 36, 111-124. (Year: 2011)
	V	Huisman, Menno V., et al., Thromb Haemost (2012); 107: 838-847. (Year: 2012)
	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.

U.S. Patent and Trademark Office
PTO-892 (Rev. 01-2001)

Notice of References Cited

Part of Paper No. 20221012

Search Notes 	Application/Control No. 17/241,793	Applicant(s)/Patent Under Reexamination PILGAONKAR et al.
	Examiner LYNDSEY M BECKHARDT	Art Unit 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	10/12/2022	LMB

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* 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	10/12/2022	LMB
Google (keyword) see attached	10/12/2022	LMB

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/LMB/	
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Doc code: IDS

PTO/SB/08a (03-15)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2016. 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 contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	17241793
	Filing Date	2021-04-27
	First Named Inventor	Pilgaonkar
	Art Unit	
	Examiner Name	
	Attorney Docket Number	16326.0018USC1

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Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6087380		2000-07-11	Hauel, et al.	
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Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050234104		2005-10-20	Schmid, et al.	
	2	20110129538		2011-06-02	Landerer, et al.	
	3	20040109890		2004-06-10	Sugimoto	
	4	20050123606		2005-06-09	Kidane	
	5	20060183779		2006-08-17	Brauns	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17241793
	Filing Date		2021-04-27
	First Named Inventor	Pilgaonkar	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		16326.0018USC1

	6	20060074056		2006-04-06	Vaisburg, et al.	
	7	20050038077		2005-02-17	Kohlrausch	
	8	20080069891		2008-03-20	Habib	

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	1	2005028468	WO		2005-03-31	Boehringer Ingelheim PH		
	2	2012001156	WO		2012-01-05	Krka Tovama Zdravil		
	3	9837075	WO		1998-08-27	Boehringer Ingelheim PH		
	4	0012064	WO		2000-03-09	Chen		
	5	101632668	CN		1020-01-27	Brauns		
	6	1366760	EP		2002-02-12	Sugimoto		

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	17241793
	Filing Date	2021-04-27
	First Named Inventor	Pilgaonkar
	Art Unit	
	Examiner Name	
	Attorney Docket Number	16326.0018USC1

7	2001524131	JP		2001-11-27	Chen		
8	2002316923	JP		2002-10-31	Sugimoto		
9	2002523443	JP		2002-07-30	Chen		
10	2005046663	WO		2005-05-26	Kidane		
11	2005121102	WO		2005-12-22	Torkelson		
12	2005519099	JP		2005-06-30	Brauns		
13	2007092026	WO		2007-08-16	Leibovici		
14	2007510655	JP		2007-04-26	Kidane		
15	2008501702	JP		2008-01-24	Torkelson		
16	2008534681	JP		2008-08-28	Leibovici		
17	2476054	CA		2003-09-12	Brauns		

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17241793
	Filing Date		2021-04-27
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	Art Unit		
	Examiner Name		
Attorney Docket Number		16326.0018USC1	

18	9850019	WO	1998-11-12	Chen		
19	H04103525	JP	1992-04-06	Masatsune		
20	03074056	WO	2003-09-12	Boehringer Ingelheim		
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	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.	
	2	Australian Public Assessment Report for Dabigatran Etxilate Mesylate, May 2011	
	3	Belousov, Yu B., et al., Rational Pharmacotherapy in Cardiology, Vol. 8, No. 1, pp. 37-44, 2012, English Abstract	
	4	Bozhkova, S.A., Traumatology and Orthopedics, Vol, 1, No. 59, pp 138-143, 2011, English Abstract	
	5	Stangier, Clin Pharmacokinet 2008: 47 (5) 285-295	

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	Filing Date		2021-04-27
	First Named Inventor	Pilgaonkar	
	Art Unit		
	Examiner Name		
Attorney Docket Number		16326.0018USC1	

6	International Search Report for PCT/EP2013/053426 dated 16 April 2013
7	PubChem, Dabigatran Etexilate (accessed 03/21/2016), pp. 1-25
8	Vippagunta et al., "Crystalline Solids," Advanced Drug Delivery Reviews, (2001), 48, pp. 3-26
9	Muller, Inorganic Chemistry (1993) pp 14-15
10	Wikipedia, Dabigatran (09/25/2015) pp. 1-4

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Examiner Signature	/LYNDSEY M BECKHARDT/	Date Considered	10/12/2022
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PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	1	("11013729").pn.	(US-PGPUB; USPAT)	ADJ	ON	ON	2022/09/22 11:51 AM
L2	444	dabigatran SAME thromboembolic	(US-PGPUB; USPAT)	ADJ	ON	ON	2022/10/11 08:03 AM
L3	95	((("PILGAONKAR") near3 ("Pratibha")) OR ("RUSTOMJEE") near3 ("Maharukh")) OR ("GANDHI") near3 ("Anilkumar"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	ADJ	ON	ON	2022/10/11 09:45 AM
L4	1	"17241793"	(US-PGPUB; USPAT)	ADJ	ON	ON	2022/10/12 12:25 PM
L5	49859	(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).cpc.	(US-PGPUB; USPAT)	ADJ	ON	ON	2022/10/12 12:25 PM
L6	2	"20060183779"	(US-PGPUB; USPAT)	ADJ	ON	ON	2022/10/12 12:37 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Bibliographic Data

Application No: 17/241,793

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.
04/27/2021	424	1613	16326.0018USC1
RULE			

APPLICANTS

Breckenridge Pharmaceutical, Inc., Berlin, CT, UNITED STATES

INVENTORS

Pratibha S. PILGAONKAR, Mumbai, INDIA

Maharukh T. RUSTOMJEE, Mumbai, INDIA

Anilkumar S. GANDHI, Mumbai, INDIA

CONTINUING DATA

This application is a CON of 14379613 08/19/2014 PAT 11013729

14379613 is a 371 of PCT/EP2013/053426 02/21/2013

FOREIGN APPLICATIONS

INDIA IN461/MUM/2012 02/21/2012

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MINNEAPOLIS, MN 55402-0903

UNITED STATES

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Web Search History

date, time	web site	search string
10/12/2022 10:36:04 AM	Google	dabigatran etexilate
10/12/2022 10:36:08 AM	Google	dabigatran etexilate particle
10/12/2022 10:43:24 AM	Google	Dabigatran etexilate, a thrombin inhibitor for the prevention of venous thromboembolism and stroke
10/12/2022 10:46:14 AM	Google	dabigatran etexilate stroke and embolism
10/12/2022 10:46:28 AM	Google	system embolism risk of stroke venous thromboembolic
10/12/2022 10:46:43 AM	Google	system embolism risk of stroke venous thromboembolic and dabigatran



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/241,793	04/27/2021	Pratibha S. PILGAONKAR	16326.0018USC1

CONFIRMATION NO. 1465

POA ACCEPTANCE LETTER

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



Date Mailed: 03/02/2022

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/rmohamed/



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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
17/241,793	04/27/2021	OPAP	1820	16326.0018USC1	18	3

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

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CC000000132180195

Date Mailed: 03/02/2022

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Inventor(s)

Pratibha S. PILGAONKAR, Mumbai, INDIA;
Maharukh T. RUSTOMJEE, Mumbai, INDIA;
Anilkumar S. GANDHI, Mumbai, INDIA;

Applicant(s)

Breckenridge Pharmaceutical, Inc., Berlin, CT;

Assignment For Published Patent Application

Breckenridge Pharmaceutical, Inc., Berlin, CT

Power of Attorney:

Erich Gess--28510
Melissa Hayworth--45774
Karen Beckman--80008

Domestic Priority data as claimed by applicant

This application is a CON of 14/379,613 08/19/2014 PAT 11013729
which is a 371 of PCT/EP2013/053426 02/21/2013

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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	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO.	TOT CLAIMS	IND CLAIMS
17/241,793	04/27/2021		1820	16326.0018USC1 70204.0018USC1	18	3

CONFIRMATION NO. 1465

FILING RECEIPT

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P.O. BOX 2903
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Date Mailed: 05/05/2021

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Maharukh T. RUSTOMJEE, Mumbai, INDIA;
Anilkumar S. GANDHI, Mumbai, INDIA;

Applicant(s)

Breckenridge Pharmaceutical, Inc., Berlin, CT

~~--TOWA Pharmaceutical Europe, S.L. Unipersonal, Martorelles (Barcelona), SPAIN;--~~

Assignment For Published Patent Application

~~--TOWA Pharmaceutical Europe, S.L. Unipersonal, Martorelles (Barcelona), SPAIN~~

Breckridge Pharmaceutical, Inc., Berlin, CT

Power of Attorney: None**Domestic Priority data as claimed by applicant**

This application is a CON of 14/379,613 08/19/2014 now US Patent 11,013,729 05/25/2021
which is a 371 of PCT/EP2013/053426 02/21/2013

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Projected Publication Date: 08/12/2021

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

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Electronic Acknowledgement Receipt	
EFS ID:	45109605
Application Number:	17241793
International Application Number:	
Confirmation Number:	1465
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:	16326.0018USC1
Receipt Date:	28-FEB-2022
Filing Date:	27-APR-2021
Time Stamp:	19:36:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request under 37CFR1.46(c) to correct, update, change applicant	70204-0018USC1-Request-Change-Applicant.PDF	122677	no	1
			aa12c29e35ecdad1f4aa1e954a2ce1b610c079ab		

Warnings:

Information:					
2	Application Data Sheet	70204-0018USC1-SADS.PDF	138676	no	9
			a3d90565c714b815c07e2df0fe73c7f5e9fe041f9d		
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Power of Attorney	70204-0018USC1-POA.PDF	1144222	no	2
			b2f31a3a2b5416349fd7e5147be4b445e94a41f9d		
Warnings:					
Information:					
4	Assignee showing of ownership per 37 CFR 3.73	70204-0018USC1-373c.PDF	118704	no	3
			869fc3f9833ce22f853d88796880757fdd46f40f		
Warnings:					
Information:					
5	Request for Corrected Filing Receipt	70204-0018USC1-Corrected_OFR.PDF	2724015	no	3
			1bea099f5624387382a792a33c33f53ee596906b		
Warnings:					
Information:					
Total Files Size (in bytes):			4248294		
<p>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.</p> <p><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.</p> <p><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.</p> <p><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.</p>					

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	PILGAONKAR et al.	Confirmation No.	1465
Application No:	17/241,793	Examiner:	
Filed:	April 27, 2021	Group Art Unit:	
Customer No.	23552	Docket No.:	70204.0018USC1
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

REQUEST TO CHANGE APPLICANT UNDER 37 C.F.R. § 1.46(c)

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

Attention: Commissioner for Patents

It is requested that the Applicant in the above-referenced application be changed to Breckenridge Pharmaceutical, Inc. Submitted with this request is a Supplemental Application Data Sheet showing the requested change, a marked copy of the Official Filing Receipt showing the updated Applicant, and the Power of Attorney and Statement under 373(c).

If necessary, please charge any fees required to Deposit Account No. 13-2725 (Docket # 70204.0018USC1).

Respectfully submitted,

Date: February 28, 2022

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

MECHANT & GOULD P.C.
PO Box 2903
Minneapolis, MN 55402
Telephone No. 703.684.2522
Facsimile No. 703.684.2501

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USCT 70204.0018USC1
		Application Number	17/241,793
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
<p>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.</p> <p>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.</p>			

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 ⁱ		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 ⁱ	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 ⁱ		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 ⁱ	IN		
Inventor 3					Remove
Legal Name					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1 70204.0018USC1
		Application Number	17/241,793
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

Prefix	Given Name	Middle Name	Family Name	Suffix
	Anilkumar	S.	GANDHI	
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service				
City	Mumbai	Country of Residence ⁱ	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 ⁱ	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	16326.0018USC1 70204.0018USC1	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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1 <u>70204.0018USC1</u>
		Application Number	<u>17/241,793</u>
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	<u>23552</u>		

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		<u>Patented</u> Pending		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
<u>17241793</u>	Continuation of	<u>14379613</u>	<u>2014-08-19</u>	<u>11013729</u>	<u>2021-05-25</u>
Prior Application Status		Expired		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
<u>14379613</u>	a 371 of international	<u>PCT/EP2013/053426</u>	<u>2013-02-21</u>		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.					

Foreign Priority Information:

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16926.0018USC1 70204.0018USC1
		Application Number	17/241,793
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

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)¹ 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).

Application Number	Country ¹	Filing Date (YYYY-MM-DD)	Remove Access Code ¹ (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	16926-0018USC1 70204.0018USC1
		Application Number	17/241,793
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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1 70204.0018USC1
		Application Number	17/241,793
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			
<p>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.</p>			
<input type="button" value="Clear"/>			
☒ 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:			
Name of the Deceased or Legally Incapacitated Inventor: <input type="text"/>			
If the Applicant is an Organization check here. ☒			
Organization Name	TOWA Pharmaceutical Europe, S.L. Unipersonal Breckenridge Pharmaceutical, Inc.		
Mailing Address Information For Applicant:			
Address 1	Poligon Industrial de Martorelles 15 Massirio Drive		
Address 2	Carrer de Sant Martí, 75-97 Suite 201		
City	Martorelles (Barcelona) Berlin	State/Province	CT
Country	ES US	Postal Code	08107 06037
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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	16326.0018USC1 <u>70204.0018USC1</u>
	Application Number	<u>17/241,793</u>
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. ☒			
Organization Name		TOWA Pharmaceutical Europe, S.L. Unipersonal <u>Breckenridge Pharmaceutical, Inc.</u>	
Mailing Address Information For Assignee including Non-Applicant Assignee:			
Address 1		Poigon Industrial de Martorelles <u>15 Massirio Drive</u>	
Address 2		Carrer de Sant Martí, 75-97 <u>Suite 201</u>	
City		Martorelles (Barcelona) <u>Berlin</u>	State/Province <u>CT</u>
Country i	ES <u>US</u>	Postal Code	08107 <u>06037</u>
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)	2022-02-28
First Name	Melissa	Last Name	Hayworth	Registration Number 45774
Additional Signature may be generated within this form by selecting the Add button.				

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1 70204.0018USC1
		Application Number	17/241,793
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 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 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.

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
17/241,793	April 27, 2021

(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:
- 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):

Breckenridge Pharmaceutical, Inc.

- ☐ 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	<i>Bruce D. DeRenzi</i>	Date (Optional)	2/10/22
Name	Bruce D. DeRenzi		
Title	Associate General Counsel and Head of Litigation		

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.

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

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
Karen L. Beckman	80008

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Breckenridge Pharmaceutical, Inc.
Application No./Patent No.: 17/241,793 Filed/Issue Date: April 27, 2021
Titled: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
Breckenridge Pharmaceutical, Inc., 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 058976, Frame 0770, 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.

[Page 1 of 2]

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.

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/

February 18, 2022

Signature

Date

Melissa M. Hayworth

45774

Printed or Typed Name

Title or Registration Number

[Page 2 of 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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/241,793	04/27/2021	Pratibha S. PILGAONKAR	16326.0018USC1

CONFIRMATION NO. 1465

IMPROPER CFR REQUEST



OC000000131994024

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

Date Mailed: 02/25/2022

RESPONSE TO REQUEST FOR CORRECTED FILING RECEIPT

Power of Attorney, Claims, Fees, System Limitations, and Miscellaneous

In response to your request for a corrected Filing Receipt, the Office is unable to comply with your request because:

- Any request to correct or update the name of the applicant must include an application data sheet (ADS) in compliance with 37 CFR 1.76 specifying the correct or updated name of the applicant in the applicant information section. Any request to change the applicant after an original applicant has been specified under 37 CFR 1.46(b) must include a new ADS in compliance with 37 CFR 1.76 specifying the applicant in the applicant information section and comply with 37 CFR 3.71 and 3.73. See 37 CFR 1.46(c).

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.

/zabaha/



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
17/241,793	04/27/2021	Pratibha S. PILGAONKAR	16326.0018USC1

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

CONFIRMATION NO. 1465
IMPROPER CPOA LETTER



Date Mailed: 02/25/2022

NOTICE REGARDING POWER OF ATTORNEY

This is in response to the power of attorney filed 02/18/2022. The power of attorney in this application is not accepted for the reason(s) listed below:

- The power of attorney has not been accepted because the party who is giving power has not been identified. Power of attorney may only be signed by the applicant for patent (37 CFR 1.42) or the patent owner. A party who is not the applicant must become the applicant in accordance with 37 CFR 1.46(c) and appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. For a reissue application, reexamination proceeding, or supplemental examination proceeding, a patent owner who was not the applicant under 37 CFR 1.46 must appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. See 37 CFR 1.32(b)(4).

/zabaha/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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
17/241,793	April 27, 2021

(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:
- 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):

Breckenridge Pharmaceutical, Inc.

- ☐ 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

Bruce D. DeRenzi

Date (Optional)

2/10/22

Name

Bruce D. DeRenzi

Title

Associate General Counsel and Head of Litigation

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.

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

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
Karen L. Beckman	80008

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Breckenridge Pharmaceutical, Inc.
Application No./Patent No.: 17/241,793 Filed/Issue Date: April 27, 2021
Titled: ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE
Breckenridge Pharmaceutical, Inc., 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 058976, Frame 0770, 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.

[Page 1 of 2]

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.

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/

February 18, 2022

Signature

Date

Melissa M. Hayworth

45774

Printed or Typed Name

Title or Registration Number

[Page 2 of 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.

Electronic Acknowledgement Receipt	
EFS ID:	45038036
Application Number:	17241793
International Application Number:	
Confirmation Number:	1465
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:	16326.0018USC1
Receipt Date:	18-FEB-2022
Filing Date:	27-APR-2021
Time Stamp:	17:06:24
Application Type:	Utility under 35 USC 111(a)

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	70204-0018USC1-POA.PDF	1144222	no	2
			b2f31a3a2b5416349fd7e5147be4b445b4a41f9d		

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	70204-0018USC1-373c.PDF	118704	no	3
			869fc3f9833ce22f853d88796880757fdd46f40f		
Warnings:					
Information:					
Total Files Size (in bytes):				1262926	
<p>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.</p> <p><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.</p> <p><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.</p> <p><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.</p>					

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	17241793
	Filing Date	2021-04-27
	First Named Inventor	Pilgaonkar
	Art Unit	
	Examiner Name	
	Attorney Docket Number	16326.0018USC1

U.S.PATENTS							Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	
	1	6087380		2000-07-11	Hauel, et al.		
If you wish to add additional U.S. Patent citation information please click the Add button.							Add
U.S.PATENT APPLICATION PUBLICATIONS							Remove
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	
	1	20050234104		2005-10-20	Schmid, et al.		
	2	20110129538		2011-06-02	Landerer, et al.		
	3	20040109890		2004-06-10	Sugimoto		
	4	20050123606		2005-06-09	Kidane		
	5	20060183779		2006-08-17	Brauns		

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17241793
	Filing Date		2021-04-27
	First Named Inventor	Pilgaonkar	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		16326.0018USC1

	6	20060074056		2006-04-06	Vaisburg, et al.	
	7	20050038077		2005-02-17	Kohlrausch	
	8	20080069891		2008-03-20	Habib	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ² i	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1	2005028468	WO		2005-03-31	Boehringer Ingelheim PH		
	2	2012001156	WO		2012-01-05	Krka Tovarna Zdravil		
	3	9837075	WO		1998-08-27	Boehringer Ingelheim PH		
	4	0012064	WO		2000-03-09	Chen		
	5	101632668	CN		1020-01-27	Brauns		
	6	1366760	EP		2002-02-12	Sugimoto		

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	17241793
	Filing Date	2021-04-27
	First Named Inventor	Pilgaonkar
	Art Unit	
	Examiner Name	
	Attorney Docket Number	16326.0018USC1

7	2001524131	JP		2001-11-27	Chen		
8	2002316923	JP		2002-10-31	Sugimoto		
9	2002523443	JP		2002-07-30	Chen		
10	2005046663	WO		2005-05-26	Kidane		
11	2005121102	WO		2005-12-22	Torkelson		
12	2005519099	JP		2005-06-30	Brauns		
13	2007092026	WO		2007-08-16	Leibovici		
14	2007510655	JP		2007-04-26	Kidane		
15	2008501702	JP		2008-01-24	Torkelson		
16	2008534681	JP		2008-08-28	Leibovici		
17	2476054	CA		2003-09-12	Brauns		

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17241793
	Filing Date		2021-04-27
	First Named Inventor	Pilgaonkar	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		16326.0018USC1

18	9850019	WO	1998-11-12	Chen
19	H04103525	JP	1992-04-06	Masatsune
20	03074056	WO	2003-09-12	Boehringer Ingelheim
21				

If you wish to add additional Foreign Patent Document citation information please click the Add button

Add

NON-PATENT LITERATURE DOCUMENTS

Remove

Examiner Initials*	Cite No	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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	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.	
	2	Australian Public Assessment Report for Dabigatran Etxilate Mesylate, May 2011	
	3	Belousov, Yu B., et al., Rational Pharmacotherapy in Cardiology, Vol. 8, No. 1, pp. 37-44, 2012, English Abstract	
	4	Bozhkova, S.A., Traumatology and Orthopedics, Vol, 1, No. 59, pp 138-143, 2011, English Abstract	
	5	Stangier, Clin Pharmacokinet 2008: 47 (5) 285-295	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17241793
	Filing Date		2021-04-27
	First Named Inventor	Pilgaonkar	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		16326.0018USC1

6	International Search Report for PCT/EP2013/053426 dated 16 April 2013
7	PubChem, Dabigatran Etexilate (accessed 03/21/2016), pp. 1-25
8	Vippagunta et al., "Crystalline Solids," Advanced Drug Delivery Reviews, (2001), 48, pp. 3-26
9	Muller, Inorganic Chemistry (1993) pp 14-15
10	Wikipedia, Dabigatran (09/25/2015) pp. 1-4

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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		17241793
	Filing Date		2021-04-27
	First Named Inventor	Pilgaonkar	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		16326.0018USC1

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).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

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)	2021-10-15
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.**

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 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 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.

Electronic Acknowledgement Receipt	
EFS ID:	44040164
Application Number:	17241793
International Application Number:	
Confirmation Number:	1465
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:	16326.0018USC1
Receipt Date:	15-OCT-2021
Filing Date:	27-APR-2021
Time Stamp:	12:26:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	16326-0018USC1-IDS- Transmittal.PDF	77753	no	1
			903a1129fad335a5816f07e8848841de682c6955		

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	0018USC1_IDS.PDF	1036562	no	7
			a92690405eee1e43a4684b0adf550ad256b bad42		
Warnings:					
Information:					
Total Files Size (in bytes):			1114315		
<p>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.</p> <p><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.</p> <p><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.</p> <p><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.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Pilgaonkar et al.	Examiner:	
Serial No.:	17/241,793	Group Art Unit:	
Filed:	April 27, 2021	Docket No.:	16326.0018USC1
Customer No.:	23552	Confirmation No.:	1465
Title:	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

INFORMATION DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b))

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

The items of information listed on the enclosed Form SB08 are brought to the attention of the Examiner as a formality in the above-referenced application. Applicant notes that all of the items listed on the submitted Form SB08 were cited in the parent application U.S. Application No. 14/379,613.

In accordance with 37 C.F.R. §1.98(d), copies of the documents listed on the enclosed Form SB08 are not provided because these documents were previously cited by or submitted to the U.S. Patent and Trademark Office in parent application U.S. Application No. 14/379,613 to which the present application claims priority.

Pursuant to the provisions of M.P.E.P. 609, it is requested that the Examiner return a copy of the attached Form SB08, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

Respectfully submitted,

October 15, 2021

/Melissa M. Hayworth/

Melissa M. Hayworth
Registration No. 45,774

MERCHANT & GOULD PC
PO Box 2903
Minneapolis, MN 55402
Telephone No. 703.684.2522
Facsimile No. 612.332.9081





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
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/241,793	04/27/2021	Pratibha S. PILGAONKAR	16326.0018USC1

CONFIRMATION NO. 1465

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

PUBLICATION NOTICE



OC000000127656912

Title:ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE

Publication No.US-2021-0244719-A1

Publication Date:08/12/2021

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 publicly 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 Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, 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 <https://portal.uspto.gov/pair/PublicPair>. 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 Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101



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
17/241,793	04/27/2021		1820	16326.0018USC1	18	3

CONFIRMATION NO. 1465

FILING RECEIPT

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



CC000000123341749

Date Mailed: 05/05/2021

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)

TOWA Pharmaceutical Europe, S.L. Unipersonal, Martorelles (Barcelona), SPAIN;

Assignment For Published Patent Application

TOWA Pharmaceutical Europe, S.L. Unipersonal, Martorelles (Barcelona), SPAIN

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 14/379,613 08/19/2014
which 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 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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: 05/04/2021

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/241,793**

Projected Publication Date: 08/12/2021

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).

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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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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.

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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).

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 17/241,793	
APPLICATION AS FILED - PART I							
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	18 minus 20 =	*				x 100 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 480 =	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
			TOTAL			TOTAL	1820
* If the difference in column 1 is less than zero, enter "0" in column 2.							
APPLICATION AS AMENDED - PART II							
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	x =		x =
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =		x =
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
			TOTAL ADD'L FEE			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.							

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	16326.0018USC1
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		
<p>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.</p> <p>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.</p>			

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				<input type="button" value="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 Residenceⁱ		IN	
Mailing Address of Inventor:					
Address 1	221 Annexe Bldg.				
Address 2	Goregaon-Mulund Link Road				
City	Mumbai	State/Province			
Postal Code	400 078	Countryⁱ	IN		
Inventor	2				<input type="button" value="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 Residenceⁱ		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	Countryⁱ	IN		
Inventor	3				<input type="button" value="Remove"/>
Legal Name					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

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

Residence Information (Select One)		US Residency	☒ Non US Residency	Active US Military Service
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All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

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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	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	16326.0018USC1	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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1
		Application Number	
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	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	14379613	2014-08-19
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.			Add

Foreign Priority Information:

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1
		Application Number	
Title of Invention	ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN ETEXILATE		

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).

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

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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	16326.0018USC1
		Application Number	
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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1
		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		<input type="button" value="Remove"/>
<p>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.</p>			
		<input type="button" value="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:			
<div style="border: 1px solid black; height: 15px; width: 100%;"></div>			
Name of the Deceased or Legally Incapacitated Inventor: <div style="border: 1px solid black; width: 400px; height: 20px;"></div>			
If the Applicant is an Organization check here. ☒			
Organization Name	TOWA Pharmaceutical Europe, S.L. Unipersonal		
Mailing Address Information For Applicant:			
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City	Martorelles (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.			<input type="button" value="Add"/>

Assignee Information including Non-Applicant Assignee Information:

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1
		Application Number	
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.			
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If the Assignee or Non-Applicant Assignee is an Organization check here. ☒			
Organization Name	TOWA Pharmaceutical Europe, S.L. Unipersonal		
Mailing Address Information For Assignee including Non-Applicant Assignee:			
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Address 2	Carrer de Sant Martí, 75-97		
City	Martorelles (Barcelona)	State/Province	
Country i	ES	Postal Code	08107
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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)	2021-04-27	
First Name	Melissa	Last Name	Hayworth	Registration Number	45774
Additional Signature may be generated within this form by selecting the Add button. Add					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	16326.0018USC1
		Application Number	
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.**

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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 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 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.

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 method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation comprising administering to the patient in need thereof 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.
2. The method of claim 1, wherein the composition is administered as a unit dosage form comprising from 50 mg to 200 mg of dabigatran etexilate mesylate.
3. The method of claim 2, wherein the unit dosage form is a capsule.
4. The method of claim 1, wherein the composition further comprises at least one pharmaceutically acceptable excipient.
5. The method of claim 1, wherein the composition comprises from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.
6. The method of claim 1, wherein the composition comprises from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.
7. The method of claim 4, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.
8. A method for treating or preventing venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery comprising

administering to the patient in need thereof 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.

9. The method of claim 8, wherein the composition is administered as a unit dosage form comprising from 50 mg to 200 mg of dabigatran etexilate mesylate.

10. The method of claim 9, wherein the unit dosage form is a capsule.

11. The method of claim 8, wherein the composition further comprises at least one pharmaceutically acceptable excipient.

12. The method of claim 8, wherein the composition comprises from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.

13. The method of claim 8, wherein the composition comprises from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.

14. The method of claim 11, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

15. The method of claim 8, wherein the venous thromboembolic events are deep venous thrombosis (DVT) and pulmonary embolism (PE).

16. A method for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation or for preventing venous thromboembolic events in adult

patients who have undergone elective total hip replacement surgery comprising administering to the patient in need thereof 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.

17. The method of claim 16, wherein the capsule contains from 50 mg to 200 mg of dabigatran etexilate mesylate.

18. The method of claim 16, wherein the first type of particles of the capsule comprise at least one pharmaceutically acceptable excipient.

**ORAL PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN
ETEXILATE**

This application is a continuation of U.S. Patent Application No. 14/379,613 filed
5 August 19, 2014, entitled "Oral Pharmaceutical Compositions of Dabigatran Etexilate",
the contents of which are hereby incorporated by reference in their entirety.

Field of Invention

The present invention relates to oral pharmaceutical compositions comprising
10 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
15 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
20 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
25 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,
30 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
5 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
10 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
15 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
20 thrombin time, under the name 1-methyl-2-[N-[4-(N-n-hexyloxy carbonylamidino) phenyl] aminomethyl] benzimidazol-5-ylcarboxylic acid-N-(2-pyridyl)-N-(2-ethoxy carbonyl ethyl) amides.

Dabigatran is currently available as dabigatran etexilate mesylate (DEM) under the
25 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
30 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.

10

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.

20

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.

25

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

30

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
5 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
10 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
15 especially when (a) absorption of the active is rapid with faster T_{max} (~ 45 minutes – 1
hour), (b) significant bioactivation is involved and (c) negligible and variable absorption
at higher pH.

Detailed Description of the Invention

20 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)
25 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
30 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
5 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-(hexyloxy carbonylamino-imino-methyl)-
10 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).
15 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
20 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
25 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.

30 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.

- 5 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).

- 10 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
15 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.
20

- 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.
25

- 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
30 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.

- 5 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
10 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
15 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
20 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.
25

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
30 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

5 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

10 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

15 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)

20 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

25 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

30 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
5 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
10 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
15 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
20 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.

25 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.

30 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.

5

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.

- 5 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
- 10 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 exchange resins (such as Polacrillin potassium, Polacrilex) Neusilins, low substituted hydroxypropyl cellulose and the like, combinations thereof and other such materials known to those of ordinary skill in the
- 15 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
- 20 (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
- 25 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.

- 30 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,
5 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
10 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"
15 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.

20 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,
25 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
30 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 include, but are not limited to, powder, granules, pellets, beads, minitabets or the like. The granules may be prepared by methods such as, but not limited to, wet
5 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
10 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.

15

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.

20 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
25 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,
30 minitabets, 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.

- 5 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.
- 10 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.
- 15 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
- 20 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
- 25 rapid with faster T_{max} (~ 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
- 30 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

- 5 (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;
- 10 (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;
- 15 (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.

20 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;
- 25 (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;
- 30 (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.

5

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;
- 10 (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;
- 15 (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;
- 20 (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

- 25 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.

- 30 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
 5 combined with other active agents or pharmaceutically acceptable salts thereof including, but not limited to, atorvastatin, dipyridamole, mepidamole and the like or combinations thereof.

The invention is further illustrated by the following examples, which are for illustrative
 10 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

15

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

20

*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
 25 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

- 5 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

10

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

- 15 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

5 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

10

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

15

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.

20

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

5 *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
 10 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

15 *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.

5 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

10 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.

15 **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:

- 20 (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)

25

(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

5

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.

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(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
5 minutes – 1 hour), (b) significant bioactivation is involved and (c) negligible and variable absorption at higher pH.

Doc Code: Oath

Document Description: Oath or declaration filed

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Adapted from PTO/AIA-08 (08-12)

Approved for use through 01/31/2014. OMB 0551-0052

U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

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

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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.

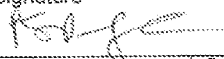
[Page 1 of 2]

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(P151 - rev. 11/2012)

DECLARATION — Utility or Design Patent Application

Direct all correspondence to:	☒ The address associated with Customer Number: 25,666	OR	☐ Correspondence address below
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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	
		31 st 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			

[Page 2 of 2]

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SUPPLEMENTAL SHEET FOR DECLARATION	ADDITIONAL INVENTOR(S)
	Supplemental Sheet (for PTO/AIA/06.09)

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	<i>M.T. Rustomjee</i>		Date <i>31/7/2014</i>
Residence: City	Mumbai	State	Country INDIA
221 Annexe Bldg, Goregaon-Mulund Link Road			
Mailing Address			
City	Mumbai	State	Zip 400 078 Country INDIA

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SUPPLEMENTAL SHEET FOR DECLARATION	ADDITIONAL INVENTOR(S)
	Supplemental Sheet (for PTO/AIA/08,09) Page <u>2</u> of <u>2</u>

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 <u>31st July-2014</u>	
Residence: City <u>Mumbai</u>	State	Country <u>INDIA</u>	
Mailing Address <u>221 Annexe Bldg, Goregaon-Mulund Link Road</u>			
City <u>Mumbai</u>	State	Zip <u>400 078</u>	Country <u>INDIA</u>

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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:		Melissa M. Hayworth/Lisa Kenney		
Attorney Docket Number:		16326.0018USC1		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	320	320
UTILITY SEARCH FEE	1111	1	700	700
UTILITY EXAMINATION FEE	1311	1	800	800
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 (\$)				1820

Electronic Acknowledgement Receipt	
EFS ID:	42568647
Application Number:	17241793
International Application Number:	
Confirmation Number:	1465
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:	16326.0018USC1
Receipt Date:	27-APR-2021
Filing Date:	
Time Stamp:	16:19:38
Application Type:	Utility under 35 USC 111(a)

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	16326-0018USC1_ADS_aia0014.PDF	1256347	no	9
			b6f7ddc304189dc391b2d0a95c0bc4ad7ecf795b		
Warnings:					
Information:					
2		16326-0018USC1_Application.PDF	223918	yes	29
			72a6ff6f5b2cace5de807e79404b318de6457cc9		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Abstract		29	29	
	Claims		26	28	
	Specification		1	25	
Warnings:					
Information:					
3	Oath or Declaration filed	16326-0018USC1_Declaration.PDF	338369	no	4
			2a301a0ddc0eab8261ede68d732abe494667d3ed		
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	35017	no	2
			0f7d3e9a4d2ef27edf0201e0613d1941bbb0f319		
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