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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 01-1306-1-C1 | 5127 |

28519 7590 06/20/2013

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| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |
| ART UNIT | PAPER NUMBER |
| 1629 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 06/20/2013 | 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):

USPTO.e-Office.rdg@boehringer-ingelheim.com



IPR2025-01107
MSN Exhibit 1008
Page 1 of 304

| Office Action Summary | Application No. 11/381,890 | Applicant(s) BRAUNS, ULRICH | |
|---|---|---|---|
| | Examiner SABIHA N. QAZI | Art Unit 1629 | AIA (First Inventor to File) Status No |

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

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 _____.

☐ 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) *1-6,8-15 and 17-22* is/are pending in the application.

5a) Of the above claim(s) *15* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-6,8-14 and 17-22* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

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

**Certified copies:**

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Interim copies:**

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.



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## Non-Final Office Action

Claims 1-6, 8-14 and 17-22 are pending. No claim is allowed. Amendments are entered.

## Summary of this Office Action

1. Continued Examination under 37 CFR 1.114
2. 35 USC § 103(a) Rejection
3. Response to Remarks
4. Communication

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***Continued Examination Under 37 CFR 1.114***

*1.* A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 03/02/2011 has been entered.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

**Claim Rejections - 35 USC § 103-- Rejection**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8-14 and 17-22 rejected under 35 U.S.C. 103 (a) as being unpatentable over Mehta (US Patent 6,620,439), Eisert et al (US Patent 6,015,577), Gruber et al. (US Patent 4,438,091), Hauel et al. (WO 98/37075), Bastin, R. ET al. (Organic Process Res. and Development (2000), Berge et al., and Bach et al. and Ileum et al. These references teach formulations which embrace Applicants claimed invention. See the entire documents.

**Determining the scope and contents of the prior art**

Mehta teaches According to the present invention, the time specific delayed release dosage formulation is characterized by having a biologically inert pellet coated by at least one layer of drug(s) in admixture with a suitable binder agent; which is coated with an outer layer referred to herein as "the rate controlling layer." See the entire document. The reference teaches a dosage formulation for once daily administration that provides initial delay in pharmaceutical release followed by controlled release of the pharmaceutical. It teaches a method for preparing a time specific delayed, controlled release formulation of dosage, which method includes coating a single pellet with at least one dosage layer, which is coated by at least one seal coat and at least one outer rate controlling layer of water soluble polymer coat. The dosage formulation of this invention provides substantially a drug free interval of about 0 to 5 hours followed by a drug delivery interval at a rate permitting bioavailability thereof for up to about 24 hours. Following oral administration.(abstract).

The dosage formulations and methods of the present invention are useful for treating the foregoing morning pathologies because the present dosage formulations and methods provide therapeutically effective amounts of drug in a time specific controlled release manner, delivering drug to the blood stream at the time needed most. The once daily, prior to sleep administration of the dosage formulation of the invention provides an alternative to prior art dosage formulations, which require the presence of several core pellets, enteric coating polymers, organic acids and solvents, and extensive mixing of pellets to achieve a once a day effect, and/or do not achieve a sustained and optimal amount of drug at a time when needed most, see lines 24-37 in column 5.

According to the present invention, the time specific delayed release dosage formulation is characterized by having a biologically inert pellet coated by at least one layer of drug(s) in admixture with a suitable binder agent; which is coated with an outer layer referred to herein as "the rate controlling layer." See lines 3-8 in column 6.

The drug layer is applied to biologically inert pharmaceutically acceptable pellets in admixture with a suitable binder agent. Many types of pellets that are suitable for use in the methods and formulations of the present invention are commercially available from a number of pharmaceutical supply companies; for example, non-pareils, sugar and/or starch-based pellets. Non-pareil pellets of particle size 25 to 30 mesh are particularly preferred, although any non-pareil pellet of mesh size within the range of 14 mesh to 60 mesh are also preferred for use in this invention.

Suitable binder agents for use in the drug layer of the coated pellets of the present invention include, for example, water soluble polymers such as hydroxypropylmethyl cellulose (3 to 6 cps, preferably 6 cps), hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinylpyrrolidone and the like. Preferably, hydroxypropylmethyl cellulose, and most preferably, hydroxypropylmethyl cellulose-E-6 is used in the practice of the present invention. Preferably the amount of binder agent included in the drug layer is in a ratio of binder agent to drug of from about 0.5:20, preferably about 0.7:10, most preferably about 1:8. The drug layer may also contain a suitable carrier or diluent, and may optionally contain a surfactant.

In a preferred embodiment, the drug layer is coated with an optional sealing layer. The sealing layer contains a water soluble polymer, which may be the same or different from the binder agent present in the drug layer. For example, the sealing agent may include a water soluble polymer such as hydroxypropylmethyl cellulose (3 to 6 cps, preferably 6 cps), hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose,

polyvinylpyrrolidone and the like. Preferably, hydroxypropylmethyl cellulose, and most preferably, hydroxypropylmethyl cellulose-E-6 is used in the sealing layer.

In a preferred embodiment of the invention the binder agent in the drug layer and the innermost drug sealing layer is hydroxypropylmethyl cellulose and the outer rate controlling layer is Eudragit NE 30 D.

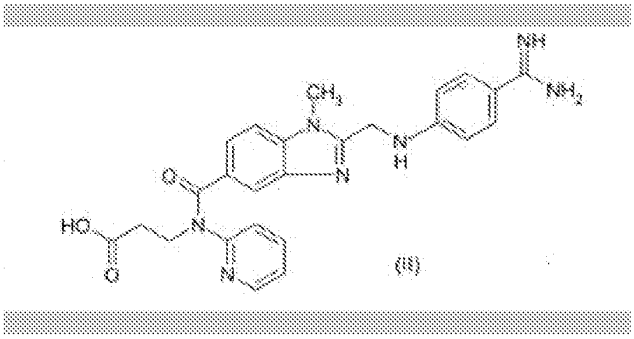
The outer rate controlling layer is prepared as dispersion and may be mixed with a suspension of lubricant agent, such as calcium stearate, magnesium stearate, zinc stearate, stearic acid, talc or a combination thereof to form the time specific controlled release coating mixture. In particular, it is preferred that the outer rate controlling layer contains an amount of magnesium stearate sufficient to provide delayed release of diltiazem for up to about 4-5 hours after administration. In another embodiment of the invention the outer rate controlling layer is coated with an enteric coating polymer, which may also contain a plasticizer. A preferred enteric coating polymer is Eudragit L 30D. Suitable plasticizers for inclusion in the enteric layer include, for example, triethyl citrate, polyethylene glycol, dibutyl phthalate, diethylphthalate and triacetin. The optional enteric coating, which is pH dependent and resistant to gastric fluids, may comprise from about 4 to 10%, preferably about 4 to 6% of the total weight of the diltiazem formulation. The enteric coating may also be coated with one or more layers of a sealant or a binding agent.

Preferably, the pharmaceutical loaded pellets of the invention provide in total a potency of approximately 50% (w/w) based upon the total weight of the layered pellets, although the potency can be adjusted as desired. When the pharmaceutical agent included in the layering is diltiazem, it is preferred that the pellet be formulated at about 45 to about 55% potency (w/w). However, the skilled practitioner can make the present dosage formulation at any desired drug potency.

Gruber teaches a core material comprising an organic acid, a drug layer and an additional outer layer. It teaches a formulation comprising an organic acid in the core such as citric or tartaric acid. The pellets are in size from 0.3-1mm (column 5, lines 13-30). The pellets are covered with an active layer which comprises a binder such as cellulose ethers such as methylcellulose and hydroxycellulose (col. 7, lines 50-65). The pellets are formed via known methods such as spheronization and fluidized bed formation and packaged into hard capsules (col. 8, lin. 4-16). The pellets are covered by an enteric protective polymer (line 1-10, col. 7). See the entire document, examples and claims.

Eisert et al. US '577 teach pharmaceutical compositions comprising an active substance layer and an outer layer. Core materials consists of an organic acid such as tartaric acid, citric acid, pellets that measure from 0.5-0.9 mm. The organic acid has water solubility of 13g/100ml. See the entire document.

Hauel et al. teaches a compound of formula (1), its composition, physiologically acceptable salts and method of use. See the entire document, especially claims, abstracts and examples. See example 90 in column 52 and claim 8, lines 61-67 in col. 18. It teaches physiologically acceptable salts of the compound. The reference teaches the compound. The specification also discloses that the active compound used in the claimed composition is known in the art. The compound is commonly known as BIBR 1048. The reference discloses that this compound has thrombin inhibiting effect and the effect of prolonging the thrombin time.



BASTIN et al. teaches the salt selection and optimization procedures for pharmaceutical new chemical entities. It teaches that salts are most commonly employed for modifying aqueous solubility, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form. It is possible to fully develop one salt form (abstract). See the entire document especially the abstract, (column 1, page 427), investigations into possibilities of salt formation (column 2, page 427), Table 1 on page 428, choice of the salt former (column 2 on page 428), second para on page 433, Table 2 on page 429, Table 3 on page 430, Table 7 on page 432 optimization of the drug substance form for development (column 2, page 433) and examples.

BERGE et al. teaches pharmaceutical salts and that salt performance can be predicted by considering some techniques. (See second paragraph in column 2, page 1). The reference teaches that mesylate salt is included in FDA approved commercially marketed salts (Table 1 on page 2). See the entire document especially, potentially useful salts on page 2, table III on page 5, where mesylate salt is included in potentially useful salt forms of pharmaceutical agents.

BACH teaches pharmaceutically acceptable additional salts of non-toxic organic acids which includes methanesulfonate (see the entire document especially lines 38-66

in column 2 and example 16. The reference teaches preferred methanesulfonate salt (lines 46-51 in column 13).

Furthermore, the reference teaches as preferred **additional soluble salt methanesulfonate salt in particular for intravenous or intramuscular administration**.

ILLUM teaches methane sulphonate salt of morphine and compositions thereof. These salts can provide physically stable aqueous solutions of the drug for parenteral or non-parenteral administration. The reference also teaches comparative stability of methanesulphonic salts (see example 3). See the entire document especially lines 43-67 in column 2; lines 30-61 in column 4; examples and claims.

**Ascertaining the differences between the prior art and the claims at issue**

Mehta, Gruber and Eisert does not teach specific compound which is used in present claim. They teach active substance at outer layer and using organic acids such as tartaric acid and citric acid which are in present claims. Hauel et al teaches the same compound as in claim 1 as thrombin inhibiting effect. Therefore in would have been obvious to apply the teaching of Mehta and Gruber to prepare a composition for oral administration containing active substance outside the core and contain organic acids preparing any pharmaceutical salts as taught by Bastin. For mesylate salt of BIBR as in claim 22 Berge, Bach and Ileum teaches mesylate salts and its advantages.

**Resolving the level of ordinary skill in the pertinent art and considering objective evidence present in the application indicating obviousness or nonobviousness**

It would have been obvious to one skilled in the art at the time of the invention to prepare a composition at the time the invention was filed where drug/active substance is outside layer and tartaric acid and citric acid (organic acids) are used in layer to keep the desired pH for solubility. One skilled in art would know to apply the said coatings taught by these references to compound of Hauel et al. discloses the same compound (BIBR) which is used in present invention to prepare formulations. One skilled in the art would know the salt selection and optimization procedures for pharmaceutical new or known chemical entities because Bastin reference teaches that salts are most commonly employed for modifying aqueous solubility, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form. It is possible to fully develop one salt form.

Therefore, it would have been obvious to one skilled in the art to prepare a pharmaceutical composition containing an organic acid and an active drug substance layer which is BIBR and one or more binders and optionally a separating agent that encloses said core material because the references cited above teach such compositions.

Examiner notes, that claim 22 recites another salt which is mesylate of the same compound as in claim 1 (BIBR 1048) which is considered obvious in view of teaching of Bastin. Berge, Ileum and Bach et al. are added to address mesylate salt compositions, the advantages of mesylate salts are especially taught by these references.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill might reasonably infer from the teachings. *In re opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA 1976). A reference is not limited to working examples. *In re Fracalossi* 215 USPQ 569 (CCPA 1982).

Accordingly, the burden of proof is upon applicants to show that instantly claimed subject matter is different and unobvious over those taught by prior art. See *In re Brown*, 173 USPQ 685, 688; *In re Best*, 195 USPQ 430 and *In re Marosi*, 218 USPQ 289, 293.

In absence of any criticality and/or unexpected results presently claimed invention is considered obvious over the prior art of record.

Applicants claim contain the term “comprising”. The transitional phrases "comprising", "consisting essentially of" and "consisting of" define the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., >Mars Inc. v. H.J. Heinz Co., 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term 'comprising,' the terms 'containing' and 'mixture' are open-ended.").< Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). >In Gillette Co. v. Energizer Holdings Inc., 405 F.3d 1367, 1371-73, 74 USPQ2d 1586, 1589-91 (Fed. Cir. 2005), the court held that a

claim to "a safety razor blade unit comprising a guard, a cap, and a group of first, second, and third blades" encompasses razors with more than three blades because the transitional phrase "comprising" in the preamble and the phrase "group of" are presumptively open-ended. "The word 'comprising' transitioning from the preamble to the body signals that the entire claim is presumptively open-ended." Id. In contrast, the court noted the phrase "group consisting of" is a closed term, which is often used in claim drafting to signal a "Markush group" that is by its nature closed. Id. The court also emphasized that reference to "first," "second," and "third" blades in the claim was not used to show a serial or numerical limitation but instead was used to distinguish or identify the various members of the group. Id.< See [MPEP 2111.03 Transitional Phrases [R-3]].

The Court has held that "the test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965). "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir.1997). An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

See KSR Supreme Court of United States Decision (Decided April 30, 2007, KSR INTERNATIONAL CO. v. TELEFLEX INC. et al. No. 04-1350) where it states that (1) “However, the issue is not whether a person skilled in the art had the motivation to combine the electronic control with an adjustable pedal assembly, but whether a person skilled in the art had the motivation to attach the electronic control to the support bracket of pedal assembly”. (2) "The results of ordinary innovation are not the subject of exclusive rights under the patent laws".

In the light of the forgoing discussion, the Examiner’s ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

***Claim Rejections - 35 USC § 112***

1. The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 2, -14 and 17, 19-22 rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Following reasons apply:

3. Claims depend on claim1 or 18 which is improper dependency on claim 18. Applicant should correct when responding to this office action.

## Response to Remarks

Applicant's response and RCE filed on 03/02/2011 is hereby acknowledged. New rejection is being made.

In order to expedite the prosecution Applicant may consider calling the Examiner to discuss any issues related to this office action.

## Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SABIHA N. QAZI whose telephone number is (571)272-0622. The examiner can normally be reached on any business day except Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melenie McCormick can be reached on (571) 272-8037. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/SABIHA N QAZI/

Primary Examiner, Art Unit 1629

| Notice of References Cited | Application/Control No. 11/381,890 | Applicant(s)/Patent Under Reexamination BRAUNS, ULRICH | |
|---|---|---|---|
| | Examiner SABIHA N. QAZI | Art Unit 1629 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-6,620,439 | 09-2003 | Mehta, Atul M. | 424/497 |
| * | B | US-6,015,577 | 01-2000 | Eisert et al. | 424/451 |
| * | C | US-4,438,091 | 03-1984 | Gruber et al. | 424/465 |
| * | D | US-6,120,802 | 09-2000 | Breitenbach et al. | 424/464 |
| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
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| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
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| | N | | | | | |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
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| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| INFORMATION DISCLOSURE STATEMENT BY APPLICATION (Not for submission under 37 CFR 1.99) (Use several sheets if necessary) Comparable to PTO/SB/08a (05-07) | | |
|---|---|---|
| | Application Number: | 11/381,890 |
| | Filing Date: | May 5, 2006 |
| | First Named Inventor: | Ulrich BRAUNS |
| | Art Unit: | 1628 |
| | Examiner Name: | Sabiha Naim QAZI |
| | Attorney Docket Number: | 01-1306-1-C1 |

| U.S. PATENTS | | | | | | |
|---|---|---|---|---|---|---|
| Examiner Initial* | Cite No. | Patent Number | Kind Code | Issue Date yyyy/mm/dd | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear or Relevant Comments |
| | | 3,887,705 | A | 1975/06/03 | Serre et al. | |
| | | 3,968,111 | A | 1976/07/06 | Bach et al. | |
| | | 4,572,833 | A | 1986/02/25 | Pedersen et al. | |
| | | 5,051,262 | A | 1991/09/24 | Panoz et al. | |
| | | 5,286,736 | A | 1994/02/15 | Soyka et al. | |
| | | 5,387,593 | A | 1995/02/07 | Mattson et al. | This patent appears to be an English language equivalent to EP 0 547 517. |
| | | 5,478,828 | A | 1995/12/26 | Mattson et al. | This patent appears to be an English language equivalent to EP 0 547 517. |
| | | 5,482,948 | A | 1996/01/09 | Soyka et al. | This patent appears to be an English language equivalent to EP 0 547 517. |
| | | 5,637,320 | A | 1997/06/10 | Bourke et al. | |
| | | 6,087,380 | A | 2000/07/11 | Hauel et al. | |
| | | 6,120,802 | A | 2000/09/19 | Breitenbach et al. | |
| | | 6,387,917 | B1 | 2002/05/14 | Illum et al. | |
| | | 6,414,008 | B1 | 2002/07/02 | Hauel et al. | |
| | | 7,070,805 | B2 | 2006/07/04 | Shimizu et al. | |

| U.S. PATENT APPLICATION PUBLICATIONS | | | | | | |
|---|---|---|---|---|---|---|
| Examiner Initial* | Cite No. | Publication Number | Kind Code | Publication Date yyyy/mm/dd | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear or Relevant Comments |
| | | 2001/0010825 | A1 | 2001/08/02 | Shimizu et al. | |
| | | 2004/0258749 | A1 | 2004/12/23 | Guldner et al. | This patent appears to be an English language equivalent to WO 2003/030869. |
| | | 2008/0317848 | A2 | 2008/12/25 | Gramatte et al. | This patent appears to be an English language equivalent to WO 2003/030869 (which is a Republication of 2004/0258749) |

| **Examiner**: /Sabiha Qazi/ | Date Considered: 06/16/2013 |
|---|---|
| *Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.Q./

| INFORMATION DISCLOSURE STATEMENT BY APPLICATION (Not for submission under 37 CFR 1.99) (Use several sheets if necessary) Comparable to PTO/SB/08a (05-07) | | |
|---|---|---|
| | Application Number: | 11/381,890 |
| | Filing Date: | May 5, 2006 |
| | First Named Inventor: | Ulrich BRAUNS |
| | Art Unit: | 1628 |
| | Examiner Name: | Sabiha Naim QAZI |
| | Attorney Docket Number: | 01-1306-1-C1 |

| FOREIGN PATENT DOCUMENTS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Examiner Initial* | Cite No. | Foreign Document Number | Country Code | Kind Code | Publication Date | Name of Patentee or Applicant of cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear or Relevant Comments | √[1] |
| | | 0 547 517 | EP | A1 | 1993/06/23 | Dr. Karl Thomae GmbH | US Patent No. 5,387,593; 5,478,828 and 5,482,948 cited herein appear to be English language equivalents. | |
| | | 2003/030869 | WO | A1 | 2003/04/17 | Apogepha Arzneimittel GmbH | US Patent Application Publication No. 2004/0258749 and 2008/0317848 cited herein appear to be English language equivalents. | |
| | | 2004/092129 | WO | A1 | 2004/10/28 | LG Life Sciences Ltd. | | |
| | | | | | | | | |

| NON-PATENT LITERATURE DOCUMENTS | | | |
|---|---|---|---|
| Examiner Initial* | 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. | √[2] |
| | | BERGE, STEPHEN, M; Pharmaceutical Salts; Journal of Pharmaceutical Sciences; Review Article (1977) Vol. 66, No. 1 pages 1-19. | |
| | | ~~International Search Report for PCT/EP03/02184 mailed August 12, 2003.~~ | |
| | | Non-Final Office Action dated June 29, 2007 from U.S. Application 10/934,140 filed September 3, 2004. | |
| | | Response dated December 31, 2007 from Non-Final Office Action dated June 29, 2007; U.S. Application 10/934, 140 filed on September 3, 2004. | |
| | | Non-Final Office Action dated April 4, 2008 from U.S. Application 10/934,140 filed September 3, 2004. | |
| | | Response dated July 2, 2008 from Non-Final Office Action dated April 4, 2008; U.S. Application 10/934, 140 filed on September 3, 2004. | |
| | | Final Office Action dated December 2, 2008 from U.S. Application 10/934,140 filed September 3, 2004. | |

[1] √ indicates English Language translation is attached

[2] √ indicates English Language translation is attached

| **Examiner**: /Sabiha Qazi/ | Date Considered: 06/16/2013 |
|---|---|
| *Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.Q./

IPR2025-01107
MSN Exhibit 1008
Page 20 of 304

| | | |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICATION** (Not for submission under 37 CFR 1.99) (Use several sheets if necessary) Comparable to PTO/SB/08a (05-07) | Application Number: | 11/381,890 |
| | Filing Date: | May 5, 2006 |
| | First Named Inventor: | Ulrich BRAUNS |
| | Art Unit: | 1628 |
| | Examiner Name: | Sabiha Naim QAZI |
| | Attorney Docket Number: | 01-1306-1-C1 |

| | | | |
|---|---|---|---|
| | | Response dated March 2, 2009 from Non-Final Office Action dated December 2, 2008; U.S. Application 10/934, 140 filed on September 3, 2004. | |
| | | Non-Final Office Action dated June 26, 2009 from U.S. Application 10/934,140 filed September 3, 2004. | |
| | | Response dated November 27, 2009 from Non-Final Office Action dated June 26, 2009; U.S. Application 10/934, 140 filed on September 3, 2004. | |
| | | Final Office Action dated March 25, 2010 from U.S. Application 10/934,140 filed September 3, 2004. | |

| | |
|---|---|
| **Examiner**: /Sabiha Qazi/ | Date Considered: 06/16/2013 |
| *Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.Q./

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11381890 | BRAUNS ET AL. |
| | **Examiner** | **Art Unit** |
| | Sabiha Qazi | 1628 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

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

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/11/2009 | 06/16/2013 | | | | | | | |
| | 1 | ✓ | ✓ | | | | | | | |
| | 2 | ✓ | ✓ | | | | | | | |
| | 3 | ✓ | ✓ | | | | | | | |
| | 4 | ✓ | ✓ | | | | | | | |
| | 5 | ✓ | ✓ | | | | | | | |
| | 6 | ✓ | ✓ | | | | | | | |
| | 7 | - | | | | | | | | |
| | 8 | ✓ | ✓ | | | | | | | |
| | 9 | ✓ | ✓ | | | | | | | |
| | 10 | ✓ | ✓ | | | | | | | |
| | 11 | ✓ | ✓ | | | | | | | |
| | 12 | ✓ | ✓ | | | | | | | |
| | 13 | ✓ | ✓ | | | | | | | |
| | 14 | ✓ | ✓ | | | | | | | |
| | 15 | - | N | | | | | | | |
| | 16 | - | | | | | | | | |
| | 17 | ✓ | ✓ | | | | | | | |
| | 18 | ✓ | ✓ | | | | | | | |
| | 19 | ✓ | ✓ | | | | | | | |
| | 20 | ✓ | ✓ | | | | | | | |
| | 21 | ✓ | ✓ | | | | | | | |
| | 22 | ✓ | ✓ | | | | | | | |

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11381890 | BRAUNS ET AL. |
| | Examiner | Art Unit |
| | Sabiha Qazi | 1628 |

| CPC- SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| CPC COMBINATION SETS - SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US CLASSIFICATION SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| 514 | 338, 576 | 10/08/10 | QAZI |
| 546 | 273.7 | 10/08/10 | QAZI |
| UPDATE | UPDATE | 06/16/2013 | QAZI |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| INVENTOR SEARCH, WEST | 10/09/10 | QAZI |
| TEXT SEARCH | 10/12/10 | QAZI |
| STN DATABASE SEARCH, REGISTRY, CAPLUS, TEXT SEARCH, INVENTOR SEARCH | 08/03/2009 | QAZI |
| STN DATBASE SEARCH, REGISTRY, HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS, INVENTOR SEARCH | 09/08/08 | QAZI |
| UPDATE | 06/16/2013 | QAZI |

| INTERFERENCE SEARCH | | | |
|---|---|---|---|
| US Class/ CPC Symbol | US Subclass / CPC Group | Date | Examiner |
| 514 | 338, 576 | 10/8/10 | QAZI |
| 546 | 273.7 | 10/8/10 | QAZI |

| | |
|---|---|
| | /SABIHA N QAZI/<br>Primary Examiner.Art Unit 1629 |

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

# REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
## (Submitted Only via EFS-Web)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Application Number | 11381890 | Filing Date | 2006-05-05 | Docket Number (if applicable) | 01-1306-1-C1- | Art Unit | 1628 |
| First Named Inventor | Ulrich BRAUNS | | | Examiner Name | Sabiha Naim QAZI | | |

**This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.**
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

### SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

### MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

### FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 022955

### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Signature of Registered U.S. Patent Practitioner | | | |
|---|---|---|---|
| Signature | /Wendy Petka/ | Date (YYYY-MM-DD) | 2011-03-02 |
| Name | Wendy A. Petka | Registration Number | 53459 |

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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

# Privacy Act Statement

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

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

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

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Application of | : Ulrich BRAUNS, et al. | ) Art Unit: | 1628 |
| U.S. Appln. No. | : 11/381,890 | ) Examiner: | Sabiha Naim QAZI |
| Confirmation No. | : 5127 | | |
| U.S. Filing Date | : May 5, 2006 | | |
| Title of Invention | : ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |
| Atty. Docket No. | : 01-1306-1-C1 | | |

VIA EFS Web
Director for Patents
Alexandria, VA 22313-1450

**CERTIFICATION STATEMENT, FEE AUTHORIZATION & TRANSMITTAL LETTER FOR INFORMATION DISCLOSURE STATEMENT**

Sir:

Transmitted herewith concerning the subject application is an Information Disclosure Statement (Form 1449A/B) under 37 C.F.R. §§1.56 and 1.97, as more specifically described hereinbelow.

☐ INFORMATION PREVIOUSLY CITED OR SUBMITTED
U. S. Application No. ("the parent application") is relied on by the above-identified application for an earlier effective filing date under 35 U.S.C. 120. The patents, publications, pending U. S. applications, or other information listed in the instant information disclosure statement were previously cited by the Office in the parent application or submitted to the Office in the parent application in an information disclosure statement that complied with 37 CFR 1.98(a)-(c). 37 CFR 1.98(d)

☒ 1.97(b). This Statement is being filed: i) within three (3) months of the filing date of a national application other than a continued prosecution application under 37 C.F.R. §1.53 (d); ii) within three (3) months of the date of entry of the national stage as set forth in 37 C.F.R. §1.491 in an international application; iii) before the mailing of a first Office action on the merits; or iv) before the mailing of a first Office action after the filing of a request for continued examination under 37 C.F.R. §1.114.

☐ 1.97(c). This Statement is being filed after the time period specified in 37 C.F.R. §1.97(b), but before the mailing date of: i) a final action under 37 C.F.R. §1.113, ii) a notice of allowance under 37 C.F.R. §1.311, or iii) an action that otherwise closes prosecution in the application. This Statement is being accompanied by:

☐ A statement as specified in 37 C.F.R. §1.97(e) [see below]; or

☐ The fee set forth in 37 C.F.R. §1.17(p).

☐ The Director is hereby authorized to charge payment of the $180.00 fee set forth in 37 C.F.R. §1.17(p) to Deposit Account No. 02-2955.

☐ 1.97(d). This Statement is being filed after the period specified in 37 C.F.R. §1.97(c) but on or before payment of the issue fee. This Statement is accompanied by a statement as specified in 37 C.F.R. §1.97(e) [see below] and the fee set forth in 37 C.F.R. §1.17(p).

☐ 1.97(e).

☐ Each item of information contained in the instant information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three (3) months prior to the filing of the instant information disclosure statement; or

☐ No item of information contained in the instant 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 this certification after making reasonable inquiry, no item of information contained in the instant information disclosure statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three (3) months prior to the filing of the instant information disclosure statement.

☐ The fee set forth in 37 C.F.R. §1.17(p).

☐ The Director is hereby authorized to charge payment of the $180.00 fee set forth in 37 C.F.R. §1.17(p) to Deposit Account No. 02-2955.

☐ 1.704(d). Each item of information contained in the accompanying information disclosure statement was first cited in any communication from a foreign patent office in a counterpart application, which communication was not received by any individual designated in section 1.56(c) more than thirty (30) days prior to the filing of the accompanying information disclosure statement.

☒ The Director is hereby authorized to charge payment of any additional filing fees required under 37 C.F.R. §1.16 and any patent application processing fees under 37 C.F.R. §1.17, or credit any overpayment of same, to Deposit Account No. 02-2955.

International Search Report and Non-English Language References

☒ An English-language search report or equivalent paper from a foreign patent office is provided.

☒ A foreign-language search report or equivalent paper from a foreign patent office is provided, and pertinent parts are translated substantively below:

X = document of particular relevance when it is taken alone

Y = document of particular relevance when it is combined with another such document

A = document defining the general state of the art

O = non-written disclosure

P = intervening document

T = document cited to understand the theory or principle underlying the invention

E = patent document which has the benefit of a date earlier than the filing date and which was published only on or after this filing date

D = cited in the application

L = cited for another reason

& = publication of member of same patent family

☒ Translation of other relevant information on foreign search report:

In the search report, "Seite" means page, "Seiten" means pages, "Verbindungen der Formel" means Compounds of formula, "Beispiele" means examples, and "das ganze Dokument" means the entire document, "Spalte" means column, "Zeile" means line, "Abbildungen" means Figures, "Anspruch" means Claim, "Zusammenfassung" means abstract/summary, and "Tabelle" means table, and "Tabellen" means tables "in der Anmeldung erwaehnt" means cited in the application, "Schema" means scheme, "und" means and, "Absatz" means paragraph, "abbildung" means figure, "Absendedatum" means date of dispatch, "Anmeldetag" means filing date, "Eintragungstag" means registration date, and Bekanntmachung im Patentblatt" means publication date in the official journal.

Respectfully submitted,

/Wendy Petka/
Wendy A. Petka
Attorney for Applicants
Reg. No. 53,459

Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877
Tel: (203) 791-6614
Fax: (203) 798-4408

Dated: March 2, 2011

# INTERNATIONAL SEARCH REPORT

Ir onal Application No
PCT/EP 03/02184

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0 547 517 A (THOMAE GMBH DR K)<br>23 June 1993 (1993-06-23)<br>page 50, line 23 - line 28<br>--- | 1-11 |
| X | US 4 438 091 A (BAUER ECKHART ET AL)<br>20 March 1984 (1984-03-20)<br>column 3, line 30 - line 48<br>column 4, line 29 - line 57<br>column 7, line 24 -column 8, line 19 | 1-11 |
| Y | examples 1,2,5<br>--- | 1-11 |
| Y | PATENT ABSTRACTS OF JAPAN<br>vol. 007, no. 248 (C-193),<br>4 November 1983 (1983-11-04)<br>& JP 58 134033 A (FUJISAWA YAKUHIN KOGYO KK;OTHERS: 01),<br>10 August 1983 (1983-08-10)<br>abstract<br>---<br>-/-- | 1-11 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 1 August 2003 | 12/08/2003 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | VON EGGELKRAUT, S |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02184

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| E | WO 03 030869 A (SCHEITHAUER STEFFEN ;PAMPERIN DIRK (DE); PLOEN JAN (DE); GRAMATTE) 17 April 2003 (2003-04-17) page 3, line 5 -page 4, line 4 page 7, line 5 - line 32 page 16 -page 17; example 2 | 1-11 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

| Patent document cited in search report | Publication date | Patent familiy member(s) | Publication date |
|---|---|---|---|

Continuation of I.2

The current Claims 1-11 relate to a product and method defined (*inter alia*) by the following parameters: P1: active ingredient for oral administration with a dosage number greater than 1 at pH >5.
In the given context the use of these parameters has to appear to be lacking in clarity (PCT Article 6). It is impossible to compare the parameters chosen by the applicant with the relevant disclosure in the prior art. The lack of clarity is such that it makes it impossible to conduct a meaningful complete search. The search was therefore limited to pharmaceutical preparations comprising a large number of pellets consisting of a core material, a layer of active ingredient, optionally an insulating layer and optionally a coating, the core material being an organic acid, possibly with other adjuvants. As active ingredients the substances named on page 1, lines 18-32, were included in the search.

The applicant is advised that claims or parts of claims relating to inventions in respect of which no international search report has been established normally cannot be the subject of an international preliminary examination (PCT Rule 66.1(e)). In its capacity as International Preliminary Examining Authority the EPO generally will not carry out a preliminary examination for subjects that have not been searched. This also applies to cases where the claims were amended after receipt of the international search report (PCT Article 19) or where the applicant submits new claims in the course of the procedure under PCT Chapter II.



IPR2025-01107
MSN Exhibit 1008
Page 32 of 304

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/02184

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MSN Exhibit 1008
Page 33 of 304

# INTERNATIONALER RECHERCHENBERICHT

| | onales Aktenzeichen |
|---|---|
| | PCT/EP 03/02184 |

**A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES**
IPK 7 A61K9/16 A61K9/50

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

**B. RECHERCHIERTE GEBIETE**

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole )
IPK 7 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE, PAJ

**C. ALS WESENTLICH ANGESEHENE UNTERLAGEN**

| Kategorie° | Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile | Betr. Anspruch Nr. |
|---|---|---|
| X | EP 0 547 517 A (THOMAE GMBH DR K)<br>23. Juni 1993 (1993-06-23)<br>Seite 50, Zeile 23 - Zeile 28<br>--- | 1-11 |
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| Y | Beispiele 1,2,5<br>--- | 1-11 |
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[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist
"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist
"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist
"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

| Datum des Abschlusses der internationalen Recherche | Absendedatum des internationalen Recherchenberichts |
|---|---|
| 1. August 2003 | 12/08/2003 |

| Name und Postanschrift der Internationalen Recherchenbehörde | Bevollmächtigter Bediensteter |
|---|---|
| Europäisches Patentamt, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | VON EGGELKRAUT, S |

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

## INTERNATIONALER RECHERCHENBERICHT

| | |
|---|---|
| | ›nales Aktenzeichen |
| | PCT/EP 03/02184 |

**C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN**

| Kategorie° | Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile | Betr. Anspruch Nr. |
|---|---|---|
| E | WO 03 030869 A (SCHEITHAUER STEFFEN ;PAMPERIN DIRK (DE); PLOEN JAN (DE); GRAMATTE) 17. April 2003 (2003-04-17) Seite 3, Zeile 5 -Seite 4, Zeile 4 Seite 7, Zeile 5 - Zeile 32 Seite 16 -Seite 17; Beispiel 2 | 1-11 |

Formblatt PCT/ISA/210 (Fortsetzung von Blatt 2) (Juli 1992)

## INTERNATIONALER RECHERCHENBERICHT

...nationales Aktenzeichen
PCT/EP 03/02184

**Feld I** Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 2 auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. ☐ Ansprüche Nr.
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich

2. ☒ Ansprüche Nr.
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich

siehe Zusatzblatt WEITERE ANGABEN PCT/ISA/210

3. ☐ Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

**Feld II** Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 3 auf Blatt 1)

Die internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. ☐ Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche.

2. ☐ Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die Behörde nicht zur Zahlung einer solchen Gebühr aufgefordert.

3. ☐ Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.

4. ☐ Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

**Bemerkungen hinsichtlich eines Widerspruchs**

☐ Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.

☐ Die Zahlung zusätzlicher Recherchengebühren erfolgte ohne Widerspruch.



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WEITERE ANGABEN PCT/ISA/ 210

Fortsetzung von Feld I.2

Die geltenden Patentansprüche 1-11 sind auf ein Produkt/Verfahren, das (u.a.) mittels folgender Parameter definiert wird, zu beziehen:
P1: Wirkstoff zur oralen Verbareichung mit einer Dosenumber groesser als 1 bei pH>5.
Die Verwendung dieser Parameter muss im gegebenen Zusammenhang als Mangel an Klarheit im Sinne von Art. 6 PCT erscheinen. Es ist unmöglich, die vom Anmelder gewählten Parameter mit dem zu vergleichen, was der Stand der Technik hierzu offenbart. Der Mangel an Klarheit ist dergestalt, daß er eine sinnvolle vollständige Recherche unmöglich macht. Daher wurde die Recherche beschränkt auf pharmazeutische Zusammensetzungen umfassend eine Vielzahl von Pellets, die jeweils aus einem Kernmaterial, einer Wirkstoffschicht und optional einer Isolierschicht und optional aus einem Überzug besteht, wobei das Kernmaterial eine organische Säure ist, evtl. mit anderen Hilfstoffen. Als Wirkstoffe wurden die auf Seite 1, Zeilen 18-32 genannten Stoffe in die Suche miteinbezogen.

Der Anmelder wird darauf hingewiesen, daß Patentansprüche, oder Teile von Patentansprüchen, auf Erfindungen, für die kein internationaler Recherchenbericht erstellt wurde, normalerweise nicht Gegenstand einer internationalen vorläufigen Prüfung sein können (Regel 66.1(e) PCT). In seiner Eigenschaft als mit der internationalen vorläufigen Prüfung beauftragte Behörde wird das EPA also in der Regel keine vorläufige Prüfung für Gegenstände durchführen, zu denen keine Recherche vorliegt. Dies gilt auch für den Fall, daß die Patentansprüche nach Erhalt des internationalen Recherchenberichtes geändert wurden (Art. 19 PCT), oder für den Fall, daß der Anmelder im Zuge des Verfahrens gemäß Kapitel II PCT neue Patentansprüche vorlegt.

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Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internales Aktenzeichen
PCT/EP 03/02184

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MSN Exhibit 1008
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|---|---|---|
| | Application Number: | 11/381,890 |
| | Filing Date: | May 5, 2006 |
| | First Named Inventor: | Ulrich BRAUNS |
| | Art Unit: | 1628 |
| | Examiner Name: | Sabiha Naim QAZI |
| | Attorney Docket Number: | 01-1306-1-C1 |

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| Examiner Initial* | Cite No. | Patent Number | Kind Code | Issue Date yyyy/mm/dd | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear or Relevant Comments |
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| Examiner Initial* | Cite No. | Publication Number | Kind Code | Publication Date yyyy/mm/dd | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear or Relevant Comments |
| | | 2001/0010825 | A1 | 2001/08/02 | Shimizu et al. | |
| | | 2004/0258749 | A1 | 2004/12/23 | Guldner et al. | This patent appears to be an English language equivalent to WO 2003/030869. |
| | | 2008/0317848 | A2 | 2008/12/25 | Gramatte et al. | This patent appears to be an English language equivalent to WO 2003/030869 (which is a Republication of 2004/0258749) |

| **Examiner**: | Date Considered: |
|---|---|
| *Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | |

| INFORMATION DISCLOSURE STATEMENT BY APPLICATION (Not for submission under 37 CFR 1.99) (Use several sheets if necessary) Comparable to PTO/SB/08a (05-07) | | |
|---|---|---|
| | Application Number: | 11/381,890 |
| | Filing Date: | May 5, 2006 |
| | First Named Inventor: | Ulrich BRAUNS |
| | Art Unit: | 1628 |
| | Examiner Name: | Sabiha Naim QAZI |
| | Attorney Docket Number: | 01-1306-1-C1 |

| FOREIGN PATENT DOCUMENTS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Examiner Initial* | Cite No. | Foreign Document Number | Country Code | Kind Code | Publication Date | Name of Patentee or Applicant of cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear or Relevant Comments | √[1] |
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| | | | | | | | | |

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|---|---|---|---|
| Examiner Initial* | 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. | √[2] |
| | | BERGE, STEPHEN, M; Pharmaceutical Salts; Journal of Pharmaceutical Sciences; Review Article (1977) Vol. 66, No. 1 pages 1-19. | |
| | | International Search Report for PCT/EP03/02184 mailed August 12, 2003. | |
| | | Non-Final Office Action dated June 29, 2007 from U.S. Application 10/934,140 filed September 3, 2004. | |
| | | Response dated December 31, 2007 from Non-Final Office Action dated June 29, 2007; U.S. Application 10/934, 140 filed on September 3, 2004. | |
| | | Non-Final Office Action dated April 4, 2008 from U.S. Application 10/934,140 filed September 3, 2004. | |
| | | Response dated July 2, 2008 from Non-Final Office Action dated April 4, 2008; U.S. Application 10/934, 140 filed on September 3, 2004. | |
| | | Final Office Action dated December 2, 2008 from U.S. Application 10/934,140 filed September 3, 2004. | |

[1] √ indicates English Language translation is attached

[2] √ indicates English Language translation is attached

| **Examiner**: | Date Considered: |
|---|---|
| *Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | |



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MSN Exhibit 1008
Page 40 of 304

| INFORMATION DISCLOSURE STATEMENT BY APPLICATION (Not for submission under 37 CFR 1.99) (Use several sheets if necessary) Comparable to PTO/SB/08a (05-07) | | |
|---|---|---|
| | Application Number: | 11/381,890 |
| | Filing Date: | May 5, 2006 |
| | First Named Inventor: | Ulrich BRAUNS |
| | Art Unit: | 1628 |
| | Examiner Name: | Sabiha Naim QAZI |
| | Attorney Docket Number: | 01-1306-1-C1 |

| | | | |
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| **Examiner**: | Date Considered: |
|---|---|
| *Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | |



**IPR2025-01107**
**MSN Exhibit 1008**
**Page 41 of 304**

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11381890 |
| **Filing Date:** | 05-May-2006 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Filer:** | Wendy Ann Petka/Beatriz Guerra |
| **Attorney Docket Number:** | 01-1306-1-C1 |

Filed as Large Entity

## Utility under 35 USC 111(a) Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| Request for continued examination | 1801 | 1 | 810 | 810 |
| | | **Total in USD ($)** | | **810** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 9568604 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28519 |
| **Filer:** | Wendy Ann Petka/Beatriz Guerra |
| **Filer Authorized By:** | Wendy Ann Petka |
| **Attorney Docket Number:** | 01-1306-1-C1 |
| **Receipt Date:** | 02-MAR-2011 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 14:23:00 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $810 |
| RAM confirmation Number | 656 |
| Deposit Account | 022955 |
| Authorized User | |
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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Request for Continued Examination (RCE) | 01-1306-1-C1-2011-03-02-RCE.pdf | 768739<br>fe40a65816c0e4597e64df583bdd1ef72ebcf326 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Transmittal Letter | 01-1306-1-C1-2011-03-02-IDSTransmittal.pdf | 31023<br>7cbd908a850555425291e0e242e2b77651c59cb7 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Foreign Reference | EP0547517.pdf | 3011698<br>725511128a8ed6c9e67b41d97e61bfc47784f5d8 | no | 57 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Foreign Reference | WO03030869.pdf | 2792217<br>6569d27c909afc4863db72031a28d76c5e56602d | no | 66 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Foreign Reference | WO2004092129.pdf | 1011057<br>545e2499e9647e32826d87680ea5796c7ab171d5 | no | 30 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | NPL Documents | 01-1307-ISR.pdf | 2218092<br>9e4b95e80836997873447e09de58c3d49a147802 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 7 | NPL Documents | 01-1307-2007-06-29-OA.pdf | 347744<br>2eab47f7859f6e88c78774ed2479058f4aff14f7 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 8 | NPL Documents | 01-1307-2007-12-31-Resp-OA-Supp-IDS.pdf | 155150<br>bdbff7a25e2bbc891f4a9b3424af1bfd3496b954 | no | 20 |

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|---|---|---|---|---|---|
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | NPL Documents | 01-1307-2008-04-04-OA.pdf | 232149<br>31a88927b642cb8f52ae3fcfda541cb2652a97b9 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 10 | NPL Documents | 01-1307-2008-07-02-ROA.pdf | 42868<br>f0fc450d8e88612ddf269d088471a9d6cf371a1d | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 11 | NPL Documents | 01-1307-2008-12-02-FOA.pdf | 446238<br>a04777d89ee0ac3a3c40b0aa8d14b9e81b8bc2e2 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 12 | NPL Documents | 01-1307-2009-03-02-Reply-Final-Rejection.pdf | 51298<br>7d5644cf7c75f16ba21b26b6bfd9cb8e636545f7 | no | 11 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 13 | NPL Documents | 01-1307-2009-06-26-OA.pdf | 287970<br>4e8d3d4ea76f3e999614d7eb15f2c89ec37b468d | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 14 | NPL Documents | 01-1307-2009-11-27-ROA-IFW.pdf | 519125<br>ecfc5a8b1edd0a5f636ad66b207a360b0c33b268 | no | 16 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 15 | NPL Documents | 01-1307-2010-03-25-FOA.pdf | 286429<br>c6407607b595c4d3272708652e77d954e6aff612 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 16 | Information Disclosure Statement (IDS) Filed (SB/08) | 01-1306-1-C1-2011-03-02-IDSForm.pdf | 38370<br>95f795bd109451313f0ecd952c8a430f9536fefc | no | 3 |
| **Warnings:** | | | | | |
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| 17 | NPL Documents | Berge-1-19.pdf | 2492975<br>43e99d443e6cf938173f1eac07ea2e9d44c93756 | no | 19 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 18 | Fee Worksheet (PTO-875) | fee-info.pdf | 31395<br>2101aa82072b69e1115b408cc578963537cfed40 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 14764537 | | |

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**New International Application Filed with the USPTO as a Receiving Office**
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

| Complete if Known | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | ~~1614~~ 1616 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No [1] | Document Number Number-Kind Code [2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | US- 4,675, 405 A | 6/1987 | Musser, et al | |
| | | US- 5,416,099 A | 5/1995 | Hartman, et al | |
| | | US- 6,414,008 B1 | 7/2002 | Hausel, et al | |
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| | | US- 4,367,217 | 01/04/1983 | Gruber, et al | |
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| | | US- 5,434,150 | 07/18/1995 | Austel, V. et al | |
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| | | US- | | | |

Change(s) applied to document,
/A.M./
2/14/2011

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No [1] | Foreign Patent Document Country Code [3] Number [4] Kind Code [5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T [6] |
|---|---|---|---|---|---|---|
| | | DE 102 45 624 A1 | 04/08/2004 | BI Pharma GmbH | English Abstract for DE 102 45 624 | |
| SR | | DE 41 29 603 A1 | 03/11/1993 | Dr. Karl Thomae | XR: US 5,434,150 | |
| | | EP 0 540 051 A1 | 05/05/1993 | Dalichi Pharm. Co. | | |
| | | EP 0 623 596 A1 | 11/09/1994 | Bristol-Myers Squibb | | |
| | | EP 0 655 439 A2 | 05/31/1995 | Eli Lilly and Co. | | |

| Examiner Signature | SABIHA QAZI | Date Considered | 3/31/07 |
|---|---|---|---|

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 01-1306-1-C1 | 5127 |

28519 7590 01/28/2011

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |
| ART UNIT | PAPER NUMBER |
| 1628 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 01/28/2011 | ELECTRONIC |

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

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| APPLICATION NO./ CONTROL NO. | FILING DATE | FIRST NAMED INVENTOR / PATENT IN REEXAMINATION | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 11381890 | 5/5/2006 | BRAUNS ET AL. | 01-1306-1-C1 |

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

| EXAMINER | |
|---|---|
| Sabiha Qazi | |
| **ART UNIT** | **PAPER** |
| 1628 | 20110124 |

DATE MAILED:

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**Commissioner for Patents**

Please note the following:
1. The request R48 filed by Applicants on 02/02/2007 to correct the inventorship by deleting Inventor Norbert Hauel is accepted and his name wil be deleted as requested.
2. Please find enclosed a copy of issue classification containing the corrected claim index. Claim 18 is renumbered as claim 2 so that the renumbered claims will depend on a lower numbered claim.

Communication
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day except Wednesday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fetterolf Brandon can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sabiha Qazi/
Primary Examiner, Art Unit 1628

PTO-90C (Rev.04-03)

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11381890 | BRAUNS ET AL. |
| | **Examiner** | **Art Unit** |
| | Sabiha Qazi | 1628 |

| ORIGINAL | | INTERNATIONAL CLASSIFICATION | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CLASS | SUBCLASS | CLAIMED | | | | | NON-CLAIMED | | | | | | | | | |
| 514 | 338 | A | 6 | 1 | K | 47 / 00 (2006.01.01) | | | | | | | | | | |
| CROSS REFERENCE(S) | | A | 6 | 1 | K | 31 / 495 (2006.01.01) | | | | | | | | | | |
| CLASS | SUBCLASS (ONE SUBCLASS PER BLOCK) | | | | | | | | | | | | | | | |
| 514 | 576 | | | | | | | | | | | | | | | |
| 546 | 273.7 | | | | | | | | | | | | | | | |

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

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 15 | 17 | | | | | | | | | | | | |
| 3 | 2 | 2 | 18 | | | | | | | | | | | | |
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| 6 | 5 | 18 | 21 | | | | | | | | | | | | |
| 7 | 6 | 19 | 22 | | | | | | | | | | | | |
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| - | 15 | | | | | | | | | | | | | | |
| - | 16 | | | | | | | | | | | | | | |

| NONE<br><br>(Assistant Examiner) (Date) | **Total Claims Allowed:**<br>19 | |
|---|---|---|
| /Sabiha Qazi/<br>Primary Examiner.Art Unit 1628 01/24/2011<br><br>(Primary Examiner) (Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>1 |



IPR2025-01107
MSN Exhibit 1008
Page 51 of 304

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28519 7590 12/14/2010

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |
| ART UNIT | PAPER NUMBER |
| 1628 | |

DATE MAILED: 12/14/2010

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 01-1306-1-C1 | 5127 |

TITLE OF INVENTION: ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PI ACID ETHYL ESTER AND THE SALTS THEREOF

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1510 | $300 | $0 | $1810 | 03/14/2011 |

**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.**

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PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

IPR2025-01107
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28519 7590 12/14/2010

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|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 01-1306-1-C1 | 5127 |

TITLE OF INVENTION: ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PI ACID ETHYL ESTER AND THE SALTS THEREOF

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1510 | $300 | $0 | $1810 | 03/14/2011 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| QAZI, SABIHA NAIM | 1628 | 514-338000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
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2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

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

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

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

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

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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 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, 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.

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**IPR2025-01107**
**MSN Exhibit 1008**
**Page 53 of 304**

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Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 01-1306-1-C1 | 5127 |

28519 7590 12/14/2010

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |
| ART UNIT | PAPER NUMBER |
| 1628 | |

DATE MAILED: 12/14/2010

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

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

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

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

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



PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

| Notice of Allowability | Application No. | Applicant(s) | |
|---|---|---|---|
| | 11/381,890 | BRAUNS ET AL. | |
| | Examiner | Art Unit | |
| | Sabiha Qazi | 1628 | |

*-- 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 *7/22/10*.

2. ☒ The allowed claim(s) is/are *1-6,8-14 and 17-22*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   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. *10/383,198* .
      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**.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ 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. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 9/21/07,9/10/07,9/20/06
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *10/25/10* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☒ Other *Corrected IDS filed on 4/9/2007*.

/Sabiha Qazi/
Primary Examiner, Art Unit 1628



**IPR2025-01107**
**MSN Exhibit 1008**
**Page 55 of 304**

| *Examiner-Initiated Interview Summary* | Application No. 11/381,890 | Applicant(s) BRAUNS ET AL. | |
|---|---|---|---|
| | Examiner Sabiha Qazi | Art Unit 1628 | |

**All Participants:**

(1) *Sabiha Qazi, Ph. D. (Examiner)*.

(2) *John A. Sopp (Attorney)*.

**Status of Application:** _____

(3) _____.

(4) _____.

**Date of Interview:** *25 October 2010*

**Time:** _____

**Type of Interview:**
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☐ No
If Yes, provide a brief description: .

**Part I.**

Rejection(s) discussed:
*N/A*

Claims discussed:
*1, 15, 14, 18, 21 and 22*

Prior art documents discussed:
*N/A*

**Part II.**

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
*See Continuation Sheet*

**Part III.**

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.
☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

/Sabiha Qazi/
Primary Examiner, Art Unit 1628

(Applicant/Applicant's Representative Signature – if appropriate)



**IPR2025-01107**
**MSN Exhibit 1008**
**Page 56 of 304**

Continuation of Substance of Interview including description of the general nature of what was discussed: Examiner called to discuss a copending application 10/934,140 for double patenting. Claims of the present application are considered obvious over the claims of copending application. The application is not on record. Mr. Sopp told the Examiner that he will file a terminal disclaimer in the copending application.
Examiner also requested to cancel claim 15 which is a withdrawn claim. Mr. Sopp has authorized the examiner to cancel claim 15 by examiner's amendment. .

**EXAMINER'S AMENDMENT**

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

Authorization for this examiner's amendment was given in a telephone interview with Attorney John A. Sopp on 10/25/10.

The application has been amended as follows:

Withdrawn claim 15 is cancelled.

**Communication**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day except Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fetterolf Brandon can be reached on (571) 272-2919. The

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Sabiha Qazi/
Primary Examiner, Art Unit 1628

| Notice of References Cited | Application/Control No. 11/381,890 | Applicant(s)/Patent Under Reexamination BRAUNS ET AL. | |
|---|---|---|---|
| | Examiner Sabiha Qazi | Art Unit 1628 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-6,015,577 | 01-2000 | Eisert et al. | 424/451 |
| | B | US- | | | |
| | C | US- | | | |
| | D | US- | | | |
| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11381890 | BRAUNS ET AL. |
| | Examiner | Art Unit |
| | Sabiha Qazi | 1628 |

| SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| 514 | 338, 576 | 10/08/10 | QAZI |
| 546 | 273.7 | 10/08/10 | QAZI |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| INVENTOR SEARCH, WEST | 10/09/10 | QAZI |
| TEXT SEARCH | 10/12/10 | QAZI |
| STN DATABASE SEARCH, REGISTRY, CAPLUS, TEXT SEARCH, INVENTOR SEARCH | 08/03/2009 | STIC |
| STN DATBASE SEARCH, REGISTRY, HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS, INVENTOR SEARCH | 09/08/08 | STIC |

| INTERFERENCE SEARCH | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| 514 | 338, 576 | 10/8/10 | QAZI |
| 546 | 273.7 | 10/8/10 | QAZI |

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|---|---|
| | /Sabiha Qazi/<br>Primary Examiner.Art Unit 1628 |

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11381890 | BRAUNS ET AL. |
| | **Examiner** | **Art Unit** |
| | Sabiha Qazi | 1628 |

| ORIGINAL | | INTERNATIONAL CLASSIFICATION | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CLASS | SUBCLASS | CLAIMED | | | | | NON-CLAIMED | | | | | | | | | |
| 514 | 338 | A | 6 | 1 | K | 47 / 00 (2006.01.01) | | | | | | | | | | |
| CROSS REFERENCE(S) | | A | 6 | 1 | K | 31 / 495 (2006.01.01) | | | | | | | | | | |
| CLASS | SUBCLASS (ONE SUBCLASS PER BLOCK) | | | | | | | | | | | | | | | |
| 514 | 576 | | | | | | | | | | | | | | | |
| 546 | 273.7 | | | | | | | | | | | | | | | |

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

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
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| 5 | 5 | 18 | 21 | | | | | | | | | | | | |
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| - | 16 | | | | | | | | | | | | | | |

| NONE | **Total Claims Allowed:** | |
|---|---|---|
| (Assistant Examiner) (Date) | 19 | |
| /Sabiha Qazi/<br>Primary Examiner.Art Unit 1628 10/26/2010 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) (Date) | 1 | 1 |



IPR2025-01107
MSN Exhibit 1008
Page 62 of 304

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

| Complete if Known | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | 1614 1616 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No 1 | Document Number Number-Kind Code2 (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | US- 4,675, 405 A | 6/1987 | Musser, et al | |
| | | US- 5,416,099 A | 5/1995 | Hartman, et al | |
| | | US- 6,414,008 B1 | 7/2002 | Hausel, et al | |
| | | US- 6,469,039 B1 | 10/2002 | Hausel, et al | |
| | | US- 2003/0004181 A1 | 1/2003 | Hausel, et al | |
| | | US- 6,710,055 B2 | 3/2004 | Hausel, et al | |
| | | US- 6,087,380 | 7/2000 | Hausel, et al | |
| | | US- 2005/0234104 A1 | 10/2005 | Schmid, et al | |
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| | | US- 4,367,217 | 01/04/1983 | Gruber, et al | |
| | | US- 5,800,836 | 09/01/1998 | Morella, et al | |
| | | US- 5,434,150 | 07/18/1995 | Austel, V. et al | |
| | | US- | | | |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No 1 | Foreign Patent Document Country Code3 Number 4 Kind Code5 (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T6 |
|---|---|---|---|---|---|---|
| | | DE 102 45 624 A1 | 04/08/2004 | BI Pharma GmbH | English Abstract for DE 102 45 624 | |
| | | DE 41 29 603 A1 | 03/11/1993 | Dr. Karl Thomae | XR: US 5,434,150 | |
| | | EP 0 540 051 A1 | 05/05/1993 | Dalichi Pharm. Co. | | |
| | | EP 0 623 596 A1 | 11/09/1994 | Bristol-Myers Squibb | | |
| | | EP 0 655 439 A2 | 05/31/1995 | Eli Lilly and Co. | | |

| Examiner Signature | SABIHA QAZI | Date Considered | 3/31/07 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional) 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3) 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible 6 Applicant is to place a check mark here if English language Translation is attached

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 4

| Complete if Known | |
|---|---|
| Application Number | 11/381,690 |
| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | 1614 1616 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No 1 | Document Number Number-Kind Code2 (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | US- | | | |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No 1 | Foreign Patent Document Country Code3 Number4 Kind Code5 (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | |
|---|---|---|---|---|---|---|
| | | WO 98/37075 | 08/27/1998 | BI Pharma KG | | |
| SBQ | | WO 03/007984 | 01/30/2003 | BI Pharma KG | | |
| | | DE 19752843 A1 | 07/01/1999 | Altana Pharma AG | English Abstract Enclosed | |
| | | EP 0088191 A2 | 01/05/1983 | Dr. Karl Thomae | XR: US 4,427,648 | |
| | | EP 0032562 A1 | 07/29/1981 | Dr. Karl Thomae | XR: US 4,367,217 | |

| Examiner Signature | SABIHA QAZI | Date Considered | 3/31/07 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

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

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 3 of 4

| Complete if Known | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | 1614 1615 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

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| Examiner Initials* | Cite No.[1] | Document Number Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| SQ | | WO 94/03160 | 02/17/1994 | FH Faulding & Co. | XR: US 5,800,836 | |
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| Examiner Signature | SABIHA QAZI | Date Considered | 3/31/07 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 4 of 4

| *Complete If Known* | |
|---|---|
| *Application Number* | 11/381,890 |
| *Filing Date* | 05/05/2006 |
| *First Named Inventor* | U. BRAUNS, et al. |
| *Art Unit* | 1614 ~ 1615 |
| *Examiner Name* | Sabiha Naim Qazi |
| *Attorney Docket Number* | 1/1308-1-C1 |

**NON PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc ), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | | HAUEL, N. H , "Structure-Based Design of Novel Potent Nonpeptide Thrombin Inhibitors", J Med. Chem. 2002, 45, 1757-1766, XP-001088844 | |
| | | CAIRA, M. R.; "Crystalline Polymorphism of Organic Compounds", Topics in Current Chemistry, Bd. 198, XP 001156954, pp 163-208 , 1998 . | |
| | | NAGAHARA, T. ET AL, "Dibasic (Amidinoaryl) propanoic Acid Derivatives as Novel Blood Coagulation Factor Xa Inhibitors", J. Med. Chem. 1994, 37, pgs 1200-1207 | |
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| SQ | | MUNGALL, Dennis, , BIBR-1048 Boehringer Ingelheim, Current Opinion in Investigational Drugs, 2002 3(6) 905-907 - XP-001147306 | |
| | | STANGIER, ET AL; Abstract of J thrombosis and Haemotosis, Vol. 1, Supplement 1, July 12-18, 2003 | |
| | | GUSTAFSSON, D , Abstract of J. Intern. Med 2003, Oct 254 (4); 322-34; PMID: 12974871 | |
| | | STANGIER, ET AL; Abstract of The J. of Clinical Pharmacology, 2005; 45: 555-563 | |
| | | | |
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| Examiner Signature | SABIHA QAZI | Date Considered | 3/31/07 |
|---|---|---|---|

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1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.
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Alexandria, Virginia 22313-1450
www.uspto.gov

# BIB DATA SHEET

**CONFIRMATION NO. 5127**

| SERIAL NUMBER | FILING or 371(c) DATE<br>RULE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | 514 | 1628 | 01-1306-1-C1 |

**APPLICANTS**

Ulrich Brauns, Biberach, GERMANY;
Norbert Hauel, Schemmerhofen, GERMANY;

**** CONTINUING DATA ***************************

This application is a CON of 10/383,198 03/06/2003
which claims benefit of 60/421,896 10/29/2002
and claims benefit of 60/409,762 09/11/2002

**** FOREIGN APPLICATIONS ***************************

GERMANY 10209985.5 03/07/2002
GERMANY 10245624.0 09/30/2002

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

05/11/2006

| Foreign Priority claimed ☑ Yes ☐ No<br>35 USC 119(a-d) conditions met ☑ Yes ☐ No<br>Verified and Acknowledged /SABIHA NAIM QAZI/ Examiner's Signature | ☐ Met after Allowance<br>sqazi Initials | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|---|
| | | GERMANY | 1 | 15 | 2 |

**ADDRESS**

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368
UNITED STATES

**TITLE**

ADMINISTRATION FORM FOR THE ORAL APPLICATION OF
3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZ(
ACID ETHYL ESTER AND THE SALTS THEREOF

| FILING FEE RECEIVED | | |
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| 2220 | FEES: Authority has been given in Paper<br>No._____ to charge/credit DEPOSIT ACCOUNT<br>No._____ for following: | ☐ All Fees<br>☐ 1.16 Fees (Filing)<br>☐ 1.17 Fees (Processing Ext. of time)<br>☐ 1.18 Fees (Issue)<br>☐ Other _____<br>☐ Credit |

# WEST Search History

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DATE: Friday, October 08, 2010

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| ☐ | L1 | 514/338.ccls. | 2264 |
| ☐ | L2 | 514/576.ccls. | 272 |
| ☐ | L3 | Brauns-Ulrich.in. | 9 |
| *DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ* | | | |
| ☐ | L4 | Brauns-Ulrich.in. | 24 |
| ☐ | L5 | Hauel-Norbert.in. | 163 |
| ☐ | L6 | 546/273.7.ccls. | 546 |

END OF SEARCH HISTORY



IPR2025-01107
MSN Exhibit 1008
Page 68 of 304

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 2

| *Complete if Known* | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | May 5, 2006 |
| First Named Inventor | BRAUNS, Ulrich |
| Art Unit | 1616 |
| Examiner Name | Qazi, Sabiha Naim |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number Number-Kind Code[2] *(if known)* | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
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| | | US- 2005/0234104 | 10/20/2005 | Schmid, R., et al | |
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| | | US- | | | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)* | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | JP 58134033 | 08/10/1983 | Fujisawa Pharm. | Abstract only | |
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| Examiner Signature | /Sabiha Qazi/ | Date Considered | 11/03/2010 |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 2 of 2

| *Complete if Known* | |
|---|---|
| *Application Number* | 11/381,890 |
| *Filing Date* | May 5, 2006 |
| *First Named Inventor* | Brauns, Ulrich |
| *Art Unit* | 1616 |
| *Examiner Name* | Qazi, Sabiha Naim |
| *Attorney Docket Number* | 1/1306-1-C1 |

**NON PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
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| | | The Merck Index 14th Edition, Merck & Co., NJ, USA, 2001, No. 9156, 4308, and 845, Ecuador, (Dec. 2006) | |
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| Examiner Signature | /Sabiha Qazi/ | Date Considered | 11/03/2010 |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 1

| *Complete if Known* | |
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| *Filing Date* | May 5, 2006 |
| *First Named Inventor* | Brauns, Ulrich, et al |
| *Art Unit* | 1616 |
| *Examiner Name* | Qazi, Sabiha Naim |
| *Attorney Docket Number* | 1/1306-1-C1 |

**NON PATENT LITERATURE DOCUMENTS**

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|---|---|---|---|
| /S.Q./ | | GENNARO, ALFONSO, R.; Remington Farmacia 19th Edition, Panamericana Espana 1988, p. 2470, Ecuador (December 2006) | |
| | | DUPLICATE | |

| Examiner Signature | /Sabiha Qazi/ | Date Considered | 11/03/2010 |
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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

# WEST Search History

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DATE: Wednesday, October 13, 2010

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| ☐ | L1 | organic acids | 290706 |
| ☐ | L2 | organic acids | 290706 |
| ☐ | L3 | tartaric acid | 108777 |
| ☐ | L5 | citric acid | 227735 |
| ☐ | L6 | citric acid | 227735 |
| ☐ | L7 | tartaric acid | 108777 |
| ☐ | L8 | tartaric acid | 108777 |
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| ☐ | L10 | l7 and BIBR | 50 |
| ☐ | L11 | l7 and BIBR 1048 | 23 |
| ☐ | L12 | l6 and BIBR 1048 | 24 |

END OF SEARCH HISTORY



IPR2025-01107
MSN Exhibit 1008
Page 73 of 304

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| In re Application of: Ulrich BRAUNS et al. | | : | |
| | | : | Examiner: Sabiha Naim Qazi |
| Serial No.: | 11/381,890 | : | Group Art Unit: 1612 |
| Filed: | May 5, 2006 | : | |
| For: | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |

# APPEAL BRIEF

Mail Stop: Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the decision of the Examiner finally rejecting claims 1-6, 8-14 and 17-22 of the above-identified application. A Notice of Appeal was filed on March 22, 2010. A request for a two month extension of time is filed herewith.

## (i) REAL PARTY IN INTEREST

The application is assigned of record to BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, who is the real party in interest herein.

## (ii) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

## (iii) STATUS OF THE CLAIMS

Claims rejected: Claims 1-6, 8-14 and 17-22.

Claims allowed: (none)



IPR2025-01107
MSN Exhibit 1008
Page 74 of 304

Claims canceled: Claims 7 and 16.

Claims withdrawn: Claim 15.

Claims on Appeal: Claims 1-6, 8-14 and 17-22 (Copy of claims on appeal in attached Appendix).

## (iv) STATUS OF AMENDMENTS

No amendments after the Final Rejection have been proposed by Appellants.

## (v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention (independent claim 1) is directed to a pharmaceutical composition for oral administration (see, e.g., page 2, lines 17-19, of the instant specification). The composition comprises: (a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 mL at 20° C (see, e.g., page 2, lines 21-23; page 3, line 13, to page 4, line 19; page 6, lines 3-6; and Fig. 1, of the instant specification); and (b) an active substance layer containing one or more binders and optionally a separating agent (see, e.g., page 5, lines 5-9, of the instant specification), that encloses said core material (see, e.g., page 3, lines 17-21, and Fig. 1, of the instant specification), wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof (see, e.g., page 1, line 18, to page 2, line 19, of the instant specification).

Appellants' invention (independent claim 18) is directed to a pharmaceutical composition for oral administration (see, e.g., page 2, lines 17-19, of the instant specification). The composition comprises: (a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 160 mL at 25° C (see, e.g., page 2, lines 21-23; page 3, line 13, to page 4, line 19; page 6, lines 3-6; and Fig. 1, of the instant specification); and (b) an active substance layer containing one or more binders and optionally a separating agent (see, e.g., page 5, lines 5-9, of the instant specification), that encloses said core material (see, e.g., page 3, lines 17-21, and Fig. 1, of the instant specification), wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof (see, e.g., page 1, line 18, to page 2, line 19, of the instant specification).



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As disclosed in the specification at pages 7-11, compositions for oral use according to the claimed invention were shown in clinical trials to have significantly improved bioavailability over different prior art formulations of the same active.

## (vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following outstanding grounds of rejection are requested to be reviewed on appeal. For each ground, any separate consideration of the claims subject to that rejection is indicated.

**1.** The rejection of claims 2-6, 8-14 and 17-22, on appeal under 35 U.S.C. §112, second paragraph, for improper claim dependency.

**2.** The rejection of claim 1 under 35 U.S.C. §112, second paragraph, for indefiniteness.

**3.** The rejection of claims 1-6, 8-14 and 17-22, on appeal, under 35 U.S.C. §103, for allegedly being obvious from WO 98/37075 (WO '075), Crotts *et al.* (US Pub. No. 2003/001723; US Patent 7,316,819), Hatano *et al.* (US Patent 6,309,666), Bastin *et al.* (Organic Process Res. And Development 2000) and Akira *et al.* (Abstract of JP 58-134033).

**3a.** Claims 1-6, 8-9, 13 and 17-18, on appeal, are grouped together.

**3b.** Claims 10-12, on appeal, are separately grouped together for the reasons given in the argument.

**3c.** Claims 14 and 19, on appeal, are separately grouped together for the reasons given in the argument.

**3d.** Claims 20-22, on appeal, are separately grouped together for the reasons given in the argument.

## (vii) ARGUMENT

**1.** Claims 2-6, 8-14 and 17-22, on appeal, are not indefinite due to improper claim dependency, thus, the rejection of these claims under 35 U.S.C. 112, second paragraph, should be reversed.

The claims are rejected for indefiniteness because claim 2 depends (in part) on claim 18. Claim 2 is a multiply dependent claim depending alternatively on claim 1 or claim 18



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(claims 5, 6, 8-10 and 13-14 also are multiply dependent on claims 1 and 18). It is alleged in the Office action that a claim cannot depend on a later claim, e.g., claim 2 cannot depend on claim 18, and that this fact – alone – justifies the rejection.

Appellants urge that this manner of claim dependency, however, does not provide a basis for an indefiniteness rejection. The mere fact that the claim depends on a claim which follows it numerically does not support an indefiniteness rejection. The meaning of the claim is clear and there is no allegation that the meaning is not clear.

Although the Board, of course, is not bound by the MPEP, reference to MPEP §608.01(n), which recites as follows, is instructive here:

> However, in situations where a claim refers to a *numerically following claim* and *the dependency is clear,* both as presented and as it will be renumbered at issue, all claims should be examined on the merits and no objection as to form need be made. In such cases, *the examiner will renumber the claims into proper order at the time the application is allowed.* (See Example B, below.) [emphasis added]

It is thus made clear that the renumbering of the claims is merely a procedural issue to be handled by the Examiner upon allowance of the application. The claim numbering does not give rise to indefiniteness or support a rejection under 35 U.S.C. §112, second paragraph. Thus, the rejection should be reversed.

**2.** Claim 1, on appeal, is not indefinite due to the "substantially" term, thus, the rejection of this claim under 35 U.S.C. 112, second paragraph, should be reversed.

Claim 1 on appeal is rejected as indefinite under 35 U.S.C. §112, second paragraph, based on the term "substantially spherical core." It is alleged in the Final Office action that the "substantially" term used in this context is "unclear" and not defined in the specification. Appellants disagree.

The use of the term "substantially" in claims has been held in many court decisions to not give rise to indefiniteness. See, for example, Seattle Box Co., Inc. v. Industrial Crating & Packing, Inc., 221 USPQ 568 (Fed. Cir. 1984), at 575-576; Standard Oil Company (Indiana) v. Montedison, etc., 206 USPQ 676 (Dist. Del. 1980), at 714; In re Mattison, 509 F.2d 563, 184 USPQ 484 (CCPA 1975); and Andrew Corp. v. Gabriel Electronics, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988). See also MPEP 2173.05(b), Part D. The use of the term "substantially" in patent claims is well known to be a modifier of terms to cover differences from the exact term which are so close to the strict meaning of the term that the difference is



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not of any significant consequence. In the instant case, one accepted definition of a "sphere" may be a three-dimensional closed surface such that every point on the surface is equidistant from the center. As one of skill in the art in the pharmaceutical industry would appreciate, the preparation of particles may result in a substantially spherical shape even though not every point on the surface is exactly equidistant from the center but, for all intents and purposes, it is considered spherical.

Furthermore, maintaining the rejection on the basis that the "substantially" term is not defined in the specification fails to take into account the knowledge of one of ordinary skill in the art. Here, the meaning of "substantially spherical" would be evident to one of ordinary skill in the art. For example, appellant points to the instant specification on page 6, lines 3-6, which recites "…roughly spherical particles of the desired size … can be produced by methods known and established in pharmaceutical technology." Thus, the specification makes clear that one of ordinary skill in the pharmaceutical arts is well aware of what "substantially spherical" would mean in the context of providing a core for a pharmaceutical composition. The indefiniteness rejection is not supported where the meaning of the term is well understood within the art.

For all of the above reasons, it is urged that this rejection under 35 U.S.C. §112, second paragraph, should also be reversed.

**3a.** Claims 1-6, 8-9, 13 and 17-18, on appeal, are not obvious over WO 98/37075 (WO '075), Crotts *et al.* (2003/001723; US Patent 7,316,819), Hatano *et al.* (US Patent 6,309,666), Bastin *et al.* (Organic Process Res. And Development 2000) and Akira *et al.* (Abstract of JP 58-134033); thus, the rejection under 35 U.S.C. § 103 (a) should be reversed.

WO 98/37075 discloses the active compound recited in the instant claims. See, e.g., Example 90 of the reference which uses different nomenclature but discloses the same compound as ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate recited in the claims. The instant specification admits this fact in the paragraph bridging pages 1-2. The compounds in WO '075 are taught as useful for inhibiting thrombin and prolonging thrombin time (see Abstract).

The claims on appeal, however, are not directed merely to this active compound. As recited in the Summary of the Invention above, the claims on appeal are directed to a particular composition containing this active compound which composition contains a

substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a particular water solubility (i.e., > 1 g / 250 mL at 20° C for claim 1 and > 1 g / 160 mL at 25° C for claim 18) and wherein the active is contained in an active substance layer containing one or more binders and optionally a separating agent that encloses said core material. As disclosed in the specification at pages 7-11, such claimed compositions for oral use were shown in clinical trials to have significantly improved bioavailability over different prior art formulations of the same active.

WO '075 only discloses the active compound. It provides no disclosure or suggestion of the particular manner of formulation recited in the claims on appeal which give the invention its novel characteristics.

Appellants urge that the combination of five references cited to support the rejection do not provide one of ordinary skill in the art a reason to provide the active disclosed in WO '075 in a formulation as recited by the claims on appeal. For the reasons detailed below, applicants submit: (1) that one of ordinary skill in the art is not provided with a sufficient reason to combine the five references relied upon, (2) one of ordinary skill in the art is not provided with a sufficient reason to combine the cited references in a manner which would result in or suggest the invention of the claims on appeal, and (3) the combination of references, if made, would not result in the claimed invention.

Although the five cited references all, generally, have some connection to the field of pharmaceuticals, no relation is seen among them which would give a reason for one of ordinary skill in the art to combine their teachings. WO '075 is directed to novel disubstituted bicyclic heterocycle compounds useful for inhibiting thrombin and prolonging thrombin time (see Abstract). Crotts relates to a composition for delivering of a peptide compound (see Abstract). Hatano relates to a pharmaceutical composition in general, with no specific active, having a hard capsule center which contains a medicament and an acid and is coated with a low pH-soluble polymer film and an enteric coating; see the Abstract and page 4, line 46, to page 5, line 20. Bastin relates to selecting appropriate salt forms for new pharmaceuticals in general, but not for any particular pharmaceutical. Akira teaches adding an acidic substance to compositions containing the medication cinnazine to improve solubility. The active compounds in the WO '075, Crotts and Akira disclosures are wholly unrelated in structure and use. Particularly, Crotts relates to administration of peptides which are known in the art to have very different considerations for administration than small molecule compounds such as taught in WO '075. Further, the cinnazine compound in Akira is



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structurally unrelated to the compounds of WO '075. For example, cinnazine does not have the bicyclic group which is a characterizing feature of the WO '075 compounds, nor a group corresponding to the A or E groups in the WO '075 compounds. Hatano and Bastin provide general teachings which could, potentially, be applied to pharmaceuticals generally but which provide no indication of particular applicability to compounds such as those of WO '075 or similar compounds. The lack of any established relation between the types of compounds of WO '075, Crotts and Akira and the lack of specificity of Hatano and Bastin are such that there is no apparent reason why one of ordinary skill in the art would have a reason to select various parts of these references and combine them. As detailed below, the Final Office action also fails to provide any explanation of why one of ordinary skill in the art would combine certain selected parts of these unconnected references.

The Final Office action appears to give no articulated reasoning with some rational underpinning for why one of ordinary skill in the art would combine the references in the manner alleged to render the claimed invention obvious. The Final Office action states what each of the five references discloses. At pages 9-10 of the Final Office action, the reason given for why one of ordinary skill in the art would combine the references merely summarizes again what each of the references discloses individually. There is no discussion of any relation between the references which would give one of ordinary skill in the art a reason to combine the features of one with the other. The "reason" given is thus merely the type of conclusory statement that the Supreme Court indicated as inadequate to support an obviousness rejection in KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385, at 1396 (2007), stating: "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." As further stated in KSR "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." Appellants believe no reason is provided in the Final Office action, nor is such a reason apparent from the references themselves.

To the contrary, appellants urge that, from a reading of the references as a whole, one of ordinary skill in the art would have no reason to combine them in a manner which would result in the claimed invention.

Crotts (citations to '819 patent) provides a pharmaceutical composition for oral delivery of a peptide in the form of a lamination having at least two layers (see, e.g., the



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Abstract and col. 2, lines 18-28 and 55-64). The Crotts composition has one layer containing a pH-lowering agent (i.e., an acid) and a layer laminated on this layer which contains the peptide. This laminated construct is then provided with an enteric coating surrounding the laminated construct (see, e.g., the Abstract and col. 2, lines 18-28 and 55-64). It is clear from Crotts (see, e.g., the method of making at col. 8, lines 23-34, and in the Examples) and from the plain meaning of the word "lamination" that the internal laminate part of the Crotts construct has two layers in contact along one plane. The first layer material is pressed in a die and then the second layer material is added to the die and pressed as a second layer onto the pressed first layer material. This provides a conventional layering (like a layer cake) and not a construct which has a core and "an active substance layer .. that encloses said core material" as recited in the claims on appeal. In the Crotts construct, the enteric coating – not the active substance layer – encloses the laminated core construct. Thus, even if the active material of WO '075 were provided in a construct according to Crotts, such a construct would not meet the elements of the claimed invention.

In any event, Crotts provides no reason for one of ordinary skill in the art to provide the active of WO '075 in a construct according to Crotts. The problem addressed by the Crotts invention relates to the limited bioavailablity of a peptide that results from proteolytic enzyme degradation in both the stomach and intestines, which renders the peptide inactive. The enteric coating in Crotts is designed to allow the pharmaceutical composition to pass through the stomach and enter the intestine, where basic to neutral pH predominates and proteases have basic to neutral pH optima. The pH-lowering agent in Crotts temporarily lowers the local intestinal pH, causing the peptide to be released, the activity of the basic to neutral intestinal proteases to be reduced, and the peptide to be protected from potential degradation. The solubility enhancer or surfactant also used in Crotts then aids or promotes the passage of the peptide through the intestinal epithelial barrier for delivery. See, e.g., col. 3, line 53, to col. 4, line 27 of the Crotts '819 patent. There is no basis to conclude that the compounds of WO '075 would have such a problem to be addressed. To the contrary, the WO '075 compounds are not peptides at all and there would be no reason for one of ordinary skill in the art to apply a solution to a problem related to peptides to compositions for administering the WO '075 compounds.

It is alleged in the Final Office action (page 13) that Crotts' teachings are applicable to administering agents other than peptides and citation is made to cols. 5-7 of Crotts. There is no mention here of applying the Crotts invention to administering agents other than peptides.



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The discussion at cols. 5-7 of Crotts relates to the excipients used in the peptide compositions, not other actives.

Hatano teaches a construct wherein an acid and a medicament (which may be the same compound) are provided together in a hard capsule center. See, e.g., page 4, line 46, to page 5, line 20, which describes that the center hard capsule contains both the medicament and the acid. See also Figs. 1-3 and the description thereof at col. 13, lines 6-26, making clear that the homogeneous center portion, **1**, of the constructs contains both the medicament and the acid. There is no teaching of any differentiation in location between the medicament and the acid in the Hatano capsules. Thus, as with Crotts, the Hatano construct does not have a "core material comprised of one or more pharmaceutically acceptable organic acids" and "an active substance layer .. that encloses said core material" as recited in the claims on appeal. Thus, even if the active material of WO '075 were provided in a construct according to Hatano, such a construct would not meet the elements of the claimed invention.

Similar to Hatano, Akira gives no indication that the acid is separate from the medicament, cinnazine. To the contrary, Akira recites: "adding an acidic substance to cinnazine." Thus, as with Crotts and Hatano, Akira does not teach or suggest a "core material comprised of one or more pharmaceutically acceptable organic acids" and "an active substance layer .. that encloses said core material" as recited in the claims on appeal. Thus, even if the active material of WO '075 were provided according to Akira, such a construct would not meet the elements of the claimed invention.

Bastin teaches nothing about administration forms. It is relied upon for its teachings regarding salts and is pertinent only to Issues **3c** and **3d** below.

As can be seen from the above discussions, even if the reference teachings are combined, such a combination would not meet all the elements of the claims. None of the references teaches a pharmaceutical composition with a "core material comprised of one or more pharmaceutically acceptable organic acids" and "an active substance layer .. that encloses said core material." Certainly then, the combination of references could not suggest such a composition. Thus, while appellants maintain that there is no sufficient reason to combine the references in the first place, appellants also maintain that such a combination would not result in or suggest the claimed invention. Additionally, no reason at all is provided on the record for one of ordinary skill in the art to modify the constructs of the cited references in a way to arrive at the claimed invention. The references teach specific manners of constructs to solve particular problems discussed therein. Modifying such a construct in a



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manner not suggested in any of the references would be completely contrary to the reference teachings.

For all of the above reasons, it is urged that one of ordinary skill in the art would not have combined the cited references and, even if combined, such combination does not suggest the claimed invention to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be reversed.

**3b.** Claims 10-12, on appeal, are not obvious over WO 98/37075 (WO '075), Crotts *et al.* (2003/001723; US Patent 7,316,819), Hatano *et al.* (US Patent 6,309,666), Bastin *et al.* (Organic Process Res. And Development 2000) and Akira *et al.* (Abstract of JP 58-134033); thus, the rejection under 35 U.S.C. § 103 (a) should be reversed.

The reasons provided in Issue **3a** above apply equally in overcoming the rejection of these claims on appeal. However, additional reasons for overcoming the rejection apply to claims 10-12, on appeal.

Claims 10-12, on appeal, recite an "insulating layer" provided between the "core material comprised of one or more pharmaceutically acceptable organic acids" and the "active substance layer .. that encloses said core material." In each of the particular administration forms disclosed in the references, the medicament is either mixed with the acid or in a layer which is in contact with a layer containing the acid. In Crotts, the laminate provides two layers in contact, one with the acid and one with the medicament. The enteric coating is provided around this laminate, not between the layers. In Hatano and Akira, the acid is mixed together with the medicament. In none of the references, is there any suggestion or reason given for providing an insulating layer between the portion of the construct containing the medicament and the portion of the construct containing the acid. Thus, there is no suggestion at all of the insulating layer element of the claims in any of the cited references. Further, the Final Office action fails to address where this claim element is found in the cited references.

For this additional reason, the rejection of these claims on appeal under 35 U.S.C. §103 should be reversed.

**3c.** Claims 14 and 19, on appeal, are not obvious over WO 98/37075 (WO '075), Crotts *et al.* (2003/001723; US Patent 7,316,819), Hatano *et al.* (US Patent 6,309,666), Bastin *et al.* (Organic Process Res. And Development 2000) and Akira *et al.* (Abstract of JP 58-134033); thus, the rejection under 35 U.S.C. § 103 (a) should be reversed.



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The reasons provided in Issue **3a** above apply equally in overcoming the rejection of these claims on appeal. However, additional reasons for overcoming the rejection apply to claims 14 and 19, on appeal.

Claims 14 and 19, on appeal, recite that the active agent is provided in the particular form of its mesylate salt (i.e., methanesulfonate salt). WO '075 discloses generally that salts of the active compound there can be used. It also has a specific disclosure of preferred salts which, in English, recites as follows (see U.S. Patent No. 6,087,380, cited by INPADOC as in the same family):

> Moreover, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids. Examples of suitable acids include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.
>
> In addition, the new compounds of formula I thus obtained, if they contain a carboxyl group, may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, more particularly, for pharmaceutical use, into the physiologically acceptable salts thereof. Examples of suitable bases include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

Thus, there is no suggestion in the reference specific to mesylate salts of these active compounds.

Bastin is a general reference which discusses procedures for evaluating whether to use salts of pharmaceuticals and how to go about selecting a particularly suitable salt. In Table 1, it lists 47 particular salt forms which it indicates as being most frequently used. Mesylate is one of the 47 salt forms listed. Bastin provides absolutely no indication that mesylate salts would be particularly preferable for the WO '075 compounds or any connection between the selection of mesylate and these particular compounds.

Applicants urge that Bastin does not support the proposition that it would be obvious to provide any and all pharmaceutical compounds in any one of the 47 salt forms listed there. To the contrary, Bastin makes clear that the salt form selected has to be particularly tailored to the specific active compound; see the Abstract. Further, the WO '075 reference itself directs one of ordinary skill in the art towards particular salt forms and does not include mesylate. One of ordinary skill in the art would certainly look first to the teachings of WO '075 itself, which is specific to these compounds, rather than the mere general teachings of Bastin.



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Applicants urge, therefore, that one of ordinary skill in the art would not have had a reason to provide the active agents of WO '075 in a mesylate salt form based on the cited references.

For this additional reason, the rejection of these claims on appeal under 35 U.S.C. §103 should be reversed.

**3d.** Claims 20-22, on appeal, are not obvious over WO 98/37075 (WO '075), Crotts *et al.* (2003/001723; US Patent 7,316,819), Hatano *et al.* (US Patent 6,309,666), Bastin *et al.* (Organic Process Res. And Development 2000) and Akira *et al.* (Abstract of JP 58-134033); thus, the rejection under 35 U.S.C. § 103 (a) should be reversed.

The reasons provided in Issue **3a** above apply equally in overcoming the rejection of these claims on appeal. However, additional reasons for overcoming the rejection apply to claims 20-22, on appeal.

Both of the reasons discussed for Issues **3b** and **3c** apply to claims 20-22, on appeal, and those reasons are incorporated herein by reference. These claims require both the insulating layer discussed in Issue **3b** and the particular mesylate salt discussed in Issue **3c**. The combination of these additional distinctions provides an additive effect of distinguishing these claims from the cited prior art. Thus, the rejection of these claims under 35 U.S.C. §103 should be reversed.

For all of the above reasons, it is urged that the decision of the Examiner rejecting claims 1-6, 8-14 and 17-22, on appeal, is in error and should be reversed.

The Appeal Brief fee of $540.00 is filed/paid herewith. The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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**(viii) CLAIMS APPENDIX**

**1.** A pharmaceutical composition for oral administration comprising:
(a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 mL at 20° C; and
(b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material, wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof.

**2.** Pharmaceutical composition according to claim 1 or 18, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, aspartic acid and any combination thereof.

**3.** Pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid and any combination thereof.

**4.** Pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable organic acid is tartaric acid.

**5.** Pharmaceutical composition according to claim 1 or 18, wherein the content of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate in the pharmaceutical composition is 5 to 60 %.

**6.** Pharmaceutical composition according to claim 1 or 18, wherein the content of pharmaceutically acceptable organic acid is 20 to 90 %.

**8.** Pharmaceutical composition according to claim 1 or 18, wherein said binder is selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethyl-



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celluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone, vinyl acetate and any combination thereof.

**9.** Pharmaceutical composition according to claim 1 or 18, wherein said core material has an average particle size of 0.4 to 1.5 mm.

**10.** Pharmaceutical composition according to claim 1 or 18, wherein said core material and the active substance layer are separated from one another by an insulating layer comprised of a water-soluble polymer, optionally with the addition of suitable plasticisers, separating agents and pigments.

**11.** Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of gum arabic.

**12.** Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of a partially or totally synthetic polymer selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone, vinyl acetate, and any combination thereof.

**13.** Pharmaceutical composition according to claim 1 or 18, wherein the composition containing the active substance is packed into hard capsules.

**14.** Pharmaceutical composition according to claim 1 or 18, wherein ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate is used as the active substance.

**17.** Pharmaceutical composition of claim 13, wherein the hard capsule is hydroxypropylmethylcellulose (HPMC).

**18.** A pharmaceutical composition for oral administration comprising:



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(a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 160 mL at 25° C; and
(b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material, wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof.

**19.** Pharmaceutical composition of claim 1 or 18, wherein the active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate and the pharmaceutically acceptable organic acid is tartaric acid.

**20.** The pharmaceutical composition according to claim 10, wherein the core material consists of tartaric acid and gum arabic, the insulating layer consists of gum arabic and talc and the active substance layer consists of talc, hydroxypropylcellulose and ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate.

**21.** The pharmaceutical composition according to claim 20, wherein the tartaric acid in the core material is present in the composition at about 61.3%, the gum arabic in the core material is present in the composition at about 3.1%, the gum arabic in the insulating layer is present in the composition at about 2.8%, the talc in the insulating layer is present in the composition at about 5.6%, the talc in the active substance layer is present in the composition at about 3.2%, the hydroxypropylcellulose in the active substance layer is present in the composition at about 4.0% and the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate in the active substance layer is present in the composition at about 20%.

**22.** The pharmaceutical composition according to claim 20, wherein the tartaric acid in the core material is present in the composition at about 38.5%, the gum arabic in the core material is present in the composition at about 1.9%, the gum arabic in the insulating



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MSN Exhibit 1008
Page 88 of 304

layer is present in the composition at about 1.7%, the talc in the insulating layer is present in the composition at about 3.5%, the talc in the active substance layer is present in the composition at about 6.4%, the hydroxypropylcellulose in the active substance layer is present in the composition at about 8.0% and the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate in the active substance layer is present in the composition at about 40%.



IPR2025-01107
MSN Exhibit 1008
Page 89 of 304

**(ix) EVIDENCE APPENDIX**

[None]

**(x) RELATED PROCEEDINGS APPENDIX**

[None]

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11381890 |
| **Filing Date:** | 05-May-2006 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Filer:** | John Albert Sopp/Diane Payne |
| **Attorney Docket Number:** | 01-1306-1-C1 |

Filed as Large Entity

## Utility under 35 USC 111(a) Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| Filing a brief in support of an appeal | 1402 | 1 | 540 | 540 |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 2 months with $0 paid | 1252 | 1 | 490 | 490 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **1030** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 8067644 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28519 |
| **Filer:** | John Albert Sopp/Diane Payne |
| **Filer Authorized By:** | John Albert Sopp |
| **Attorney Docket Number:** | 01-1306-1-C1 |
| **Receipt Date:** | 22-JUL-2010 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 14:20:00 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Credit Card |
| Payment was successfully received in RAM | $1030 |
| RAM confirmation Number | 538 |
| Deposit Account | |
| Authorized User | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 | Extension of Time | PetitionExtensionTime.pdf | 30177<br>7d49181db69eb99e8b65878b0716f8906d257454 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Appeal Brief Filed | AppealBrief.pdf | 95141<br>7a5cdfca37d3e750ee9db4c000590ded1322e02c | no | 18 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Fee Worksheet (PTO-875) | fee-info.pdf | 33008<br>5bba2d08d4810e60bcf861276a1fe8e0e502bbb0 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 158326 | |

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

**<u>New Applications Under 35 U.S.C. 111</u>**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

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

PTO/SB/22 (10-08)
Approved for use through 10/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2009** (*Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).*) | Docket Number (Optional) 01-1306-1-C1 |
|---|---|
| Application Number: 11/381,890 | Filed: May 5, 2006 |
| For: ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]- PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | |
| Art Unit: 1612 | Examiner: Sabiha Naim Qazi |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | |
|---|---|---|---|
| ☐ One month (37 CFR 1.17(a)(1)) | $130 | $65 | _____ |
| ☒ Two months (37 CFR 1.17(a)(2)) | $490 | $245 | 490.00 |
| ☐ Three months (37 CFR 1.17(a)(3)) | $1110 | $555 | _____ |
| ☐ Four months (37 CFR 1.17(a)(4)) | $1730 | $865 | _____ |
| ☐ Five months (37 CFR 1.17(a)(5)) | $2350 | $1175 | _____ |

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☒ Payment by credit card via EFS.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 13-3402 .

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent. Registration Number 33,103.

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____ .

| /John A. Sopp/ | July 22, 2010 |
|---|---|
| Signature | Date |
| John A. Sopp | (703) 243-6333 |
| Typed or printed name | Telephone Number |

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms are submitted.

PTO/SB/31 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

# NOTICE OF APPEAL FROM THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Docket Number (Optional): 01-1306-1-C1

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]
on _____

Signature _____

Typed or printed name _____

In re Application of: Ulrich Brauns

| Application Number | Filed |
|---|---|
| 11/381,890 | May 5, 2006 |

For: ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-[[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-P

| Art Unit | Examiner |
|---|---|
| 1612 | Sabiha Naim Qazi |

Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 540.00

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 022955 .

☑ A petition for an extension of time under 37 CFR 1.136(a) (PTO/SB/22) is enclosed.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☑ attorney or agent of record.
Registration number 53,459.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____

/Wendy Petka/
Signature

Wendy Petka
Typed or printed name

203-791-6614
Telephone number

03-22-2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 2 forms are submitted.

This collection of information is required by 37 CFR 41.31. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11381890 |
| **Filing Date:** | 05-May-2006 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Filer:** | Wendy Ann Petka |
| **Attorney Docket Number:** | 01-1306-1-C1 |

Filed as Large Entity

## Utility under 35 USC 111(a) Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| Notice of appeal | 1401 | 1 | 540 | 540 |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 3 months with $0 paid | 1253 | 1 | 1110 | 1110 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **1650** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 7254965 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28519 |
| **Filer:** | Wendy Ann Petka |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | 01-1306-1-C1 |
| **Receipt Date:** | 22-MAR-2010 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 14:25:46 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $1650 |
| RAM confirmation Number | 652 |
| Deposit Account | 022955 |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)<br>Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) | |

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Extension of Time | 01-1306-1-C1-2010-03-22-Petition-136-filed.pdf | 305591<br>d1480857ed44533ed8fc438e11152c507105066e | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Notice of Appeal Filed | 01-1306-1-C1-2010-03-22-NO-APPEAL-filed.pdf | 230725<br>331d2a3230619e3b8a91933e555dbcfe3dd2ebe5 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Fee Worksheet (PTO-875) | fee-info.pdf | 33081<br>594b9ac3f1bb46b2833ba9db6f9cce05760c16d8 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 569397 | | |

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

**<u>New Applications Under 35 U.S.C. 111</u>**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

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

PTO/SB/22 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE
Under the paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)**<br>**FY 2009**<br>***(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*** | Docket Number (Optional)<br>01-1306-1-C1 |
|---|---|
| Application Number 11/381,890 | Filed May 5, 2006 |
| For ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINC | |
| Art Unit 1612 | Examiner Sabiha Naim Qazi |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | | Fee | Small Entity Fee | |
|---|---|---|---|---|
| ☐ | One month (37 CFR 1.17(a)(1)) | $130 | $65 | $ |
| ☐ | Two months (37 CFR 1.17(a)(2)) | $490 | $245 | $ |
| ☑ | Three months (37 CFR 1.17(a)(3)) | $1110 | $555 | $ 1,110.00 |
| ☐ | Four months (37 CFR 1.17(a)(4)) | $1730 | $865 | $ |
| ☐ | Five months (37 CFR 1.17(a)(5)) | $2350 | $1175 | $ |

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 022955.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 53,459

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

| /Wendy Petka/ | 3-22-2010 |
|---|---|
| Signature | Date |
| Wendy Petka | 203-791-6614 |
| Typed or printed name | Telephone Number |

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☑ Total of 2 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: 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.*

UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 01-1306-1-C1 | 5127 |

28519 7590 09/23/2009

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/23/2009 | 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):

USPTO.e-Office.rdg@boehringer-ingelheim.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 11/381,890 | BRAUNS ET AL. | |
| | Examiner | Art Unit | |
| | Sabiha Qazi | 1612 | |

*-- 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 5/19/2009.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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**

4)☒ Claim(s) 1-6,8-14 and 17-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6,8-14 and 17-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on 05 May 2006 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**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).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## Final Office Action

Claims 1-6, 8-14 and 17-22 are pending. No claim is allowed. Amendments are entered.

## Summary of this Office Action dated September 09, 2009

1. Information Disclosure Statement
2. Copending Applications
3. Specification
4. 35 USC § 112 (2) Rejection
5. 35 USC § 103(a) Rejection
6. Response to Remarks
7. Conclusion
8. Communication

## Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

## Copending Applications

Applicants must bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications, which are "material to patentability" of the application in question. MPEP 2001.06(b). See Dayco Products Inc. v. Total Containment Inc., 66 USPQ2d 1801 (CA FC 2003).

## Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

## Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-6, 8-14, and 17-22 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-6, 8-14, 17-22 are improperly dependent. For example claim 2 cannot depend on claim 18. Applicant must correct the dependency of claims.

Citation of "a substantially spherical core" in claim 1 is unclear. An explanation is requested.

## Claim Rejections - 35 USC § 103-- Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

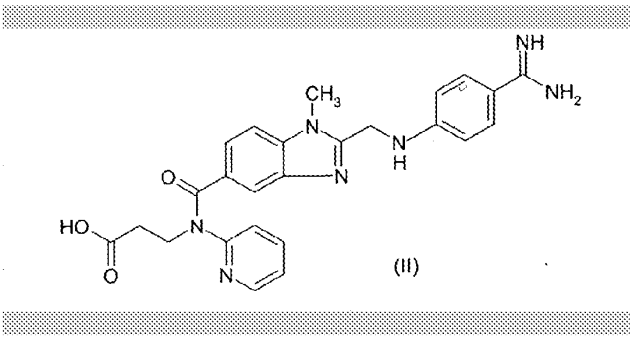
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims **1-6, 8-14 and 17-22** rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/37075, CROTTS et al. (2003/001723; US Patent 7,316,

819), HASTANO et al. (US 6,309,666), BASTIN, R. et al. (Organic Process Res. and Development (2000) and AKIRA et al.[1].

The WO reference teaches the compound. The specification also discloses that the active compound used in the claimed composition is known in the art. The compound is commonly known as BIBR 1048.




CROTTS et al. teaches a pharmaceutical composition for oral delivery of a peptide in the form of a lamination having at least two layers. The first layer of the lamination includes at least one pharmaceutically acceptable pH-lowering agent. The second layer includes a therapeutically effective amount of the peptide. The composition also includes at least one absorption enhancer effective to promote bioavailability of the peptide, which is preferably in the second layer, and an enteric coating surrounding the lamination. In a preferred dosage form of a tablet, a water-soluble coating is applied between the lamination and enteric coating which

[1] Abstract of JP 58-134033

substantially prevents contact between the pH-lowering agent and the enteric coating. In a specific composition pH-lowering agent is citric acid, and the absorption enhancer is lauroyl l-carnitine. The reference also teaches the use of binder. See the entire document especially abstract, lines 18-55 in column 2.

HATANO et al. teaches a pharmaceutical preparation in the form of a coated capsule which can release contents of a capsule at a lower part of the digestive tract comprising **(a) a hard capsule containing at least an acidic substance**, (b) a polymer film soluble at low pH which is formed on a surface of said hard capsule, and (c) an enteric coating film which is formed on a surface of said polymer film soluble at low pH. To each of the contents of the hard capsule, the sealing means, the low pH-soluble polymer film, the enteric coating film and the intermediate layer between the low pH-soluble polymer film and the enteric coating film, if necessary, there can be added various additives generally used in the art of pharmaceutical preparation, for instance, an excipient, a binder, a disintegrant, a lubricant, an aggregation-preventing agent, a coating auxiliary, a coloring agent, a masking agent, a plasticizer to improve the coating property and the film-formability etc., a surfactant, an antistatic agent, an additive for controlling transmittance of light, and the like.

The reference further teaches the pharmaceutical preparation, for **any kind of a medicament** can be delivered to any desired site between the upper part of the small intestine and the lower part of the large intestine in the digestive tract by controlling the amount of polymer(s) used for the polymer film soluble at low pH and/or by selecting the kind of the polymer film soluble at **low pH and/or the acidic substance without any complicated requirements for each medicament.** The reference teaches the use of the binders in the composition for example an oligosaccharide or sugar alcohol such as sucrose, glucose, lactose, maltose, sorbitol or mannitol; a polysaccharide such as dextrin, starch, sodium alginate, carrageenan, guar gum, arabic gum or agar; a natural high molecular substance such as tragacanth, gelatin or gluten; a cellulose derivative such as methylcellulose, ethylcellulose, sodium carboxymethylcellulose or hydroxypropylmethylcellulose; a synthetic polymer such as polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, polyethylene glycol, polyacrylic acid or polymethacrylic acid; and the like. See the entire document especially lines 39-62 in column 11, lines 24-34 and 58-65 in column 12, lines 48-63 in column 13, examples and claims.

BASTIN teaches a salt selection and optimization procedures for pharmaceutical new chemical entities. It further teaches that selection of salts is useful for development of dosage forms with good bioavailability, stability,

manufacturability. See the entire document especially abstract, table 1 on page 428, column 2 on page 428, Table 2 on page 429, table 4 on page 430.

AKIRA teaches drug composition for oral medication having improved solubility, obtained by adding an acidic substance to cinnarizine. (**Cinnarizine;1-(Diphenylmethyl)-4-(3-phenyl-2-propenyl)piperazine;1-Cinnamyl-4-diphenylmethyl piperazine;Stugeron;Mitronal**). An acidic substance (e.g., tartaric acid, citric acid, etc.) is added to cinnarizine, to give a drug composition tablet, etc. may be used as the form of the drug. When it is orally medicated, it is hardly affected by the change in pH value in tile stomach; it shows stable solubility in the digestive organs. Consequently, it has improved effects such as stable absorption in the body.

It would have been obvious to one skilled in the art at the time of the invention to prepare a coated tablet containing core with organic acids and the second layer contain active compound, binders and other material needed to prepare a tablet or a capsule because first CROTTS teaches a pharmaceutical composition for oral delivery of a peptide in the form a lamination having at least two layers. The first layer of the lamination includes at least one pharmaceutically acceptable pH-lowering agent, the second layer includes a therapeutically effective amount, second HATANO et al. pharmaceutical preparation in the form of a

coated capsule which can release contents of a capsule at a lower part of the digestive tract comprising (a) a hard capsule containing at least an acidic substance, (b) a polymer film soluble at low pH which is formed on a surface of said hard capsule, and (c) an enteric coating film which is formed on a surface of said polymer film soluble at low pH. It also teaches binder and other components needed to form the coating and tablet or capsule, third BESTIN teaches a salt selection and optimization procedures for pharmaceutical new chemical entities. It further teaches that selection of salts is useful for development of dosage forms with good bioavailability, stability, manufacturability; fourth AKIRA teaches drug composition for oral medication when an acidic substance (e.g., tartaric acid, citric acid, etc.) is added to cinnarizine, to give a drug composition tablet, etc. may be used as the form of the drug. When it is **orally** medicated, it is hardly affected by the change in pH value in tile stomach; it shows stable solubility in the digestive organs. Consequently, **it has improved effects such as stable absorption in the body.**

See KSR Supreme Court of United States Decision (Decided April 30, 2007, KSR INTERNATIONAL CO. v. TELEFLEX INC. et al. No. 04-1350) where it states that (1) "However, the issue is not whether a person skilled in the art had the

motivation to combine the electronic control with an adjustable pedal assembly, but whether a person skilled in the art had the motivation to attach the electronic control to the support bracket of pedal assembly". (2) "the results of ordinary innovation are not the subject of exclusive rights under the patent laws".

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

**Response to Remarks**

Applicants' arguments, filed , have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicant argues that dependency of claims has been considered. Examiner is aware of renumbering the claims at the time of allowance because claims are cancelled and/or amended. In the present case new claim 18 has been added and claims with lower number such as claim 2 are made dependent on claim 18. At the time of examination when claim numbers are changed Applicant should correct the depend claims. Claims are not allowed.

Examiner will surely withdraw the rejection when Applicants will correct the dependency.

Applicant's arguments about "substantially spherical" are not found persuasive because "substantially" is not defined in the specification.

Again, Applicants are attacking the references individually. It has been decided by the courts that "One cannot show nonobviousness by **attacking references individually** where the rejections are based on combinations of references." In re Keller, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Applicants are arguing about WO 98/37075 that the reference teaches the compound and does not teach a composition or formulation for oral use having improved bioavailability. This reference has been used the reference to compound BIBR 1048 which is the active agent and is used in present invention. It teaches the preparation of the compound BIBR 1048. The same reference has been cited for the preparation of the compound in example 3 of the present application.

Examiner respectfully disagrees that CROTTS as prior is "flawed". Again, Applicants are missing the priority of provisional application 60/274,317 filed on March 8, 2001. Therefore CROTTS is a prior art. Furthermore, Applicants argue that the active agent is peptide in prior art which is different from the present

invention. Examiner would like to drawn the attention of Applicants that this reference is also used to show the other agents commonly used in the oral administration. See for example columns 5-7, where the pH lowering agent, the absorption enhancer, other optional ingredients, the enteric coating, water soluble coating, the dosage form and manufacturing. See also examples.

Applicants argue that HATANO reference teaches hard capsule. Applicant's specification describes (d) Packing into capsules, on page 17, lines 13-15 discloses "hard gelatine capsules or HPMC capsules". Therefore, present invention does contain hard capsule. Further, Examiner disagrees because the reference teaches the ingredients of the composition as claimed in present invention. The preparation can be selectively released at any desired site of the lower part of the digestive tract by controlling the amount of polymers used for a low pH-soluble polymer film and by selecting the kind of a low pH-soluble polymer and acidic substance, (lines 59-65, column 6, and lines 20-67, column 5).

It has been decided by the courts that "when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v. Teleflex, 127 S,Ct. 1727, 1740 (2007)(quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976)). "[W]hen the question is whether

a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is… a person of ordinary creativity, not an automaton." Id. at 1742.

In summary Examiner concludes that presently claimed invention is *prima facie* obvious to one skilled in the art for the reasons cited above.

## Conclusion

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the

advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

## Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day except Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Sabiha Qazi/
Primary Examiner, Art Unit 1612

| Notice of References Cited | Application/Control No. 11/381,890 | Applicant(s)/Patent Under Reexamination BRAUNS ET AL. | |
|---|---|---|---|
| | Examiner Sabiha Qazi | Art Unit 1612 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-4,427,648 | 01-1984 | Brickl et al. | 424/459 |
| * | B | US-4,367,217 | 01-1983 | Gruber et al. | 424/494 |
| * | C | US-4,728,660 | 03-1988 | Haynes et al. | 514/356 |
| * | D | US-6,086,918 | 07-2000 | Stern et al. | 424/474 |
| * | E | US-6,039,975 | 03-2000 | Shah et al. | 424/473 |
| * | F | US-5,416,099 | 05-1995 | Hartman et al. | 514/323 |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11381890 | BRAUNS ET AL. |
| | **Examiner** | **Art Unit** |
| | Sabiha Qazi | 1612 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

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

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 09/11/2009 | | | | | | | | |
| | 1 | ✓ | | | | | | | | |
| | 2 | ✓ | | | | | | | | |
| | 3 | ✓ | | | | | | | | |
| | 4 | ✓ | | | | | | | | |
| | 5 | ✓ | | | | | | | | |
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| | 8 | ✓ | | | | | | | | |
| | 9 | ✓ | | | | | | | | |
| | 10 | ✓ | | | | | | | | |
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| | 12 | ✓ | | | | | | | | |
| | 13 | ✓ | | | | | | | | |
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PTO/SB/122 (01-06)
Approved for use through 12/31/2008. OMB 0651-0035
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## *Application*

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|---|---|
| Application Number | 11/381,890 |
| Filing Date | 5/5/2006 |
| First Named Inventor | Ulrich Brauns |
| Art Unit | 1612 |
| Examiner Name | Qazi, Sabiha Naim |
| Attorney Docket Number | 01-1306-1-C1 |

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I am the:

[ ] Applicant/Inventor

[ ] Assignee of record of the entire interest.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

[X] Attorney or agent of record. Registration Number 27,928.

[ ] Registered practitioner named in the application transmittal letter in an application without an executed oath or declaration. See 37 CFR 1.33(a)(1). Registration Number_____.

| | |
|---|---|
| Signature | /Mary-Ellen M. Devlin/ |
| Typed or Printed Name | Mary-Ellen M. Devlin |
| Date: May 15, 2009 | Telephone: 203-798-4866 |

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[ ] *Total of _____forms are submitted.

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

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# 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

| | |
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| **EFS ID:** | 5359738 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28501 |
| **Filer:** | Mary-Ellen M. Devlin/Susan Wasilko |
| **Filer Authorized By:** | Mary-Ellen M. Devlin |
| **Attorney Docket Number:** | 01-1306-1-C1 |
| **Receipt Date:** | 19-MAY-2009 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 14:03:29 |
| **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 | Change of Address | 01-1306-1-C1-2009-5-8-Change-correspondenceaddress.pdf | 256275<br>d3adc964f74b152b80a7781393881d4e3721219c | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| Total Files Size (in bytes): | 256275 |
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**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

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

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | |
|---|---|---|---|---|
| Application of | : | Ulrich Brauns | ) Art Unit | : 1616 |
| Serial No. | : | 11/381,890 | ) Examiner | : Sabiha Naim Qazi |
| Confirmation No.: | | 5127 | | |
| Filed | : | May 5, 2006 | | |
| Title | : | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |
| Docket No. | : | 01-1306-1-C1 | | |

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

**REPLY TO OFFICE ACTION UNDER 37 C.F.R. § 1.111**

Sir:

This Reply is being filed in response to the December 12, 2008 Office Action issued in the above-identified application. In that Office Action, a three-month shortened statutory period was set for response. Applicant hereby petitions for a three-month extension of time under 37 C.F.R. § 1.136 to respond to that action and note that the fee required under 37 C.F.R. § 1.17(a) in connection with this extension of time will be paid during electronic filing via the Revenue Accounting and Management System. Furthermore, if it is determined that any additional fees under 37 C.F.R. §§ 1.16 or 1.17 are due in connection with this Reply, authorization to charge such fees to Deposit Account No. 02-2955 will be provided during electronic filing.

Please amend the above-identified application as follows:

**Amendments to the Claims** begin on page 2 of this paper.

**Remarks** begin on page 7 of this paper.



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**MSN Exhibit 1008**
**Page 126 of 304**

**Amendments to the Claims:**

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

**Listing of Claims:**

Claim 1 (currently amended): A pharmaceutical composition for oral administration comprising:
(a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 mL at 20° C; and
(b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material, wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof.

Claim 2 (previously presented): Pharmaceutical composition according to claim 1 or 18, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, aspartic acid and any combination thereof.

Claim 3 (currently amended): Pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid and any combination thereof.

Claim 4 (original): Pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable organic acid is tartaric acid.

Claim 5 (previously presented): Pharmaceutical composition according to claim 1 or 18, wherein the content of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate in the pharmaceutical composition is 5 to 60 %.



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Claim 6 (previously presented): Pharmaceutical composition according to claim 1 or 18, wherein the content of pharmaceutically acceptable organic acid is 20 to 90 %.

Claim 7 (canceled).

Claim 8 (previously presented): Pharmaceutical composition according to claim 1 or 18, wherein said binder is selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone, vinyl acetate and any combination thereof.

Claim 9 (previously presented): Pharmaceutical composition according to claim 1 or 18, wherein said core material has an average particle size of 0.4 to 1.5 mm.

Claim 10 (previously presented): Pharmaceutical composition according to claim 1 or 18, wherein said core material and the active substance layer are separated from one another by an insulating layer comprised of a water-soluble polymer, optionally with the addition of suitable plasticisers, separating agents and pigments.

Claim 11 (original): Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of gum arabic.

Claim 12 (previously presented): Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of a partially or totally synthetic polymer selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone, vinyl acetate, and any combination thereof.

Claim 13 (previously presented): Pharmaceutical composition according to claim 1 or 18, wherein the composition containing the active substance is packed into hard capsules.

Claim 14 (previously presented): Pharmaceutical composition according to claim 1 or 18, wherein ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate is used as the active substance.

Claim 15 (withdrawn): A process for preparing a pharmaceutical composition for oral administration containing ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the physiologically acceptable salts thereof, comprising the steps of:

a) forming the core material from one or more pharmaceutically acceptable organic acid(s) with a water solubility of > 1 g / 250 ml at 20° C, optionally with the addition of binders or other technological adjuvants, by pan methods, on pelleting plates or by extrusion / spheronisation,

b) applying to the core material an insulating layer comprised of one or more water-soluble, pharmaceutically acceptable polymers optionally with the addition of plasticisers, separating agents and/or pigments,

c) applying the active substance from a dispersion which contains a binder and optionally separating agents and simultaneously and/or subsequently drying to eliminate the dispersant,

d) optionally applying a coating of film-forming agents, plasticisers and optionally pigments and

e) packing the active substance-containing pellets thus obtained into capsules.

Claim 16 (canceled).

Claim 17 (previously presented): Pharmaceutical composition of claim 13, wherein the hard capsule is hydroxypropylmethylcellulose (HPMC).



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Claim 18 (currently amended): A pharmaceutical composition for oral administration comprising:
(a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 160 mL at 25° C; and
(b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material, wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof.

Claim 19 (previously presented): Pharmaceutical composition of claim 1 or 18, wherein the active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate and the pharmaceutically acceptable organic acid is tartaric acid.

Claim 20 (previously presented): The pharmaceutical composition according to claim 10, wherein the core material consists of tartaric acid and gum arabic, the insulating layer consists of gum arabic and talc and the active substance layer consists of talc, hydroxypropylcellulose and ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate.

Claim 21 (previously presented): The pharmaceutical composition according to claim 20, wherein the tartaric acid in the core material is present in the composition at about 61.3%, the gum arabic in the core material is present in the composition at about 3.1%, the gum arabic in the insulating layer is present in the composition at about 2.8%, the talc in the insulating layer is present in the composition at about 5.6%, the talc in the active substance layer is present in the composition at about 3.2%, the hydroxypropylcellulose in the active substance layer is present in the composition at about 4.0% and the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-

yl-amino]-propionate mesylate in the active substance layer is present in the composition at about 20%.

Claim 22 (previously presented): The pharmaceutical composition according to claim 20, wherein the tartaric acid in the core material is present in the composition at about 38.5%, the gum arabic in the core material is present in the composition at about 1.9%, the gum arabic in the insulating layer is present in the composition at about 1.7%, the talc in the insulating layer is present in the composition at about 3.5%, the talc in the active substance layer is present in the composition at about 6.4%, the hydroxypropylcellulose in the active substance layer is present in the composition at about 8.0% and the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate in the active substance layer is present in the composition at about 40%.

REMARKS

Claims 1-6, 8-14 and 17-22 are pending in this application. Claims 1, 3 and 18 have been amended to improve form. No new matter has been added by way of this amendment.

Applicant notes that the Examiner in the current Office Action did not address whether the finality of the July 3, 2008 Office Action was appropriate under 37 C.F.R. 1.113. Applicant noted previously that the Examiner cited a new reference in the 103 rejection (the AKIRA reference) that did not seem to be prompted by any claim amendments. Clarification of this matter is respectfully requested, although it may be too late for the Examiner to address this at this time.

Applicant requests consideration of the above-identified application in view of the following remarks.

**(a) Claims 2-6, 8-14, 16, 17 and 19-22 are not indefinite under 35 U.S.C. 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention**

Claims 2-6, 8-14, 16, 17 and 19-22 stand rejected under 35 U.S.C. 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner first rejects claims 2-6, 8-14, 16-17 and 19-22 as being improperly dependent, e.g., claim 2 cannot depend on claim 18. Second, the Examiner asserts that the citation "a substantially spherical core" in claim 1 is unclear. Applicant respectfully traverses and addresses each of these points below.

Based on applicant's understanding of section MPEP 608.01(n), page 600-88, Part F, "Handling of Multiple Dependent Claims by the Examiner," it is not improper to have a claim refer to a numerically following claim. Part F recites the following:

> However, in situations where a claim refers to a *numerically following claim* and *the dependency is clear,* both as presented and as it will be renumbered at issue, all claims should be examined on the merits and no objection as to form need be made. In such cases, *the examiner will renumber the claims into proper order at the time the application is allowed.* (See Example B, below.) [emphasis added]

Applicant added claim 18 in a reply to Office Action dated September 10, 2007. The dependency of claim 2 (as well as the other dependent claims) on either independent

claim 1 or independent claim 18 is clear. The dependent claims further limit the subject matter of either claim 1 or 18. If the Examiner prefers that the claims be renumbered for convenience, applicant will cancel all claims and add them as newly ordered claims in the next reply to Office Action. However, applicant does not believe this is a proper 112 second paragraph rejection and respectfully requests that this rejection be withdrawn.

The use of the term "substantially" is discussed in MPEP 2173.05(b), Part D. As recited in Part D, the court in *Andrew Corp. v. Gabriel Electronics,* 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988) held that the limitation "which produces substantially equal E and H plan illumination patterns" was definite because one of ordinary skill in the art would know what was meant by "substantially equal." Here, one of skill in the art would know what the meaning of "substantially spherical" would mean. For example, one definition of a "sphere" may be a three-dimensional closed surface such that every point on the surface is equidistant from the center. As one of skill in the art in the pharmaceutical industry would appreciate, the preparation of particles may result in a substantially spherical shape even though not every point on the surface is exactly equidistant from the center. For additional support, applicant points to the specification on page 6, lines 3-6, which recites "…roughly spherical particles of the desired size … can be produced by methods known and established in pharmaceutical technology." For the above reasons, applicant respectfully requests that the term "substantially spherical core" is understood within the art.

**(b) Claims 1-6, 8-14 and 16-22 are not obvious over WO 98/37075, Crotts *et al.* (2003/001723; US Patent 7,316,819), Hastano *et al.* (US Patent 6,309,666), Bastin *et al.* (Organic Process Res. And Development 2000) and Akira *et al.* (Abstract of JP 58-134033) under 35 U.S.C. § 103 (a)**

Claims 1-6, 8-14 and 16-22 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 98/37075, CROTTS *et al.* (2003/001723; US Patent 7,316,819), HASTANO *et al.* (US Patent 6,309,666), BASTIN *et al.* (Organic Process Res. And Development 2000) and AKIRA et al. (Abstract of JP 58-134033). In essence, the Examiner requires the combination of five (5) references in order to form the basis for an obviousness rejection. Applicant respectfully traverses this rejection and addresses the differences in the art with that of the present application.

Applicant acknowledges that WO 98/37075 discloses the active compound found in present claims 1 and 18 (this is stated in the beginning of the present specification). However, applicant is not claiming the compound itself but instead is claiming a formulation or composition for oral use having improved bioavailability.



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The use of CROTTS as a 103 prior art reference is flawed for two reasons. First, the first US publication date of CROTTS was January 23, 2003 (US 2003/0017203) and the PCT publication date of CROTTS was September 19, 2002 (WO 02/072075). Both of these dates were *after* the earliest priority filing dates of the present application, i.e., DE 10209985.5, filed March 7, 2002 and 60/409,762, filed September 11, 2002. Second, the pharmaceutical composition in CROTTS and the presently claimed invention teach away from each other. For example, CROTTS relates to the limited bioavailablity of a peptide that results from proteolytic enzyme degradation in both the stomach and intestines, which renders the peptide inactive. The enteric coating in CROTTS is designed to allow the pharmaceutical composition to pass through the stomach and enter the intestine, where basic to neutral pH predominates and proteases have basic to neutral pH optima. The pH-lowering agent in CROTTS temporarily lowers the local intestinal pH, causing the peptide to be released, the activity of the basic to neutral intestinal proteases to be reduced, and the peptide to be protected from potential degradation. The solubility enhancer or surfactant, which is in close proximity to the peptide active, then aids or promotes the passage of the peptide through the intestinal epithelial barrier for delivery. *See* column 3, line 53, to column 4, line 27 of the CROTTS '819 patent.

On the other hand, the presently claimed composition strikes a balance between the *activity of the compound itself with the* acidic and basic environment, as opposed to the *activity of a peptide with proteases found in* acidic and basic environments. An important goal of the present invention is to reduce the variability of the compound of formula I in the plasma and eliminate malabsorption. As discussed in previous responses, the arrangement (e.g., see Figure 1) of the components in the present pharmaceutical composition is relevant because the active substance is sensitive to various pH levels, i.e., the compound of formula I dissolves readily in water at low pH levels but is virtually insoluble at pH levels above 5 (see specification page 8, lines 1-3). In other words, the compound of formula I will be cleaved at low pH but will be insoluble at mid- to high pH, like those pH levels found in the intestinal tract. As a result, the present composition needs to be soluble at mid- to high pH during the later part of the drug's delivery, i.e., the intestines. The acid core of the present composition serves to produce an acid microclimate in which the active substance can be cleaved at the mid- to high pH and be readily dissolved in the intestines. No where in CROTTS is the concept taught or even suggested because the CROTTS mechanism of action is different from that of the present invention.

The HATANO reference is related strictly to hard capsules for any kind of pharmaceutical delivery. For example, column 3, lines 4-21, of the '666 patent succinctly describes the teachings of this reference:

> The pharmaceutical preparation of the present invention relates to a hard capsule for delivering the contents to the lower part of the digestive tract. That is, the pharmaceutical preparation of the present invention has the following characteristics: When a pharmaceutical preparation stays in the stomach, an enteric coating film protects the pharmaceutical preparation. Successively when the preparation transits from the stomach to the upper part of the small intestine, the enteric coating film dissolves and starts to disappear. Then, the digestive juice gradually penetrates through a low pH-soluble polymer film and a hard capsule to enter the hard capsule, and thereby an acidic substance is dissolved. The solution having low pH which is produced by the dissolution of the acidic substance, dissolves the hard capsule and the low pH-soluble polymer film, resulting in disappearance thereof. Then, the contents of the hard capsule such as medicaments, pharmaceutical preparations and functional substances are quickly released. [emphasis added]

The acid substance in the hard capsule of HATANO serves to dissolve the capsule so that medicaments can be released. The present invention is unrelated to this technology. Instead, the present invention discloses filling hard capsules with the pellets (or small spheres) of compositions according to claim 1 or 18. The acid core of the present composition is strictly related to the behavior of the composition itself, not the capsule. See specification on page 7, lines 10-16, page 14, lines 9-13, page 17, lines 11-15, claim 13 and claim 15 (withdrawn). No where in HATANO is the concept taught or even suggested because HATANO relates to design of hard capsules and the present invention relates to compositions which may or may not be deposited into hard capsules.

The Examiner further draws applicant's attention to the BASTIN reference, which is a general journal article discussing salt formation. Nothing related to bioavailability is taught in this reference.

Finally, the AKIRA abstract discloses that cinnarizine has improved solubility by adding an acidic substance to it for use in oral administration. There is nothing in this disclosure to suggest the elements of the present claims and it does nothing more than disclose conventional wisdom, which, once again, is inapplicable to the present invention. As discussed previously, the presently claimed invention was developed in response to clinical trials showing that conventional tablets of formula I were not ideal for patient administration. Applicant discusses in detail this problem in the specification, e.g., starting on page 7, entitled "Clinical trials," and thereafter, and provides evidence that the claimed compositions demonstrate improved bioavailability of the active substance in patients when compared to the conventional tablets at elevated gastric pH. Among other things, this is relevant for patients who have increased gastric pH due to normal physiological variability, disease or co-medication with drugs. Because the claimed compositions of the present invention are less

sensitive to pH fluctuations, malabsorption or poor absorption by the small intestines may be prevented.

The Supreme Court addressed the issue of obviousness in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007), wherein the Court stated that the Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966), factors still control an obviousness inquiry. Those factors include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art; and (4) objective evidence of non-obviousness. Parts (1)-(3) have been discussed above. As to part (4), the combination of WO 98/37075, CROTTS, HASTANO, BASTIN and AKIRA does not form the basis for an obviousness rejection because the combination of references lack elements of the claimed invention. These include (a) the compound of formula I in combination with (b) the organic acid core material or (c) the concept of a pharmaceutical composition comprising an organic acid core surrounded by active substance layer of formula I to address bioavailability fluctuations in the intestinal tract.

The Federal Circuit recently opined on the obviousness inquiry as it relates to the chemical arts (see, Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd. and Teva Pharmaceuticals USA, Inc., Nos. 2007-1397, -1398 (Fed. Cir. 2008)). Here, the Court reiterated that "the obviousness inquiry must rely on evidence 'at the time' of the invention." Id. at 8, citing *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 n.2, (Fed. Cir. 2007). The Court also discussed and outlined assumptions that the Supreme Court made in KSR, namely (1) KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions; (2) KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound; and (3) the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," (KSR at 1742).

None of these assumptions are met with the combination of WO 98/37075, CROTTS, HASTANO, BASTIN and AKIRA because performing the clinical trials with formula I would have been a necessary element prior to identifying the problem and solving it, as it was done in the present invention. For all of the reasons outlined above, applicant kindly requests that the Examiner withdrawal the rejection of obviousness under 35 U.S.C. § 103(a) and issues a timely Notice of Allowance in this case.



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MSN Exhibit 1008
Page 136 of 304**

Respectfully submitted,

/wendy petka/

Wendy Petka
Reg. No. 53,459

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Boehringer Ingelheim Corp.
900 Ridgebury Road
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Tel: (203) 791-6614
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# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11381890 |
| **Filing Date:** | 05-May-2006 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Filer:** | Wendy Ann Petka |
| **Attorney Docket Number:** | 01-1306-1-C1 |

Filed as Large Entity

## Utility under 35 USC 111(a) Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |
| Extension - 3 months with $0 paid | 1253 | 1 | 1110 | 1110 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **1110** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 5316420 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28501 |
| **Filer:** | Wendy Ann Petka |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | 01-1306-1-C1 |
| **Receipt Date:** | 12-MAY-2009 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 10:23:29 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $1110 |
| RAM confirmation Number | 7428 |
| Deposit Account | 022955 |
| Authorized User | |

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 01-1306-1-C1-2009-05-12-ROA.pdf | 189900<br>fb1c1aec14bf3459f00eda4020716464dc5687ab | yes | 12 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Amendment/Req. Reconsideration-After Non-Final Reject | 1 | 1 |
| Application Data Sheet | 2 | 6 |
| Applicant Arguments/Remarks Made in an Amendment | 7 | 12 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (PTO-875) | fee-info.pdf | 31227<br>698c72359fe70c4c99b79ba39444881e294a0e05 | no | 2 |

**Warnings:**

**Information:**

| Total Files Size (in bytes): | 221127 |
|---|---|

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

**New Applications Under 35 U.S.C. 111**

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

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

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

**New International Application Filed with the USPTO as a Receiving Office**

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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# PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

| Application or Docket Number | Filing Date | ☐ To be Mailed |
|---|---|---|
| 11/381,890 | 05/05/2006 | |

## APPLICATION AS FILED – PART I

| | (Column 1) | (Column 2) | SMALL ENTITY ☐ RATE ($) | SMALL ENTITY ☐ FEE ($) | OR | OTHER THAN SMALL ENTITY RATE ($) | OTHER THAN SMALL ENTITY FEE ($) |
|---|---|---|---|---|---|---|---|
| FOR | NUMBER FILED | NUMBER EXTRA | | | | | |
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | | | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | | OR | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | | | X $ = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 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 | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

| AMENDMENT 05/12/2009 | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE ($) | SMALL ENTITY ADDITIONAL FEE ($) | OR | OTHER THAN SMALL ENTITY RATE ($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * 37 | Minus | ** 37 | = 0 | X $ = | | OR | X $52= | 0 |
| Independent (37 CFR 1.16(h)) | * 3 | Minus | ***3 | = 0 | X $ = | | OR | X $220= | 0 |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | 0 |

| AMENDMENT | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) | OR | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | | OR | X $ = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | | OR | X $ = | |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/NICOLE C. LAWRENCE/

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.*

UNITED STATES PATENT AND TRADEMARK OFFICE

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 01-1306-1-C1 | 5127 |

28501 7590 11/12/2008

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877-0368

| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |
| **ART UNIT** | **PAPER NUMBER** |
| 1612 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 11/12/2008 | PAPER |

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

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

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 11/381,890 | BRAUNS ET AL. | |
| | Examiner | Art Unit | |
| | Sabiha Qazi | 1612 | |

*-- 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *31 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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**

4)☒ Claim(s) *1-6 and 8-22* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-14 and 16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *15* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**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).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## Non-Final Office Action

Claims 1-6, 8-22 are pending. No claim is allowed. Amendments are entered.

### Summary of this Office Action dated Tuesday, September 23, 2008

1. Continued Examination Under 37 CFR 1.114
2. Information Disclosure Statement
3. Copending Applications
4. Specification
5. 35 USC § 112 (2) Rejection
6. 35 USC § 103(a) Rejection
7. Response to Remarks
8. Communication

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/31/08 has been entered.

**Information Disclosure Statement**

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

**Copending Applications**

Applicants must bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information

within their knowledge as to other copending United States applications, which are "material to patentability" of the application in question. MPEP 2001.06(b). See Dayco Products Inc. v. Total Containment Inc., 66 USPQ2d 1801 (CA FC 2003).

## Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

## Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 2-6, 8-14, 16, 17 and 19-22 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-6, 8-14, 16, 17 and 19-22 are improperly dependent. For example claim 2 cannot depend on claim 18. Applicant must correct the dependency of claims.

Citation of "a substantially spherical core" in claim 1 is unclear. An explanation is requested.

## Claim Rejections - 35 USC § 103-- Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

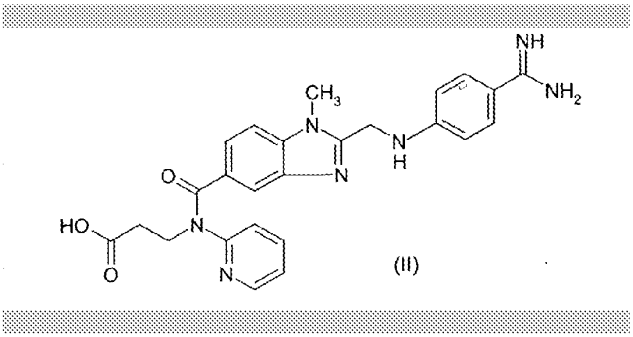
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any

inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8-14 and 16-22 rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/37075, CROTTS et al. (2003/001723; US Patent 7,316, 819), HASTANO et al. (US 6,309,666), BASTIN, R. et al. (Organic Process Res. and Development (2000) and AKIRA et al.[1].

The WO reference teaches the compound. The specification also discloses that the active compound used in the claimed composition is known in the art. The compound is commonly known as BIBR 1048.




(II)

CROTTS et al. teaches a pharmaceutical composition for oral delivery of a peptide in the form of a lamination having at least two layers. The first layer of the lamination includes at least one pharmaceutically acceptable pH-lowering agent. The second layer includes a therapeutically effective amount of the peptide. The composition also includes at least one absorption enhancer effective to promote bioavailability of the peptide, which is preferably in the second layer, and an enteric coating surrounding the lamination. In a preferred dosage form of a tablet, a water-soluble coating is applied between the lamination and enteric coating which substantially prevents contact between the pH-lowering agent and the enteric coating. In a specific composition pH-lowering agent is citric acid, and the absorption enhancer is lauroyl l-carnitine. The reference also teaches the use of binder. See the entire document especially abstract, lines 18-55 in column 2.

HATANO et al. teaches a pharmaceutical preparation in the form of a coated capsule which can release contents of a capsule at a lower part of the digestive tract comprising (a) a hard capsule containing at least an acidic substance, (b) a polymer film soluble at low pH which is formed on a surface of said hard capsule, and (c)

[1] Abstract of JP 58-134033

an enteric coating film which is formed on a surface of said polymer film soluble at low pH. To each of the contents of the hard capsule, the sealing means, the low pH-soluble polymer film, the enteric coating film and the intermediate layer between the low pH-soluble polymer film and the enteric coating film, if necessary, there can be added various additives generally used in the art of pharmaceutical preparation, for instance, an excipient, a binder, a disintegrant, a lubricant, an aggregation-preventing agent, a coating auxiliary, a coloring agent, a masking agent, a plasticizer to improve the coating property and the film-formability etc., a surfactant, an antistatic agent, an additive for controlling transmittance of light, and the like.

The reference further teaches the pharmaceutical preparation, for any kind of a medicament can be delivered to any desired site between the upper part of the small intestine and the lower part of the large intestine in the digestive tract by controlling the amount of polymer(s) used for the polymer film soluble at low pH and/or by selecting the kind of the polymer film soluble at low pH and/or the acidic substance without any complicated requirements for each medicament. The reference teaches the use of the binders in the composition for example an oligosaccharide or sugar alcohol such as sucrose, glucose, lactose, maltose, sorbitol or mannitol; a polysaccharide such as dextrin, starch, sodium alginate,

carrageenan, guar gum, arabic gum or agar; a natural high molecular substance such as tragacanth, gelatin or gluten; a cellulose derivative such as methylcellulose, ethylcellulose, sodium carboxymethylcellulose or hydroxypropylmethylcellulose; a synthetic polymer such as polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, polyethylene glycol, polyacrylic acid or polymethacrylic acid; and the like. See the entire document especially lines 39-62 in column 11, lines 24-34 and 58-65 in column 12, lines 48-63 in column 13, examples and claims.

BASTIN teaches a salt selection and optimization procedures for pharmaceutical new chemical entities. It further teaches that selection of salts is useful for development of dosage forms with good bioavailability, stability, manufacturability. See the entire document especially abstract, table 1 on page 428, column 2 on page 428, Table 2 on page 429, table 4 on page 430.

AKIRA teaches drug composition for oral medication having improved solubility, obtained by adding an acidic substance to cinnarizine. An acidic substance (e.g., tartaric acid, citric acid, etc.) is added to cinnarizine, to give a drug composition tablet, etc. may be used as the form of the drug. When it is orally medicated, it is hardly affected by the change in pH value in tile stomach; it shows stable solubility in the digestive organs. Consequently, it has improved effects such as stable absorption in the body.

It would have been obvious to one skilled in the art at the time of the invention to prepare a coated tablet containing core with organic acids and the second layer contain active compound, binders and other material needed to prepare a tablet or a capsule because first CROTTS teaches a pharmaceutical composition for oral delivery of a peptide in the form a lamination having at least two layers. The first layer of the lamination includes at least one pharmaceutically acceptable pH-lowering agent, the second layer includes a therapeutically effective amount, second HATANO et al. pharmaceutical preparation in the form of a coated capsule which can release contents of a capsule at a lower part of the digestive tract comprising (a) a hard capsule containing at least an acidic substance, (b) a polymer film soluble at low pH which is formed on a surface of said hard capsule, and (c) an enteric coating film which is formed on a surface of said polymer film soluble at low pH. It also teaches binder and other components needed to form the coating and tablet or capsule, third BESTIN teaches a salt selection and optimization procedures for pharmaceutical new chemical entities. It further teaches that selection of salts is useful for development of dosage forms with good bioavailability, stability, manufacturability; fourth AKIRA teaches drug composition for oral medication when an acidic substance (e.g., tartaric acid, citric acid, etc.) is added to cinnarizine, to give a drug composition tablet, etc. may be

used as the form of the drug. When it is orally medicated, it is hardly affected by the change in pH value in tile stomach; it shows stable solubility in the digestive organs. Consequently, it has improved effects such as stable absorption in the body.

See KSR Supreme Court of United States Decision (Decided April 30, 2007, KSR INTERNATIONAL CO. v. TELEFLEX INC. et al. No. 04-1350) where it states that (1) "However, the issue is not whether a person skilled in the art had the motivation to combine the electronic control with an adjustable pedal assembly, but whether a person skilled in the art had the motivation to attach the electronic control to the support bracket of pedal assembly". (2) "the results of ordinary innovation are not the subject of exclusive rights under the patent laws".

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

**Response to Remarks**

Applicant's arguments were fully considered but are not found persuasive. The arguments are based on previously presented claims which are now amended to a different subject matter. Now claims are drawn to composition comprising two layers.

Examiner notes that Applicants are attacking the references individually. It has been decided by the courts that "One cannot show nonobviousness by **attacking references individually** where the rejections are based on combinations of references." In re Keller, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Claim 15 is withdrawn from consideration as non elected invention.

## Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day except Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Sabiha Qazi/
Primary Examiner, Art Unit 1612

| Notice of References Cited | Application/Control No. 11/381,890 | Applicant(s)/Patent Under Reexamination BRAUNS ET AL. | |
|---|---|---|---|
| | Examiner Sabiha Qazi | Art Unit 1612 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-2003/0017203 | 01-2003 | Crotts et al. | 424/477 |
| * | B | US-7,316,819 | 01-2008 | Crotts et al. | 424/464 |
| * | C | US-6,309,666 | 10-2001 | Hatano et al. | 424/463 |
| * | D | US-6,414,008 | 07-2002 | Hauel et al. | 514/394 |
| * | E | US-5,912,014 | 06-1999 | Stern et al. | 424/474 |
| * | F | US-4,367,217 | 01-1983 | Gruber et al. | 424/494 |
| * | G | US-6,087,380 | 07-2000 | Hauel et al. | 514/336 |
| * | H | US-6,248,770 | 06-2001 | Ries et al. | 514/394 |
| * | I | US-6,469,039 | 10-2002 | Hauel et al. | 514/394 |
| | J | US- | | | |
| | K | US- | | | |
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**FOREIGN PATENT DOCUMENTS**

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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | BASTIN, Richard J. et al. (Organic Process Research and Development 2000, 4, No. 5, 427-435). |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



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**MSN Exhibit 1008**
**Page 157 of 304**

# Index of Claims

| Application/Control No. | Applicant(s)/Patent under Reexamination |
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| 11/381,890 | BRAUNS ET AL. |
| **Examiner** | **Art Unit** |
| Sabiha Qazi | 1612 |

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| Search Notes | Application/Control No. | Applicant(s)/Patent under Reexamination | |
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| | 11/381,890 | BRAUNS ET AL. | |
| | Examiner | Art Unit | |
| | Sabiha Qazi | 1612 | |

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| Class | Subclass | Date | Examiner |
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| INTERFERENCE SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
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| SEARCH NOTES (INCLUDING SEARCH STRATEGY) | | |
|---|---|---|
| | DATE | EXMR |
| stn database search | 3/23/2007 | STIC |
| inventor search | 3/23/2008 | QAZI |
| west | 3/22/2008 | |
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# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11381890 |
| **Filing Date:** | 05-May-2006 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| First Named Inventor/Applicant Name: | Ulrich Brauns |
| **Filer:** | Wendy Ann Petka/Pearlene Johnson |
| **Attorney Docket Number:** | 01-1306-1-C1 |
| Filed as Large Entity | |

**Utility Filing Fees**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| Post-Allowance-and-Post-Issuance: | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| Request for continued examination | 1801 | 1 | 810 | 810 |
| | | **Total in USD ($)** | | **810** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 3730889 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28501 |
| **Filer:** | Wendy Ann Petka/Pearlene Johnson |
| **Filer Authorized By:** | Wendy Ann Petka |
| **Attorney Docket Number:** | 01-1306-1-C1 |
| **Receipt Date:** | 05-AUG-2008 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 14:33:26 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $810 |
| RAM confirmation Number | 9404 |
| Deposit Account | 022955 |
| Authorized User | |

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes) /Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Fee Worksheet (PTO-06) | fee-info.pdf | 8325<br>8d7bb5362a4482dfaa866bc02bbe5b650624b850 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 8325 | | |

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

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

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

PTO/SB/30EFS (03/08)
Approved for use through 03/31/2008. 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.

# REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
## (Submitted Only via EFS-Web)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Application Number | 11/381,890 | Filing Date | 2006-05-05 | Docket Number (if applicable) | 01-1306-1-C1 | Art Unit | 1616 |
| First Named Inventor | Ulrich Brauns | | | Examiner Name | Sabiha Naim Qazi | | |

**This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.**
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

### SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

### MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

### FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 022955

### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (08/08)
Approved for use through 03/31/2008. 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.

| Signature of Registered U.S. Patent Practitioner | | | |
|---|---|---|---|
| Signature | /wendy petka/ | Date (YYYY-MM-DD) | 2008-07-31 |
| Name | Wendy Petka | Registration Number | 53459 |

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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

# Privacy Act Statement

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

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

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

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 Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11381890 |
| **Filing Date:** | 05-May-2006 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| First Named Inventor/Applicant Name: | Ulrich Brauns |
| **Filer:** | Wendy Ann Petka |
| **Attorney Docket Number:** | 01-1306-1-C1 |
| Filed as Large Entity | |

**Utility Filing Fees**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| Claims in excess of 20 | 1202 | 17 | 50 | 850 |
| Multiple dependent claims | 1203 | 1 | 370 | 370 |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| Post-Allowance-and-Post-Issuance: | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Extension-of-Time:** | | | | |
| Extension - 3 months with $0 paid | 1253 | 1 | 1050 | 1050 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **2270** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 3708164 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28501 |
| **Filer:** | Wendy Ann Petka |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | 01-1306-1-C1 |
| **Receipt Date:** | 31-JUL-2008 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 13:18:20 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $2270 |
| RAM confirmation Number | 7666 |
| Deposit Account | 022955 |
| Authorized User | |

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes) /Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 1-1306-1-C1-2008-07-31-RFOA.pdf | 153883<br>b94826e589087fd989ec98b04d1bbf5d3fef4215 | yes | 10 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Amendment After Final | 1 | 1 |
| Claims | 2 | 6 |
| Applicant Arguments/Remarks Made in an Amendment | 7 | 10 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Request for Continued Examination (RCE) | 1-1306-1-C1-2008-07-31-RCE-filed.pdf | 35897<br>a7739dac6c63d41ea8d041dd3ac38373eae443a1 | no | 3 |

**Warnings:**

This is not a USPTO supplied RCE SB30 form.

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 3 | Fee Worksheet (PTO-06) | fee-info.pdf | 8586<br>de88013912ce2aca6c4c93a4dd3d1f25526ccfd3 | no | 2 |

**Warnings:**

**Information:**

| | |
|---|---|
| **Total Files Size (in bytes):** | 198366 |

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | |
|---|---|---|---|---|
| Application of | : | Ulrich Brauns | ) Art Unit | : 1616 |
| Serial No. | : | 11/381,890 | ) Examiner | : Sabiha Naim Qazi |
| Confirmation No.: | | 5127 | | |
| Filed | : | May 5, 2006 | | |
| Title | : | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |
| Docket No. | : | 01-1306-1-C1 | | |

Mail Stop AF/RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**REPLY TO FINAL OFFICE ACTION**

Sir:

This Reply is being filed in response to the February 7, 2008 Final Office Action issued in the above-identified application. In that Office Action, a three-month shortened statutory period was set for response. Applicant hereby petitions for a three-month extension of time under 37 C.F.R. § 1.136 to respond to that action and note that the fee required under 37 C.F.R. § 1.17(a) in connection with this extension of time will be paid during electronic filing via the Revenue Accounting and Management System. Applicant also petitions for a Request for Continued Examination (RCE) and the fee required under 37 C.F.R. § 1.17(e) will also be paid during electronic filing. Furthermore, if it is determined that any additional fees under 37 C.F.R. §§ 1.16 or 1.17 are due in connection with this Reply or RCE, authorization to charge such fees to Deposit Account No. 02-2955 will be provided during electronic filing.

Please amend the above-identified application as follows:

**Amendments to the Claims** begin on page 2 of this paper.

**Remarks** begin on page 7 of this paper.



**IPR2025-01107**
**MSN Exhibit 1008**
**Page 172 of 304**

**Amendments to the Claims:**

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

**Listing of Claims:**

Claim 1 (currently amended): A pharmaceutical composition for oral administration comprising:
a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 mL at 20° C; and
~~a)~~ (b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material, wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof. ~~and~~
~~b) one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 ml at 20° C.~~

Claim 2 (currently amended): Pharmaceutical composition according to claim 1 or 18, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, ~~or~~ aspartic acid and ~~one of the hydrates or acid salts~~ any combination thereof.

Claim 3 (currently amended): Pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, citric acid ~~and~~ succinic acid and any combination thereof.

Claim 4 (original): Pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable organic acid is tartaric acid.



IPR2025-01107
MSN Exhibit 1008
Page 173 of 304

Claim 5 (currently amended): Pharmaceutical composition according to claim 1 or 18, wherein the content of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate ~~or the salts thereof~~ in the pharmaceutical composition is 5 to 60 %.

Claim 6 (currently amended): Pharmaceutical composition according to claim 1 or 18, wherein the content of pharmaceutically acceptable organic acid is 20 to 90 %.

Claim 7 (canceled).

Claim 8 (currently amended): Pharmaceutical composition according to claim **[[**7**]]** 1 or 18, wherein said binder is selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone, ~~and~~ vinyl acetate ~~or~~ and any combination**[[**s**]]** thereof.

Claim 9 (currently amended): Pharmaceutical composition according to claim **[[**7**]]** 1 or 18, wherein said core material has an average particle size of 0.4 to 1.5 mm.

Claim 10 (currently amended): Pharmaceutical composition according to claim **[[**7**]]** 1 or 18, wherein said core material and the active substance layer are separated from one another by an insulating layer comprised of a water-soluble polymer, optionally with the addition of suitable plasticisers, separating agents and pigments.

Claim 11 (original): Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of gum arabic.

Claim 12 (currently amended): Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of a partially or totally



**IPR2025-01107**
**MSN Exhibit 1008**
**Page 174 of 304**

synthetic polymer selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone, ~~and~~ vinyl acetate, ~~or a~~ and any combination thereof.

Claim 13 (currently amended): Pharmaceutical composition according to claim **[[**7**]]** 1 or 18, wherein the composition containing the active substance is packed into hard capsules.

Claim 14 (currently amended): Pharmaceutical composition according to claim 1 or 18, wherein ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate is used as the active substance.

Claim 15 (withdrawn): A process for preparing a pharmaceutical composition for oral administration containing ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the physiologically acceptable salts thereof, comprising the steps of:

a) forming the core material from one or more pharmaceutically acceptable organic acid(s) with a water solubility of > 1 g / 250 ml at 20° C, optionally with the addition of binders or other technological adjuvants, by pan methods, on pelleting plates or by extrusion / spheronisation,

b) applying to the core material an insulating layer comprised of one or more water-soluble, pharmaceutically acceptable polymers optionally with the addition of plasticisers, separating agents and/or pigments,

c) applying the active substance from a dispersion which contains a binder and optionally separating agents and simultaneously and/or subsequently drying to eliminate the dispersant,

d) optionally applying a coating of film-forming agents, plasticisers and optionally pigments and

e) packing the active substance-containing pellets thus obtained into capsules.



**IPR2025-01107
MSN Exhibit 1008
Page 175 of 304**

Claim 16 (canceled).

Claim 17 (previously presented): Pharmaceutical composition of claim 13, wherein the hard capsule is hydroxypropylmethylcellulose (HPMC).

Claim 18 (currently amended): A pharmaceutical composition for oral administration comprising:
a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 160 mL at 25° C; and
~~a)~~ (b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material, wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof. ~~and~~
~~b) one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 160 mL at 25° C.~~

Claim 19 (new): Pharmaceutical composition of claim 1 or 18, wherein the active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate and the pharmaceutically acceptable organic acid is tartaric acid.

Claim 20 (new): The pharmaceutical composition according to claim 10, wherein the core material consists of tartaric acid and gum arabic, the insulating layer consists of gum arabic and talc and the active substance layer consists of talc, hydroxypropylcellulose and ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate.

Claim 21 (new): The pharmaceutical composition according to claim 20, wherein the tartaric acid in the core material is present in the composition at about 61.3%, the gum arabic in the core material is present in the composition at about 3.1%, the gum arabic in the insulating layer is present in the composition at about

2.8%, the talc in the insulating layer is present in the composition at about 5.6%, the talc in the active substance layer is present in the composition at about 3.2%, the hydroxypropylcellulose in the active substance layer is present in the composition at about 4.0% and the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate in the active substance layer is present in the composition at about 20%.

Claim 22 (new): The pharmaceutical composition according to claim 20, wherein the tartaric acid in the core material is present in the composition at about 38.5%, the gum arabic in the core material is present in the composition at about 1.9%, the gum arabic in the insulating layer is present in the composition at about 1.7%, the talc in the insulating layer is present in the composition at about 3.5%, the talc in the active substance layer is present in the composition at about 6.4%, the hydroxypropylcellulose in the active substance layer is present in the composition at about 8.0% and the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate in the active substance layer is present in the composition at about 40%.

REMARKS

Claims 1-6, 8-14 and 17-22 are pending in this application. Claim 15 has been withdrawn. Claims 1 and 18 have been amended to recite the subject matter of former claim 7. Claims 1-3, 5-6, 8-10, 12-14 and 18 have been amended to improve the form and/or to recite proper dependency. Applicant has added claims 19-22 to recite specific components comprising the core material, insulating layer and active substance layer. Support for these claims is found in the specification on page 11 to page 17. Claim 7 has been canceled. Applicant makes this cancellation without prejudice or waiver of right to pursue the cancelled subject matter in a continuing application claiming priority under 35 U.S.C. § 120. No new matter has been added by way of this amendment.

Applicant requests consideration of the above-identified application in view of the following remarks.

**A. Finality of Office Action**

Applicant's representative contacted the Examiner on July 3, 2008 to discuss whether the finality of the Office Action was appropriate under 37 C.F.R. 1.113. Applicant notes that the Examiner cited a new reference in the 103 rejection (the AKIRA reference) that does not seem to be prompted by any claim amendments. Applicant made this reference of record in response to the previous Office Action. Applicant kindly asks that the Examiner reconsider the finality of the present Office Action.

**B. Rejection under 35 U.S.C. § 103(a)**

Claims 1-14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over ILLUM et al. (US Patent 6,387,917 B1), BACH et al. (3,968,111) and AKIRA et al. (Abstract of JP 58-134033). The Examiner asserts that ILLUM teaches a methane sulphonate salt of morphine, BACH teaches a methanesulfonate salt of 8,8-disubstituted-6-methylergoline and AKIRA teaches drug composition for oral medication having improved solubility, obtained by adding an acidic substance to cinnarizine. Although the references do not teach the same base as presently being claimed, the Examiner nonetheless argues that "it would have been obvious … to make a methanesulphonate salt of the known compound because prior art teaches that methane sulphonate salt[s] are non toxic, water soluble preferably useful for intravenous or intramuscular administration and AKIRA teaches the use of organic acids such as tartaric acid, citric acid et which are organic acids. Motivation has been provided by the prior art cited above to make methanesulphonate salt for enhance



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solubility, stability and non-toxic nature of this salt." Applicant respectfully traverses.

The Supreme Court addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), wherein the Court stated that the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), factors still control an obviousness inquiry. Those factors, (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art; and (4) objective evidence of non-obviousness, are discussed in more detail below.

As discussed previously, the presently claimed invention was developed in response to the clinical trials showing that conventional tablets of formula I were not ideal for patient administration. Applicant discusses in detail this problem in the specification, e.g., starting on page 7, entitled "Clinical trials," and thereafter, and provides evidence that the claimed compositions demonstrate improved bioavailability of the active substance in patients when compared to the conventional tablets at elevated gastric pH. Among other things, this is relevant for patients who have increased gastric pH due to normal physiological variability, disease or co-medication with drugs. Because the claimed compositions of the present invention are less sensitive to pH fluctuations, malabsorption or poor absorption by the small intestines may be prevented.

To this end, claims 1 and 18 have been amended to more particularly point out and claim the subject matter that applicant regards as the invention. For example, Claim 1 now recites (a) an inner substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 mL at 20° C, which is (b) surrounded by an active substance layer containing one or more binders and optionally a separating agent, where the active substance is formula I or a pharmaceutically acceptable salt thereof. The arrangement (e.g., see Figure 1) of the components in the pharmaceutical composition is relevant because the active substance is sensitive to various pH levels, i.e., the compound of formula I dissolves readily in water at low pH levels but is virtually insoluble at pH levels above 5 (see specification page 8, lines 1-3). In other words, the compound of formula I will be cleaved at low pH but will be insoluble at mid- to high pH, like those pH levels found in the intestinal tract. As a result, the composition according to this invention requires resistance to acid cleavage and solubility at mid-to high pH. The presently claimed pharmaceutical compositions achieve just that.

ILLIUM, BACH and AKIRA teach away from the claimed invention because "conventional" techniques are being disclosed. As an initial matter, none of these references teach or suggest (1) the compound of formula I, (2) the organic acid core

material or (3) the concept of a pharmaceutical composition comprising an organic acid core surrounded by active substance layer to address bioavailability fluctuations of formula I in the intestinal tract. Furthermore, ILLIUM is largely directed to solutions of the methane sulphonate salt[1] of morphine for administration by various routes. Although a solid dosage form is disclosed in ILLIUM (see Example 4), the solid form first involves mixing a solution of morphine as the methane suphonate salt with cellulose, and thereafter drying, screening and pressing into tablet form. Thus, ILLIUM does nothing more than generally disclose a suitable morphine salt homogeneously mixed with cellulose for administration. Among other things, it does not mention the importance of an acid core material to the presently claimed pharmaceutical composition.

Similar to ILLIUM, BACH discloses salts of a different active ingredient, i.e., an ergoline derivative. The Examiner directs applicant to Example 16 and column 13, lines 46-51 of BACH. Example 16, however, recites intraperioneal injection of ethanolic solutions of ergoline derivative salts. The example does not require the use of a pharmaceutically-accepable acid at all. Furthermore, lines 46-51 generally recite that the salts of the ergoline derivatives can be mixed with standard pharmaceutical excipients and loaded into empty telescoping gelatin capsules or pressed into tablets. Again, this does not suggest any of the elements in the instant claims because it relates to conventional technology, which was discontinued in making the present invention.

Finally, the AKIRA abstract discloses that cinnarizine has improved solubility by adding an acidic substance to it for use in oral administration. There is nothing in this disclosure to suggest the elements of the present claims and it does nothing more than disclose conventional wisdom, which, once again, is inapplicable to the present invention.

The Federal Circuit recently opined on the obviousness inquiry as it relates to the chemical arts (*see, Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd. and Teva Pharmaceuticals USA, Inc.*, Nos. 2007-1397, -1398 (Fed. Cir. 2008)). Here, the Court reiterated that "the obviousness inquiry must rely on evidence 'at the time' of the invention." *Id.* at 8, citing *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 n.2, (Fed. Cir. 2007). The Court also discussed and outlined assumptions that the Supreme Court made in KSR, namely (1) KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions; (2) KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the

[1] Applicant notes that the presently claimed invention is directed to pharmaceutically acceptable salts of formula I, not only the mesylate salt.



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claimed compound; and (3) the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," (*KSR* at 1742). None of these assumptions are met with the combination of ILLIUM, BACH and AKIRA because performing the clinical trials with formula I would have been a necessary element prior to identifying the problem and solving it, as it was done in the present invention. Additionally, the combination of ILLUM, BACH and AKIRA cannot provide a basis for obviousness because one of ordinary skill in the art would appreciate that the elements of the presently claimed invention are missing. Moreover, one of skill in the art would appreciate that the scope and content of the prior art teaches away from the present invention in the ways described above. For these reasons, applicant kindly requests that the Examiner withdrawal the rejection of obviousness under 35 U.S.C. § 103(a) and issues a timely Notice of Allowance in this case.

Respectfully submitted,

/wendy petka/

Wendy Petka
Reg. No. 53,459

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PTO/SB/30EFS (03/08)
Approved for use through 03/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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# REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
## (Submitted Only via EFS-Web)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Application Number | 11/381,890 | Filing Date | 2006-05-05 | Docket Number (if applicable) | 01-1306-1-C1 | Art Unit | 1616 |
| First Named Inventor | Ulrich Brauns | | | Examiner Name | Sabiha Naim Qazi | | |

**This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.**
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

### SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

### MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

### FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 022955

### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

| Signature of Registered U.S. Patent Practitioner | | | |
|---|---|---|---|
| Signature | /wendy petka/ | Date (YYYY-MM-DD) | 2008-07-31 |
| Name | Wendy Petka | Registration Number | 53459 |

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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

# Privacy Act Statement

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

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

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

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.

PTO/SB/06 (07-06)
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# PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

| Application or Docket Number | Filing Date | ☐ To be Mailed |
|---|---|---|
| 11/381,890 | 05/05/2006 | |

## APPLICATION AS FILED – PART I

| | (Column 1) | (Column 2) | SMALL ENTITY ☐ | | OR | 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 | 300 |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | | OR | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | | | X $ = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 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 | | | TOTAL | 300 |

## APPLICATION AS AMENDED – PART II

| AMENDMENT 07/31/2008 | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE ($) | ADDITIONAL FEE ($) | OR | OTHER THAN SMALL ENTITY RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * 37 | Minus | ** 20 | = 17 | X $ = | | OR | X $50= | 850 |
| Independent (37 CFR 1.16(h)) | * 3 | Minus | ***3 | = 0 | X $ = | | OR | X $210= | 0 |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☒ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | 370 |
| | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | 1220 |

| AMENDMENT | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) | | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|
| Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | | OR | X $ = | |
| Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | | OR | X $ = | |
| ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GLORIA TRAMMELL/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 1/1306-1-C1 | 5127 |

28501 7590 02/07/2008

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| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |
| **ART UNIT** | **PAPER NUMBER** |
| 1612 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 02/07/2008 | PAPER |

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

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



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Page 186 of 304

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 11/381,890 | BRAUNS ET AL. | |
| | Examiner | Art Unit | |
| | Sabiha Qazi | 1612 | |

*-- 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *21 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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**

4)☒ Claim(s) *1-15,17 and 18* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *15* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**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).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**Final Office Action**

Claims 1-15, 17 and 18 are pending. No claim is allowed. Amendments are entered.

**Summary of this Office Action dated January 19, 2008**

1. Information Disclosure Statement
2. Copending Applications
3. Specification
4. 35 USC § 103(a) Rejection
5. Conclusion
6. Communication

**Information Disclosure Statement**

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

**Copending Applications**

Applicants must bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications, which are "material to patentability" of the application in question. MPEP 2001.06(b). See Dayco Products Inc. v. Total Containment Inc., 66 USPQ2d 1801 (CA FC 2003).

**Specification**

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

**Claim Rejections - 35 USC § 103-- Rejection**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14, 17 and 18 rejected under 35 U.S.C. 103(a) as being unpatentable over ILLUM et al.[1], BACH et al.[2] and AKIRA et al.[3].

ILLUM teaches methane sulphonate salt of morphine and compositions thereof. These salts can provide physically stable aqueous solutions of the drug for parenteral or non parenteral administration. The reference also teaches comparative stability of methanesulphonic salts (see example 3). See the entire document especially lines 43-67 in column 2; lines 30-61 in column 4; examples and claims.

BACH teaches pharmaceutically acceptable additional salts of non-toxic organic acids which includes methanesulfonate (see the entire document especially lines 38-66 in column 2 and example 16. The reference teaches preferred methanesulfonate salt (lines 46-51 in column 13).

AKIRA teaches drug composition for oral medication

having improved solubility, obtained by adding an acidic substance to cinnarizine. An acidic substance (e.g., tartaric acid, citric acid, etc.) is added to cinnarizine, to give a drug composition tablet, etc. may be used as the form of the drug. When it is orally medicated, it is hardly affected by the change in pH value in tile stomach; it shows stable solubility in the digestive organs. Consequently, it has improved effects such as stable absorption in the body.

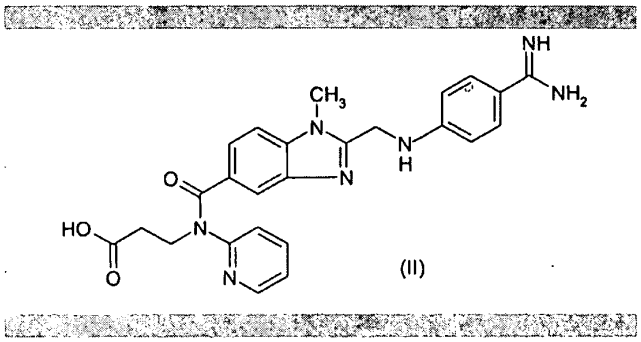
Furthermore, the reference teaches as preferred additional soluble salt methanesulfonate salt in particular for intravenous or intramuscular administration. The reference does not teach

[1] US Patent 6,387,917 B1
[2] US Patent 3,968111

[3] Abstract of JP 58-134033

the same base as presently claimed however it teaches that methanesulfonate salts are soluble and is preferably useful for intravenous or intramuscular administration.

Instant claims differ from the reference in claiming a methanesulphonate of one specific compound having the following structure with one or more pharmaceutically acceptable organic acids.




(II)

It would have been obvious to one skilled in the art at the time of invention to make a methanesulphonate salt of the known compound because prior art teaches that methane sulphonate salt are non toxic, water soluble preferably useful for intravenous or intramuscular administration and AKIRA teaches the use of organic acids such as tartaric acid, citric acid etc which are organic acids. Motivation has been provided by the prior art cited above to make methanesulphonate salt and adding organic acids for enhanced solubility, stability and non-toxic nature of this salt. The reference AKIRA teaches the advantages of acids such as citric acid and tartaric acid in a drug composition.

No new concept and/or criticality of invention were found.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a). See KSR Supreme Court of United States Decision (Decided April 30, 2007, KSR INTERNATIONAL CO. v. TELEFLEX INC. et al. No. 04-1350) where it states that (1) "However, the issue is not whether a person skilled in the art had the motivation to combine the electronic control with an adjustable pedal assembly, but whether a person skilled in the art had the motivation to attach the electronic control to the support bracket of pedal assembly". (2) "the results of ordinary innovation are not the subject of exclusive rights under the patent laws".

**Response to Remarks**

Applicant's arguments were fully considered but are not found persuasive. Since the Akira reference teaches the use of acids for stable solubility in digestive system because it not effected by the change in pH in the stomach, therefore the drug has improved effect. At the time of invention adding an acid such as tartaric acid or citric acid would have been obvious to one skilled the art. Since no criticality and/or unexpected results are noted, presently claimed invention would have obvious to one skilled in the art for the reasons cited above.

Claim 15 is withdrawn from consideration as non elected invention.

***Conclusion***

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

**Communication**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi, Ph.D. whose telephone number is 571-272-0622. The examiner can normally be reached on any business day.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Michael Woodward, Ph.D. can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SABIHA QAZI, PH.D
PRIMARY EXAMINER

PTO/SB/08b (04-07)
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 1

| Complete if Known | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | May 5, 2006 |
| First Named Inventor | Brauns, Ulrich, et al |
| Art Unit | 1616 |
| Examiner Name | Qazi, Sabiha Naim |
| Attorney Docket Number | 1/1306-1-C1 |

**NON PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| SQ | | ~~GENNARO, ALFONSO, R.; Remington Farmacia 19th Edition, Panamericana Espana 1988, p. 2470, Ecuador (December 2006)~~ No English abstract | |

| Examiner Signature | Sabiha Qazi | Date Considered | 1/18/08 |
|---|---|---|---|

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

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 2

| *Complete if Known* | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | May 5, 2006 |
| First Named Inventor | BRAUNS, Ulrich |
| Art Unit | 1618 |
| Examiner Name | Qazi, Sabiha Naim |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | US- 2003/0181488 | 09/25/2003 | Brauns, Ulrich | |
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| | | US- 2005/0038077 | 02/17/2005 | Kohlrausch, Anja, et al | |
| | | US- 2005/0095293 | 05/05/2005 | Brauns, Ulrich, et al | |
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| | | US- 2006/0222640 | 10/05/2006 | Reilly, Paul, et al. | |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| SBQ | | JP 58134033 | 08/10/1983 | Fujisawa Pharm. | Abstract only | |
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| Examiner Signature | S. Qazi | Date Considered | 01/18/2008 |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 2

| *Complete if Known* | |
|---|---|
| *Application Number* | 11/381,890 |
| *Filing Date* | May 5, 2006 |
| *First Named Inventor* | Brauns, Ulrich |
| *Art Unit* | 1616 |
| *Examiner Name* | Qazi, Sabiha Naim |
| *Attorney Docket Number* | 1/1306-1-C1 |

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|---|---|---|---|
| SQ | | The Merck Index 14th Edition, Merck & Co., NJ, USA, 2001, No. 9156, 4308, and 845, Ecuador, (Dec. 2006) | |

| Examiner Signature | Sabiha Qazi | Date Considered | 1/18/08 |
|---|---|---|---|

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## Index of Claims

| Application/Control No. | Applicant(s)/Patent under Reexamination |
|---|---|
| 11/381,890 | BRAUNS ET AL. |
| **Examiner** | **Art Unit** |
| Sabiha Qazi | 1612 |

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 1

| *Complete if Known* | |
|---|---|
| *Application Number* | 11/381,890 |
| *Filing Date* | May 5, 2006 |
| *First Named Inventor* | Brauns, Ulrich, et al |
| *Art Unit* | 1616 |
| *Examiner Name* | Qazi, Sabiha Naim |
| *Attorney Docket Number* | 1/1306-1-C1 |

**NON PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | | GENNARO, ALFONSO, R.; Remington Farmacia 19th Edition, Panamericana Espana 1988, p. 2470, Ecuador (December 2006) | |
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| Examiner Signature | | Date Considered | |
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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Application of | : Brauns, Ulrich, et al | ) Art Unit: | 1616 |
| U.S. Appln. No. | : 11/381,890 | ) Examiner: | Qazi, Sahiba |
| Confirmation No. | : 5127 | | |
| U.S. Filing Date | : May 5, 2006 | | |
| Title of Invention | : ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |
| Attny. Docket No. | : 1/1306-1-C1 | | |

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

September 21, 2007

**TRANSMITTAL LETTER FOR INFORMATION DISCLOSURE STATEMENT**

Sir:

Transmitted herewith concerning the subject application is an Information Disclosure Statement (Form 1449A/B) under 37 C.F.R. §§1.56 and 1.97, as more specifically described hereinbelow.

☐ 1.97(b). This Statement is being filed: i) within three (3) months of the filing date of a national application other than a continued prosecution application under 37 C.F.R. §1.53 (d); ii) within three (3) months of the date of entry of the national stage as set forth in 37 C.F.R. §1.491 in an international application; iii) before the mailing of a first Office action on the merits; or iv) before the mailing of a first Office action after the filing of a request for continued examination under 37 C.F.R. §1.114.

☒ 1.97(c). This Statement is being filed after the time period specified in 37 C.F.R. §1.97(b), but before the mailing date of: i) a final action under 37 C.F.R. §1.113, ii) a notice of allowance under 37 C.F.R. §1.311, or iii) an action that otherwise closes prosecution in the application. This Statement is being accompanied by:

☒ A statement as specified in 37 C.F.R. §1.97(e) [see below]; or



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Page 201 of 304

☐ The fee set forth in 37 C.F.R. §1.17(p).

☐ The Commissioner is hereby authorized to charge payment of the $180.00 fee set forth in 37 C.F.R. §1.17(p) to Deposit Account No. 02-2955.

☐ 1.97(d). This Statement is being filed after the period specified in 37 C.F.R. §1.97(c) but on or before payment of the issue fee. This Statement is accompanied by a statement as specified in 37 C.F.R. §1.97(e) [see below] and the fee set forth in 37 C.F.R. §1.17(p).

☐ 1.97(e).

☐ Each item of information contained in the instant information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three (3) months prior to the filing of the instant information disclosure statement; or

☐ No item of information contained in the instant 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 this certification after making reasonable inquiry, no item of information contained in the instant information disclosure statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three (3) months prior to the filing of the instant information disclosure statement.

☐ The fee set forth in 37 C.F.R. §1.17(p).

☐ The Commissioner is hereby authorized to charge payment of the $180.00 fee set forth in 37 C.F.R. §1.17(p) to Deposit Account No. 02-2955.

☐ 1.704(d). Each item of information contained in the accompanying information disclosure statement was first cited in any communication from a foreign patent office in a counterpart application, which communication was not received by any individual designated in section 1.56(c) more than thirty (30) days prior to the filing of the accompanying information disclosure statement.

☒ The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 C.F.R. §1.16 and any patent application processing fees under 37 C.F.R. §1.17, or credit any overpayment of same, to Deposit Account No. 02-2955.

Respectfully submitted,

/wendy petka/

Wendy Petka
Attorney for Applicant(s)
Reg. No. 53,459

Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877
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**IPR2025-01107**
**MSN Exhibit 1008**
**Page 203 of 304**

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 2224697 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28501 |
| **Filer:** | Wendy Petka/Pearlene Johnson |
| **Filer Authorized By:** | Wendy Petka |
| **Attorney Docket Number:** | 1/1306-1-C1 |
| **Receipt Date:** | 21-SEP-2007 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 13:50:39 |
| **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 | Information Disclosure Statement (IDS) Filed | 1-1306-1-C1-2007-09-21-infodiscstmt.pdf | 4457611<br>ec8e39a299c42da023cf4e7444b1195f065a6b64 | no | 2 |
| **Warnings:** | | | | | |

| Information: | | | | | |
|---|---|---|---|---|---|
| This is not an USPTO supplied IDS fillable form | | | | | |
| 2 | NPL Documents | Remington-Farmacia-19Edition.pdf | 4766480<br>81d228ad2869a55b1d0a878051ce7cc3e8d1604e | no | 54 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Information Disclosure Statement Letter | 1-1306-1-C1-2007-09-21-idstransmittal.pdf | 64022<br>1b4c0a1ea01347ddc7a04a0bd69e7f1712ce81eb | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 9288113 | | |

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

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

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

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | |
|---|---|---|---|---|
| Application of | : | Ulrich Brauns | ) Art Unit | : 1616 |
| Serial No. | : | 11/381,890 | ) Examiner | : Sabiha Naim Qazi |
| Confirmation No.: | | 5127 | | |
| Filed | : | May 5, 2006 | | |
| Title | : | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |
| Docket No. | : | 1/1306-1-C1 | | |

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

**REPLY TO OFFICE ACTION UNDER 37 C.F.R. § 1.111**

Sir:

This Reply is being filed in response to the April 9, 2007 Office Action issued in the above-identified application. In that Office Action, a three-month shortened statutory period was set for response on or before July 9, 2007.[1] Applicant hereby petitions for the necessary two-month extension of time under 37 C.F.R. § 1.136 to respond to that action and note that the fee required under 37 C.F.R. § 1.17(a) in connection with this extension of time will be paid during electronic filing via the Revenue Accounting and Management System. If it is determined that any additional fees under 37 C.F.R. §§ 1.16 or 1.17 are due in connection with this Reply, authorization to charge such fees to Deposit Account No. 02-2955 will be provided during electronic filing.

Please amend the above-identified application as follows:

**Amendments to the Claims** begin on page 2 of this paper.

**Remarks** begin on page 6 of this paper.

[1] With a two-month extension of time, the response is due on September 9, 2007. However, because September 9, 2007 is a Sunday, the response will be due on September 10, 2007 under 37 C.F.R. § 1.7.



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**Amendments to the Claims:**

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

**Listing of Claims:**

Claim 1 (previously presented): A pharmaceutical composition for oral administration comprising:
a) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof and
b) one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 ml at 20° C.

Claim 2 (original): Pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid or aspartic acid and one of the hydrates or acid salts thereof.

Claim 3 (original): Pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, citric acid and succinic acid.

Claim 4 (original): Pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable organic acid is tartaric acid.

Claim 5 (original): Pharmaceutical composition according to claim 1, wherein the content of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or the salts thereof in the pharmaceutical composition is 5 to 60 %.

Claim 6 (original): Pharmaceutical composition according to claim 1, wherein the content of pharmaceutically acceptable organic acid is 20 to 90 %.



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Claim 7 (original): Pharmaceutical composition according to claim 1 comprising a substantially spherical core material further comprised of a pharmaceutically acceptable organic acid, and active substance layer comprised of a binder and optionally a separating agent, which encloses said core material.

Claim 8 (original): Pharmaceutical composition according to claim 7, wherein said binder is selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone and vinyl acetate or combinations thereof.

Claim 9 (original): Pharmaceutical composition according to claim 7, wherein said core material has an average particle size of 0.4 to 1.5 mm.

Claim 10 (original): Pharmaceutical composition according to claim 7, wherein said core material and the active substance layer are separated from one another by an insulating layer comprised of a water-soluble polymer, optionally with the addition of suitable plasticisers, separating agents and pigments.

Claim 11 (original): Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of gum arabic.

Claim 12 (original): Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of a partially or totally synthetic polymer selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone and vinyl acetate, or a combination thereof.

Claim 13 (original): Pharmaceutical composition according to claim 7, wherein the composition containing the active substance is packed into hard capsules.



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Claim 14 (original): Pharmaceutical composition according to claim 1, wherein ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate is used as the active substance.

Claim 15 (withdrawn): A process for preparing a pharmaceutical composition for oral administration containing ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the physiologically acceptable salts thereof, comprising the steps of:

a) forming the core material from one or more pharmaceutically acceptable organic acid(s) with a water solubility of > 1 g / 250 ml at 20° C, optionally with the addition of binders or other technological adjuvants, by pan methods, on pelleting plates or by extrusion / spheronisation,

b) applying to the core material an insulating layer comprised of one or more water-soluble, pharmaceutically acceptable polymers optionally with the addition of plasticisers, separating agents and/or pigments,

c) applying the active substance from a dispersion which contains a binder and optionally separating agents and simultaneously and/or subsequently drying to eliminate the dispersant,

d) optionally applying a coating of film-forming agents, plasticisers and optionally pigments and

e) packing the active substance-containing pellets thus obtained into capsules.

Claim 16 (canceled).

Claim 17 (new): Pharmaceutical composition of claim 13, wherein the hard capsule is hydroxypropylmethylcellulose (HPMC).

Claim 18 (new): A pharmaceutical composition for oral administration comprising:



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a) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof and

b) one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 160 mL at 25° C.



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REMARKS

Claims 1-15 and 17-18 are pending in this application. Applicant has added claim 17 to recite the pharmaceutical composition of claim 13, wherein the hard capsule is a hard capsule of hydroxypropylmethylcellulose (HPMC). Support for this claim is found in the specification on page 7, line 15, page 14, line 13 and page 17, line 15. Applicant has also added claim 18. Support for this claim is found in the specification on page 2, lines 23-24. No new matter has been added by way of this amendment.

Applicant requests consideration of the above-identified application in view of the following remarks.

**A. Information Disclosure Statement**

The Examiner states that the listing of references in the specification is not a proper information disclosure statement under 37 C.F.R. § 1.98(b) and that under MPEP § 609.04(a), the list may not be incorporated into the specification but must be submitted in a separate paper. The Examiner further states that unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

Applicant points out that WO 98/37075, the only reference listed in the specification, was presented in an Information Disclosure Statement filed on May 6, 2006. This reference was subsequently considered by the Examiner, as evidenced by the signed copy of Form PTO/SB/08a accompanying the April 9, 2007 Non-final Action.

**B. Copending Applications**

In response to the Examiner's request, applicant has filed an Information Disclosure Statement concurrently herewith, listing *inter alia*, the parent application (10/383,198, US 20030181488 A1) and other copending published applications.

**C. Specification**

Applicant amended the specification to set forth a priority claim under 35 U.S.C. §§ 120 and 119(e) in a Preliminary Amendment filed on May 6, 2006. Applicant is not aware of any other corrections at this time.

**D. Claim Rejection – 35 U.S.C. § 103(a)**

***i. Joint Inventors***

A Request to Correct Inventorship under 37 C.F.R. § 1.48(b)(1) was filed on February 2, 2007. Norbert Hauel, whose invention is no longer being claimed, was



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deleted as an inventor in the present application. Ulrich Brauns remains the sole inventor to claims of this application. Applicants kindly request confirmation that the inventorship has been changed.

***ii. 35 U.S.C. § 103(a)***

Claims 1-14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over ILLUM et al. (US Patent 6,387,917 B1) and BACH et al. (3,968,111). The Examiner asserts that ILLUM teaches a methane sulphonate salt of morphine and BACH teaches a methanesulfonate salt of 8,8-disubstituted-6-methylergoline. Although the references do not teach the same base as presently being claimed, the Examiner nonetheless argues that "it would have been obvious … to make a methanesulphonate salt of the known compound because prior art teaches that methane sulphonate salt[s] are non toxic, water soluble preferably useful for intravenous or intramuscular administration. Motivation has been provided by the prior art cited above to make methanesulphonate salt for enhance solubility, stability and non-toxic nature of this salt." Applicant traverses.

The Supreme Court addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), wherein the Court stated that the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), factors still control an obviousness inquiry. Those factors, (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art; and (4) objective evidence of non-obviousness, are discussed in more detail below.

The present claims are directed to a pharmaceutical composition for oral administration comprising a single active (formula I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 mL at 20° C. The prior art teaches a methane sulphonate salt of morphine or 8,8-disubstituted-6-methylergoline for intravenous or intramuscular administration. One of skill in the art would appreciate that ILLUM and BACH lack any teaching of the second component of the present claims, that is, the water-soluble organic acid and its importance in improving bioavailability of formula I or salts thereof. Moreover, one of skill in the art would appreciate that ILLUM and BACH teach salts that are useful for intravenous or intramuscular administration, whereas the pharmaceutical compositions of the present invention are designed for oral administration. As such, ILLUM and/or BACH cannot obviate the presently claimed invention.

Objective evidence of non-obviousness in the specification also supports applicant's argument. For example, during clinical trials, it was discovered that

conventional tablets containing the compound of formula I produced highly variable plasma levels, with some cases of malabsorption, but that this did not occur when the compound was administered as an oral solution (see page 7, line 25-30). The specification discusses the sensitivity of formula I at various pH levels (page 8, lines 1-5) and how the presently claimed compositions solved this problem (page 8, lines 8 to page 10, line 11 and Figure 2). Advantages of using the preparation according to the present invention are outlined on page 10, lines 13-21, and include (1) increased bioavailability over the conventional tablet; (2) bioavailabilty largely independent of gastric pH; (3) prevention of malabsorption; and (4) suitability for all patients, especially those who have increased gastric pH caused by disease or co-medication. Neither ILLUM nor BACH provides a motivation to make the pharmaceutical compositions of the present claims because the issues found with the conventional tablets of formula I could not have been known until after clinical trials began with formula I. Neither ILLUM nor BACH teaches formula I or have studied it in clinical trials and thus, these references do not provide a basis for non-obviousness.

Based on the above arguments, applicant kindly requests that the Examiner withdrawal the rejection of obviousness under 35 U.S.C. § 103(a) and issues a timely Notice of Allowance in this case.

Respectfully submitted,

/wendy petka/

Wendy Petka
Reg. No. 53,459

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Substitute for form 1449A/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 2

| *Complete if Known* | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | May 5, 2006 |
| First Named Inventor | BRAUNS, Ulrich |
| Art Unit | 1616 |
| Examiner Name | Qazi, Sabiha Naim |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number Number-Kind Code[2] *(if known)* | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | US- 2003/0181488 | 09/25/2003 | Brauns, Ulrich | |
| | | US- 2005/0234104 | 10/20/2005 | Schmid, R., et al | |
| | | US- 2005/0038077 | 02/17/2005 | Kohlrausch, Anja, et al | |
| | | US- 2005/0095293 | 05/05/2005 | Brauns, Ulrich, et al | |
| | | US- 2005/0107438 | 05/09/2005 | Radtke, Guido, et al | |
| | | US- 2006/0247278 | 11/02/2006 | Sieger, Peter, et al | |
| | | US- 2006/0276513 | 12/07/2006 | Hauel, Norbert, et al | |
| | | US- 4,438,091 | 03/20/1984 | Gruber, Peter, et al | |
| | | US- 6,900,229 | 05/31/2005 | Hauel, Norbert, et al | |
| | | US- 7,189,743 | 03/13/2007 | Hauel, Norbert, et al | |
| | | US- 4,427,648 | 01/24/1984 | Brickl, Rolf, et al | |
| | | US- 7,202,368 | 04/10/2007 | Zerban, Georg, et al. | |
| | | US- 2007/0149589 | 06/28/2007 | Zerban, Georg, et al. | |
| | | US- 2007/0185333 | 08/09/2007 | Zerban, Georg, et al. | |
| | | US- 2007/0185173 | 09/09/2007 | Zerban, Georg, et al. | |
| | | US- 2007/0105753 | 05/10/2002 | Wolfgang, Eisert, et al. | |
| | | US- 2006/0222640 | 10/05/2006 | Reilly, Paul, et al. | |
| | | US- | | | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)* | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | JP 58134033 | 08/10/1983 | Fujisawa Pharm. | Abstract only | |
| | | | | | | |
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| | | | | | | |

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

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form 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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PTO/SB/08b (04-07)
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 2 of 2

| *Complete if Known* | |
|---|---|
| *Application Number* | 11/381,890 |
| *Filing Date* | May 5, 2006 |
| *First Named Inventor* | Brauns, Ulrich |
| *Art Unit* | 1616 |
| *Examiner Name* | Qazi, Sabiha Naim |
| *Attorney Docket Number* | 1/1306-1-C1 |

**NON PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | | The Merck Index 14th Edition, Merck & Co., NJ, USA, 2001, No. 9156, 4308, and 845, Ecuador, (Dec. 2006) | |
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| Examiner Signature | | Date Considered | |
|---|---|---|---|

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

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form 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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# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11381890 |
| **Filing Date:** | 05-May-2006 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| First Named Inventor/Applicant Name: | Ulrich Brauns |
| **Filer:** | Wendy Petka |
| **Attorney Docket Number:** | 1/1306-1-C1 |
| Filed as Large Entity | |

**Utility Filing Fees**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| Post-Allowance-and-Post-Issuance: | | | | |
| **Extension-of-Time:** | | | | |
| Extension - 2 months with $0 paid | 1252 | 1 | 450 | 450 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| Submission- Information Disclosure Stmt | 1806 | 1 | 180 | 180 |
| | | **Total in USD ($)** | | **630** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 2177929 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28501 |
| **Filer:** | Wendy Petka |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | 1/1306-1-C1 |
| **Receipt Date:** | 10-SEP-2007 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 17:03:04 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment was successfully received in RAM | $630 |
| RAM confirmation Number | 1955 |
| Deposit Account | 022955 |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17 | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes) /Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 1-1306-1-C1-2007-09-10-ROA.pdf | 156919<br>81db6b45fa6aa0d42a4af1c0fdbf932d81be4e23 | yes | 8 |
| | **Multipart Description/PDF files in .zip description** | | | | |
| | **Document Description** | | **Start** | **End** | |
| | Amendment - After Non-Final Rejection | | 1 | 1 | |
| | Claims | | 2 | 5 | |
| | Applicant Arguments/Remarks Made in an Amendment | | 6 | 8 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Information Disclosure Statement Letter | 1-1306-1-C1-2007-09-10-IDStransmittal.pdf | 75078<br>ad1f14b942b6e751318d81cbc61dde8e17735542 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Information Disclosure Statement (IDS) Filed | 1-1306-1-C1-2007-09-10-infodiscstmt.pdf | 4543336<br>876380c363c3fe7525cf1c5291b52ebdf3be35e1 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied IDS fillable form | | | | | |
| 4 | NPL Documents | 1-1306-1-C1-Merck-2006.pdf | 606809<br>f52d10a1d3aa21c5ce86e9e156085650c82f16a7 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Foreign Reference | 1-1306-1-C1-JP58134033-abstract.pdf | 75699<br>a87ec1c59cf44cd6e28b2b89f151bc279333fcfe | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Fee Worksheet (PTO-06) | fee-info.pdf | 8454<br>26674661b572fcfbc3996477f67b678a92f25e3 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 5466295 | | |

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of : Ulrich Brauns ) Art Unit: 1616
U.S. Appln. No. : 11/381,890 ) Examiner: Sabiha Naim Qazi
Confirmation No. : 5127
U.S. Filing Date : May 5, 2006
Title of Invention : ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF
Attny. Docket No.: 1/1306-1-C1

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

September 10, 2007

**TRANSMITTAL LETTER FOR INFORMATION DISCLOSURE STATEMENT**

Sir:

Transmitted herewith concerning the subject application is an Information Disclosure Statement (Form 1449A/B) under 37 C.F.R. §§1.56 and 1.97, as more specifically described hereinbelow.

☐ 1.97(b). This Statement is being filed: i) within three (3) months of the filing date of a national application other than a continued prosecution application under 37 C.F.R. §1.53 (d); ii) within three (3) months of the date of entry of the national stage as set forth in 37 C.F.R. §1.491 in an international application; iii) before the mailing of a first Office action on the merits; or iv) before the mailing of a first Office action after the filing of a request for continued examination under 37 C.F.R. §1.114.

☒ 1.97(c). This Statement is being filed after the time period specified in 37 C.F.R. §1.97(b), but before the mailing date of: i) a final action under 37 C.F.R. §1.113, ii) a notice of allowance under 37 C.F.R. §1.311, or iii) an action that otherwise closes prosecution in the application. This Statement is being accompanied by:

☐ A statement as specified in 37 C.F.R. §1.97(e) [see below]; or



IPR2025-01107
MSN Exhibit 1008
Page 221 of 304

☐ The fee set forth in 37 C.F.R. §1.17(p).

☒ The Director is hereby authorized to charge payment of the $180.00 fee set forth in 37 C.F.R. §1.17(p) to Deposit Account No. 02-2955.

☐ 1.97(d). This Statement is being filed after the period specified in 37 C.F.R. §1.97(c) but on or before payment of the issue fee. This Statement is accompanied by a statement as specified in 37 C.F.R. §1.97(e) [see below] and the fee set forth in 37 C.F.R. §1.17(p).

☐ 1.97(e).

☐ Each item of information contained in the instant information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three (3) months prior to the filing of the instant information disclosure statement; or

☐ No item of information contained in the instant 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 this certification after making reasonable inquiry, no item of information contained in the instant information disclosure statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three (3) months prior to the filing of the instant information disclosure statement.

☐ The fee set forth in 37 C.F.R. §1.17(p).

☐ The Director is hereby authorized to charge payment of the $180.00 fee set forth in 37 C.F.R. §1.17(p) to Deposit Account No. 02-2955.

☐ 1.704(d). Each item of information contained in the accompanying information disclosure statement was first cited in any communication from a foreign patent office in a counterpart application, which communication was not received by any individual designated in section 1.56(c) more than thirty (30) days prior to the filing of the accompanying information disclosure statement.



**IPR2025-01107**
**MSN Exhibit 1008**
**Page 222 of 304**

☒ The Director is hereby authorized to charge payment of any additional filing fees required under 37 C.F.R. §1.16 and any patent application processing fees under 37 C.F.R. §1.17, or credit any overpayment of same, to Deposit Account No. 02-2955.

Respectfully submitted,

/wendy petka/
Wendy Petka
Attorney for Applicant(s)
Reg. No. 53,459

Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877
Tel: (203) 791-6614



IPR2025-01107
MSN Exhibit 1008
Page 223 of 304

PTO/SB/06 (08-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

# PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 11381890

## CLAIMS AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE | SMALL ENTITY FEE | OR | OTHER THAN SMALL ENTITY RATE | OTHER THAN SMALL ENTITY FEE |
|---|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a)) | | | | | $ | OR | | $ 300 |
| TOTAL CLAIMS (37 CFR 1.16(c)) | 15 | minus 20 = | * | X $ = | | OR | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(b)) | 2 | minus 3 = | * | X $ = | | OR | X $ = | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(d)) | | | | + $ = | | OR | + $ = | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | | OR | TOTAL | 300 |

## CLAIMS AS AMENDED – PART II

5/5/06

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE | SMALL ENTITY ADDITIONAL FEE | OR | OTHER THAN SMALL ENTITY RATE | OTHER THAN SMALL ENTITY ADDITIONAL FEE |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT A | Total (37 CFR 1.16(c)) | * 15 | Minus | ** 20 | = | X $ = | | OR | X $ = | 0 |
| | Independent (37 CFR 1.16(b)) | * 2 | Minus | *** 3 | = | X $ = | | OR | X $ = | 0 |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d)) | | | | | + $ = | | OR | + $ = | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | 0 |

9/10/07

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE | ADDITIONAL FEE | OR | RATE | ADDITIONAL FEE |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT B | Total (37 CFR 1.16(c)) | * 17 | Minus | ** 20 | = | X $ = | | OR | X $ 50 = | 1 |
| | Independent (37 CFR 1.16(b)) | * 3 | Minus | *** 3 | = 1 | X $ = | | OR | X $ 200 = | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d)) | | | | | + $ = | | OR | + $ 360 = | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | 0 |

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE | ADDITIONAL FEE | OR | RATE | ADDITIONAL FEE |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT C | Total (37 CFR 1.16(c)) | * | Minus | ** | = | X $ = | | OR | X $ = | |
| | Independent (37 CFR 1.16(b)) | * | Minus | *** | = | X $ = | | OR | X $ = | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d)) | | | | | + $ = | | OR | + $ = | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest 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.*

UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 1/1306-1-C1 | 5127 |

28501 7590 04/09/2007

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877-0368

| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |
| ART UNIT | PAPER NUMBER |
| 1616 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/09/2007 | PAPER |

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

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 11/381,890 | BRAUNS ET AL. | |
| | Examiner | Art Unit | |
| | Sabiha Qazi | 1616 | |

*-- 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *15* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**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).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**Non-Final Office Action**

Claim 1-15 is pending. No claim is allowed. Amendments are entered. Elected invention of group I claims 1-14 has been examined; claim 15 is withdrawn from consideration as non-elected invention. Restriction is made FINAL.

**Summary of this Office Action dated April 02, 2007**

1. Information Disclosure Statement
2. Copending Applications
3. Specification
4. 35 USC § 103(a) 1st Rejection
5. Communication

## Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

## Copending Applications

Applicants must bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications, which are "material to patentability" of the application in question. MPEP 2001.06(b). See Dayco Products Inc. v. Total Containment Inc., 66 USPQ2d 1801 (CA FC 2003).

## Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

**Claim Rejections - 35 USC § 103-- Rejection**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

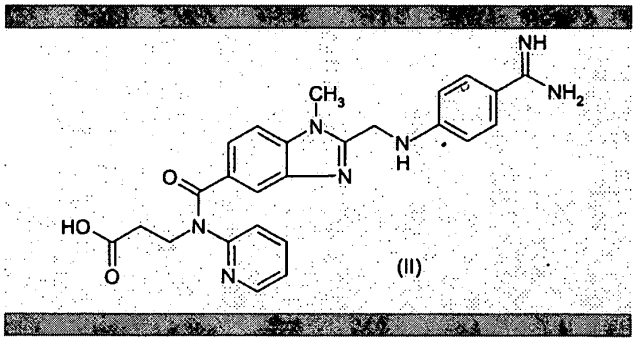
Claims 1-14 rejected under 35 U.S.C. 103(a) as being unpatentable over ILLUM et al.[1] and BACH et al.[2] ILLUM teaches methane sulphonate salt of morphine and compositions thereof. These salts can provide physically stable aqueous solutions of the drug for parenteral or non parenteral administration. The reference also teaches comparative stability of methanesulphonic salts (see example 3). See the entire document especially lines 43-67 in column 2; lines 30-61 in column 4; examples and claims.

BACH teaches pharmaceutically acceptable additional salts of non-toxic organic acids which includes methanesulfonate (see the entire document especially lines 38-66 in column 2 and example 16. The reference teaches preferred methanesulfonate salt (lines 46-51 in column 13).

Furthermore, the reference teaches as preferred additional soluble salt methanesulfonate salt in particular for intravenous or intramuscular administration. The reference does not teach the same base as presently claimed however it teaches that methanesulfonate salts are soluble and are preferably useful for intravenous or intramuscular administration.

Instant claims differ from the reference in claiming a methanesulphonate of one specific compound having the following structure.

[1] US Patent 6,387,917 B1
[2] US Patent 3,968111




It would have been obvious to one skilled in the art at the time of invention to make a methanesulphonate salt of the known compound because prior art teaches that methane sulphonate salt are non toxic, water soluble preferably useful for intravenous or intramuscular administration. Motivation has been provided by the prior art cited above to make methanesulphonate salt for enhanced solubility, stability and non-toxic nature of this salt.

No new concept and/or criticality of invention were found.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

## Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi, Ph.D. whose telephone number is 571-272-0622. The examiner can normally be reached on any business day.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Johann Richter, Ph.D. can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SABIHA QAZI, PH.D
PRIMARY EXAMINER

PTO/SB/08a (08-03)
Approved for use through 07/31/2006 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.

Substitute for form 1449A/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 4

| Complete if Known | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | 1614 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No [1] | Document Number Number-Kind Code [2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | US- 4,675, 405 A | 6/1987 | Musser, et al | |
| | | US- 5,416,099 A | 5/1995 | Hartman, et al | |
| | | US- 6,414,008 B1 | 7/2002 | Hauel, et al | |
| | | US- 6,469,039 B1 | 10/2002 | Hauel, et al | |
| | | US- 2003/0004181 A1 | 1/2003 | Hauel, et al | |
| SQ | | US- 6,710,055 B2 | 3/2004 | Hauel, et al | |
| | | US- 6,087,380 | 7/2000 | Hauel, et al | |
| | | US- 2005/0234104 A1 | 10/2005 | Schmid, et al | |
| | | US- 4,427,468 | 01/24/1984 | Brickl, et al | |
| | | US- 4,367,217 | 01/04/1983 | Gruber, et al | |
| | | US- 5,800,836 | 09/01/1998 | Morella, et al | |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No [1] | Foreign Patent Document Country Code [3] Number [4] Kind Code [5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T [6] |
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| | | EP 0 655 439 A2 | 05/31/1995 | Eli Lilly and Co. | | |

| Examiner Signature | SABIHA QAZI | Date Considered | 3/31/07 |
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional) 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3) 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible 6 Applicant is to place a check mark here if English language Translation is attached

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form 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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PTO/SB/08a (08-03)
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Substitute for form 1449A/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 2 of 4

| Complete if Known | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | 1614 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No [1] | Document Number Number-Kind Code [2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No [1] | Foreign Patent Document Country Code [3] Number [4] Kind Code [5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T [6] |
|---|---|---|---|---|---|---|
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| | | EP 0088191 A2 | 01/05/1983 | Dr. Karl Thomae | XR: US 4,427,648 | |
| | | EP 0032562 A1 | 07/29/1981 | Dr. Karl Thomae | XR: US 4,367,217 | |

| Examiner Signature | | Date Considered | |
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 3 of 4

| Complete if Known | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | 1614 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| SQ | | WO 94/03160 | 02/17/1994 | FH Faulding & Co. | XR: US 5,800,836 | |
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| Examiner Signature | | Date Considered | |
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 4 of 4

| *Complete if Known* | |
|---|---|
| *Application Number* | 11/381,890 |
| *Filing Date* | 05/05/2006 |
| *First Named Inventor* | U. BRAUNS, et al. |
| *Art Unit* | 1614 |
| *Examiner Name* | Sabiha Naim Qazi |
| *Attorney Docket Number* | 1/1306-1-C1 |

**NON PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc ), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
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| Examiner Signature | SABIHA QAZI | Date Considered | 3/31/07 |
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609 Draw line through citation if not in conformance and not considered Include copy of this form with next communication to applicant

1 Applicant's unique citation designation number (optional) 2 Applicant is to place a check mark here if English language Translation is attached

This collection of information is required by 37 CFR 1 97 and 1 98 The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U S C 122 and 37 CFR 1.14 This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form 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*

| Notice of References Cited | Application/Control No. 11/381,890 | Applicant(s)/Patent Under Reexamination BRAUNS ET AL. | |
|---|---|---|---|
| | Examiner Sabiha Qazi | Art Unit 1616 | Page 1 of 1 |

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| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-4,427,648 | 01-1984 | Brickl et al. | 424/459 |
| | B | US- | | | |
| | C | US- | | | |
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**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



IPR2025-01107
MSN Exhibit 1008
Page 237 of 304

| Search Notes | Application/Control No. | Applicant(s)/Patent under Reexamination |
|---|---|---|
| | 11/381,890 | BRAUNS ET AL. |
| | Examiner | Art Unit |
| | Sabiha Qazi | 1616 |

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| 514 | 388 | | |
| 548 | 273.4 | | |
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| SEARCH NOTES (INCLUDING SEARCH STRATEGY) | | |
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| STN DATABASE SEARCH | 3/23/2007 | STIC |
| See CORE in e-DAN for search notes. | | |
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| A Application of | : Ulrich Brauns | ) Art Unit | : 1616 |
| Serial No. | : 11/381,890 | ) Examiner | : Sabiha Naim Qazi |
| Confirmation No. | : 5127 | | |
| Filed | : May 5, 2006 | | |
| Title | : ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |
| Docket No. | : 1/1306-1-C1 | | |

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

**REPLY TO RESTRICTION REQUIREMENT**

Sir:

This Reply is in response to the December 12, 2006 Office Action issued in the above-identified application. In that Office Action, a one-month shortened statutory period was set for response. Applicant hereby petitions for the necessary one-month extension of time under 37 C.F.R. § 1.136 to respond to that action and note that the fee required under 37 C.F.R. § 1.17(a)(1) in connection with this Reply will be paid during electronic filing via the Revenue Accounting and Management System. If it is determined that any additional fees under 37 C.F.R. §§ 1.16 or 1.17 are due in connection with this Reply, the Director is hereby authorized to charge such fees to Deposit Account No. 02-2955.

In the Office Action, the Examiner imposed a two-way restriction in the present application under 35 U.S.C. §121.

In response to the restriction requirement, applicant elects the subject matter of Group I (claims 1-14) for substantive examination on the merits. Applicant points out that claim 16 was cancelled in a Preliminary Amendment filed on May 5, 2006. Applicant also notes that claims 1-14 and claim 15 are in a product and a process for making the product relationship. Accordingly, applicant respectfully submits that the



**IPR2025-01107**
**MSN Exhibit 1008**
**Page 239 of 304**

USPTO's Rejoinder Practice under MPEP 821.04(b) is applicable. Applicant will designate claim 15 as withdrawn during prosecution, and amend it accordingly, in order to maintain the right to rejoinder upon allowance of product claims. Applicant makes the above-identified election expressly without waiver of his right to file for and obtain claims directed to the non-elected subject matter in divisional or continuing applications claiming priority and benefit herefrom, or from a related application, under 35 U.S.C. § 120.

Applicant also respectfully submits that all the pending claims are allowable and therefore solicits a Notice of Allowance for all of the pending claims. If the Examiner feels that a telephone interview would be helpful in advancing prosecution of this application, the Examiner is invited to contact the attorney below.

Respectfully submitted,

/wendy petka/

Wendy Petka, Reg. No. 53,459
Attorney for Applicants

BOEHRINGER INGELHEIM CORPORATION
Patent Department
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
Telephone: (203) 791-6614
Facsimile: (203) 798-4408



**IPR2025-01107**
**MSN Exhibit 1008**
**Page 240 of 304**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | |
|---|---|---|---|---|
| Application of | : | Ulrich Brauns | ) Art Unit | : 1616 |
| Serial No. | : | 11/381,890 | ) Examiner | : Sabiha Naim Qazi |
| Confirmation No.: | | 5127 | | |
| Filed | : | May 5, 2006 | | |
| Title | : | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |
| Docket No. | : | 1/1306-1-C1 | | |

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

**REQUEST TO CORRECT INVENTORSHIP PURSUANT TO 37 C.F.R. §§ 1.48(b)(1) and 1.33(b)(1)**

Sir:

Applicants' attorney respectfully requests correction of inventorship in the above-identified application by deleting inventor, Norbert Hauel, whose invention is no longer being claimed in the above-identified application. The fee required under 37 C.F.R. § 1.17(i) in connection with this Request will be paid during electronic filing via the Revenue Accounting and Management System. If it is determined that any additional fees under 37 C.F.R. §§ 1.16 or 1.17 are due in connection with this Request, the Director is hereby authorized to charge such fees to Deposit Account No. 02-2955.

Respectfully submitted,

/wendy petka/

Wendy A. Petka
Registration No. 53,459
Attorney for Applicants

BOEHRINGER INGELHEIM CORPORATION
Patent Department
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
Telephone: (203) 798-4310
Facsimile: (203) 798-4408

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11381890 |
| **Filing Date:** | 05-May-2006 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| First Named Inventor/Applicant Name: | Ulrich Brauns |
| **Filer:** | Wendy Petka |
| **Attorney Docket Number:** | 1/1306-1-C1 |
| Filed as Large Entity | |

**Utility Filing Fees**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| Post-Allowance-and-Post-Issuance: | | | | |
| **Extension-of-Time:** | | | | |
| Extension - 1 month with $0 paid | 1251 | 1 | 120 | 120 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
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| **Miscellaneous:** | | | | |
| Processing Fee, except for Provis. apps | 1808 | 1 | 130 | 130 |
| | | **Total in USD ($)** | | **250** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 1485787 |
| **Application Number:** | 11381890 |
| **International Application Number:** | |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor/Applicant Name:** | Ulrich Brauns |
| **Customer Number:** | 28501 |
| **Filer:** | Wendy Petka |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | 1/1306-1-C1 |
| **Receipt Date:** | 02-FEB-2007 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 10:09:11 |
| **Application Type:** | Utility |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment was successfully received in RAM | $250 |
| RAM confirmation Number | 1166 |
| Deposit Account | 022955 |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17 | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes) | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Response to Election / Restriction Filed | 1-1306-1-C1-2007-2-2-ROA-Restrict.pdf | 85986 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Request under Rule 48 correcting inventorship | 1-1306-1-C1-2007-2-2-Inventor-Req-Correct.pdf | 87697 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Fee Worksheet (PTO-06) | fee-info.pdf | 8458 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 182141 | | |

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**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/381,890 | 05/05/2006 | Ulrich Brauns | 1/1306-1-C1 | 5127 |

28501 7590 12/12/2006

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877-0368

| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1616 | |

DATE MAILED: 12/12/2006

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



IPR2025-01107
MSN Exhibit 1008
Page 246 of 304

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 11/381,890 | BRAUNS ET AL. | |
| | Examiner | Art Unit | |
| | Sabiha Qazi | 1616 | |

*-- 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 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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**

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**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).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-14 and 16, drawn to pharmaceutical composition for oral administration comprising: a) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-met- hyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof and b) one or more pharmaceutically acceptable organic acids with a water solubility of >1 g/250 ml at 20.degree. C., classified in class 514, subclass.

II. Claim 15, drawn to process of making the above composition, classified in class 546, subclass 273.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions of group II and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case. In this case the product as claimed can be made by another and materially different process. The search required for the composition of group I will not be the same as the search for the process of making the composition as in group II. A reference used to rejection the invention of group I may not be used for the process as in group II.

3. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

4. A telephone call was made to Attorney Wendy A. Petka on 11/10/06 to request an oral election to the above restriction requirement, but did not result in an election being made.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

**Communication**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi, Ph.D. whose telephone number is 571-272-0622. The examiner can normally be reached on any business day.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Johann Richter, Ph.D. can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Qazi

SABIHA QAZI, PH.D
PRIMARY EXAMINER

L

## Index of Claims

| Application/Control No. | Applicant(s)/Patent under Reexamination |
|---|---|
| 11/381,890 | BRAUNS ET AL. |
| **Examiner** | **Art Unit** |
| Sabiha Qazi | 1616 |

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| √ | Rejected | – | (Through numeral) Cancelled | N | Non-Elected | A | Appeal |
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| Claim | | Date |
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| Final | Original | 12/8/06 |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 1 of 4

| Complete if Known | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | 1614 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No [1] | Document Number Number-Kind Code [2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | US- 4,675, 405 A | 6/1987 | Musser, et al | |
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| | | US- 5,800,836 | 09/01/1998 | Morella, et al | |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No [1] | Foreign Patent Document Country Code [3] Number [4] Kind Code [5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T [6] |
|---|---|---|---|---|---|---|
| | | DE 102 45 624 A1 | 04/08/2004 | BI Pharma GmbH | English Abstract for DE 102 45 624 | |
| | | DE 41 29 603 A1 | 03/11/1993 | Dr. Karl Thomae | XR: US 5,434,150 | |
| | | EP 0 540 051 A1 | 05/05/1993 | Daiichi Pharm. Co | | |
| | | EP 0 623 596 A1 | 11/09/1994 | Bristol-Myers Squibb | | |
| | | EP 0 655 439 A2 | 05/31/1995 | Eli Lilly and Co. | | |

| Examiner Signature | | Date Considered | |
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional) 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3) 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible 6 Applicant is to place a check mark here if English language Translation is attached

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form 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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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 2 of 4

| *Complete if Known* | |
|---|---|
| Application Number | 11/381,890 |
| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | 1614 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

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|---|---|---|---|---|---|---|
| | | WO 98/37075 | 08/27/1998 | BI Pharma KG | | |
| | | WO 03/007984 | 01/30/2003 | BI Pharma KG | | |
| | | DE 19752843 A1 | 07/01/1999 | Altana Pharma AG | English Abstract Enclosed | |
| | | EP 0068191 A2 | 01/05/1983 | Dr. Karl Thomae | XR: US 4,427,648 | |
| | | EP 0032562 A1 | 07/29/1981 | Dr. Karl Thomae | XR: US 4,367,217 | |

| Examiner Signature | | Date Considered | |
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*(Use as many sheets as necessary)*

Sheet 3 of 4

| *Complete if Known* | |
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| Filing Date | 05/05/2006 |
| First Named Inventor | U. BRAUNS, et al. |
| Art Unit | 1614 |
| Examiner Name | Sabiha Naim Qazi |
| Attorney Docket Number | 1/1306-1-C1 |

## U. S. PATENT DOCUMENTS

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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | WO 94/03160 | 02/17/1994 | FH Faulding & Co. | XR: US 5,800,836 | |
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| Examiner Signature | | Date Considered | |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

Sheet 4 of 4

| *Complete if Known* | |
|---|---|
| *Application Number* | 11/381,890 |
| *Filing Date* | 05/05/2006 |
| *First Named Inventor* | U. BRAUNS, et al. |
| *Art Unit* | 1614 |
| *Examiner Name* | Sabiha Naim Qazi |
| *Attorney Docket Number* | 1/1306-1-C1 |

**NON PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc ), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
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| | | | |
| | | | |

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

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

1 Applicant's unique citation designation number (optional) 2 Applicant is to place a check mark here if English language Translation is attached

This collection of information is required by 37 CFR 1 97 and 1 98 The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U S C 122 and 37 CFR 1.14 This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form 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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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Application of | : U. Brauns, et al. | ) Art Unit: | 1614 |
| U.S. Appln. No. | : 11/381,890 | ) Examiner: | Sabiha Naim Qazi |
| Confirmation No. | : 5127 | | |
| U.S. Filing Date | : 05/05/2006 | | |
| Title of Invention | : ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |
| Attny. Docket No. | : 1/1306-1-C1 | | |

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

**TRANSMITTAL LETTER FOR INFORMATION DISCLOSURE STATEMENT**

Sir:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant hereby notifies the U.S. Patent and Trademark Office of the documents listed herein and on the attached PTO-1449 form and which the Examiner may deem relevant to patentability of the claims of the above-identified application. Copies of the citations listed on the PTO-1449 form are filed in US Application No. 10/383,198, filed on 03/06/2003, Hauel, N. (Attorney Docket No. 1/1306).

☒ 1.97(b). This Statement is being filed: i) within three (3) months of the filing date of a national application other than a continued prosecution application under 33 C.F.R. §1.53 (d); ii) within three (3) months of the date of entry of the national stage as set forth in 37 C.F.R. §1.491 in an international application; iii) before the mailing of a first Office action on the merits; or iv) before the mailing of a first Office action after the filing of a request for continued examination under 37 C.F.R. §1.114.

☐ 1.97(c). This Statement is being filed after the time period specified in 37 C.F.R. §1.97(b), but before the mailing date of: i) a final action under 37 C.F.R. §1.113, ii) a notice of allowance under 37 C.F.R. §1.311, or iii) an action that otherwise closes prosecution in the application. This Statement is being accompanied by:

☐ A statement as specified in 37 C.F.R. §1.97(e) [see below]; or



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☐ The fee set forth in 37 C.F.R. §1.17(p).

☐ The Commissioner is hereby authorized to charge payment of the $180.00 fee set forth in 37 C.F.R. §1.17(p) to Deposit Account No. 02-2955.

☐ 1.97(d). This Statement is being filed after the period specified in 37 C.F.R. §1.97(c) but on or before payment of the issue fee. This Statement is accompanied by a statement as specified in 37 C.F.R. §1.97(e) [see below] and the fee set forth in 37 C.F.R. §1.17(p).

☐ 1.97(e).

☐ Each item of information contained in the instant information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three (3) months prior to the filing of the instant information disclosure statement; or

☐ No item of information contained in the instant 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 this certification after making reasonable inquiry, no item of information contained in the instant information disclosure statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three (3) months prior to the filing of the instant information disclosure statement.

☐ The fee set forth in 37 C.F.R. §1.17(p).

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☐ 1.704(d). Each item of information contained in the accompanying information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, which communication was not received by any individual designated in section 1.56(c) more than thirty (30) days prior to the filing of the accompanying information disclosure statement.

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Respectfully submitted,

/wendy petka/

Wendy A. Petka
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# Electronic Acknowledgement Receipt

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|---|---|
| **EFS ID:** | 1210045 |
| **Application Number:** | 11381890 |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor:** | Ulrich Brauns |
| **Customer Number:** | 28501 |
| **Filer:** | Wendy Petka |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | 1/1306-1-C1 |
| **Receipt Date:** | 20-SEP-2006 |
| **Filing Date:** | 05-MAY-2006 |
| **Time Stamp:** | 17:13:10 |
| **Application Type:** | Utility |
| **International Application Number:** | |

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| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes) | Multi Part | Pages |
|---|---|---|---|---|---|
| 1 | Information Disclosure Statement (IDS) Filed | 1-1306-1-C1-IDS-1449.pdf | 369766 | no | 4 |

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| 2 | Information Disclosure Statement (IDS) Filed | 1-1306-1-C1-IDS-transmittal-8-06.pdf | 67002 | no | 3 |
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| 3 | NPL Documents | Caira-Crystalline-Polymorphism.pdf | 2342951 | no | 24 |
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| 4 | NPL Documents | Gustafsson-Oral-direct.pdf | 119359 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | NPL Documents | Mungall-BIBR-1048.pdf | 71350 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | NPL Documents | Stangier-Pharmacokinetics.pdf | 132594 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 7 | Foreign Reference | DE4129603-Abstract.pdf | 93713 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 8 | Foreign Reference | DE10245624-Abstract.pdf | 86431 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | Foreign Reference | DE19752843-Abstract.pdf | 36280 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

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| 10 | Foreign Reference | EP0032562-Abstract.pdf | 48346 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 11 | Foreign Reference | EP0068191-Abstract.pdf | 46978 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 12 | Foreign Reference | DE4129603.pdf | 2310369 | no | 32 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 13 | Foreign Reference | EP540051.pdf | 6524363 | no | 94 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 14 | Foreign Reference | EP623596.pdf | 3607378 | no | 81 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 15 | Foreign Reference | EP655439.pdf | 3226889 | no | 124 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 16 | Foreign Reference | WO9837075.pdf | 7693992 | no | 201 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 17 | Foreign Reference | WO03007984.pdf | 1351108 | no | 25 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 18 | Foreign Reference | WO9401360.pdf | 537696 | no | 17 |
| **Warnings:** | | | | | |
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| 19 | NPL Documents | Hauel-J-Med-Chem.pdf | 1025242 | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 20 | NPL Documents | Nagahara-J-Med-Chem.pdf | 828921 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 21 | NPL Documents | Stangier-Thrombosis.pdf | 62497 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 22 | NPL Documents | Berkowitz-Antithrombotic.pdf | 624855 | no | 7 |
| **Warnings:** | | | | | |
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| | | **Total Files Size (in bytes):** | 31208080 | | |

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**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

**Administration form for the oral application of 3-[(2-{[4-(hexyloxycarbonyl-amino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester and the salts thereof**

## RELATED APPLICATIONS

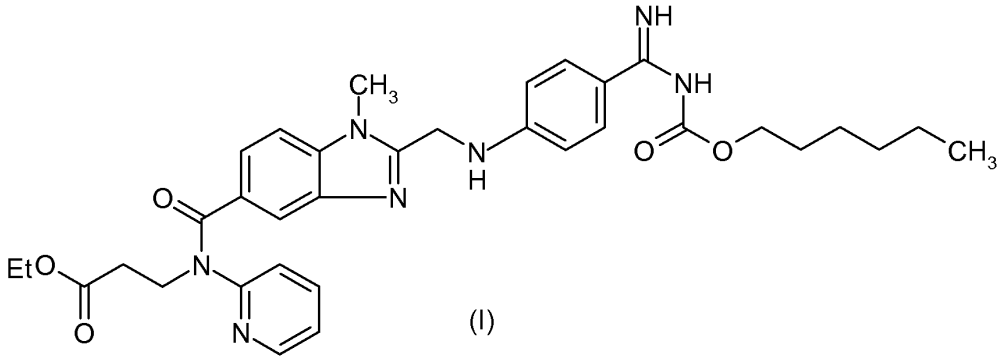
Benefit of U.S. Provisional Application Serial No. 60/421,896, filed on October 29, 2002 and U.S. Provisional Application Serial No. 60/409,762, filed on September 11, 2002 is hereby claimed, and said applications are herein incorporated by reference.

## FIELD OF INVENTION

The invention relates to administration forms for oral applications of prodrugs and in particular prodrugs of the active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmacologically acceptable salts thereof.

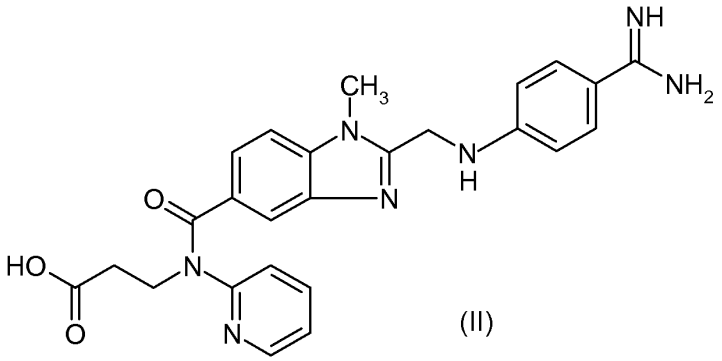
## BACKGROUND OF THE INVENTION

The invention relates to an administration form for the oral application of the active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmacologically acceptable salts thereof. This active substance having the chemical formula




(I)

is already known from WO 98/37075, which discloses compounds with a thrombin-inhibiting effect and the effect of prolonging the thrombin time, under the name 1-methyl-2-[*N*-[4-(*N*-n-hexyloxycarbonylamidino)phenyl]-amino-methyl]-benzimidazole-5-yl-carboxylic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amides. The compound of formula I is a double prodrug of the compound




(II)

i.e. the compound of formula I is only converted into the active compound, namely the compound of formula II, after entering the body. The main indication for the compound of chemical formula I is the post-operative prevention of deep-vein thrombosis.

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a schematic structure of the pharmaceutical composition.
Figure 2 shows the bioavailability of BIBR 1048.

## DESCRIPTION OF THE INVENTION

The aim of the invention is to provide an improved formulation for oral use of the compound of formula I (which is also referred to hereinafter as the "active substance").

Surprisingly it has now been found that the use of pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 ml at 20°C, preferably > 1 g / 160 ml at 25°C, in solid oral preparations leads to a significantly improved formulation of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-



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methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate as well as the pharmaceutically acceptable salts thereof.

Pharmaceutically suitable acids for the purposes of this invention are for example tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid and aspartic acid including the hydrates and acid salts thereof. Particularly suitable for the purposes of this invention are tartaric acid, fumaric acid, succinic acid and citric acid.

A preferred embodiment of the invention is a multiparticulate preparation in which the individual particles are constructed as in Figure 1.

Figure 1 shows the diagrammatic structure of the pharmaceutical composition by means of a section through a pellet suitable for the preparation of the pharmaceutical composition according to the invention. The roughly bead-shaped / spherical core region of this pellet contains/consists of the pharmaceutically acceptable organic acid. Then follows a layer, the so-called insulating layer, which separates the acid core from the layer containing the active substance. The insulating layer is in turn surrounded by the equally spherically shaped layer of active substance which may in turn be enclosed in a coating which increases the abrasion resistance and shelf life of the pellets.

One advantage of the formulation thus constructed is the spatial separation of the organic acid and active substance by the insulating layer. A further advantage of the construction of the pellets as described above is the fact that the organic acid does not go into solution until after the preparation has been taken and then produces an acid microclimate in which the active substance can dissolve.

The core material used is a pharmaceutically acceptable organic acid with a water solubility of > 1 g / 250 ml at 20° C, such as e.g. tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid and aspartic acid including the

hydrates and acid salts thereof, to which a small amount of 1 to 10 % by weight, preferably 3 to 6 % by weight of a suitable binder is optionally added. The use of a binder may be necessary, for example, if the starting acids are produced by a pan build-up process. If the method used is extrusion or spheronisation, other technological adjuvants such as microcrystalline cellulose will be needed instead of binders. It is also possible to use pure (100 %) acid as the starting material if it can be obtained in a sufficiently narrow range of particle sizes. The pharmaceutically acceptable organic acids used are preferably tartaric acid, fumaric acid, succinic acid or citric acid; tartaric acid is particularly preferred. As binder, it is possible to use gum arabic or a partially or totally synthetic polymer selected from among the hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, polyvinyl-pyrrolidone, the copolymers of N-vinylpyrrolidone and vinyl acetate, or combinations of these polymers; gum arabic is preferred. The spherical core material preferably has an average diameter of 0.4 – 1.5 mm. The content of the pharmaceutically acceptable organic acid is usually between 30 and 100 % in the core material, corresponding to an amount of between 20 and 90 %, preferably between 20 and 80 % in the finished pellet (i.e. in the pharmaceutical composition).

To increase the durability of the finished product it is advantageous to coat the core material before the application of the active substance with an insulating layer based on a water-soluble, pharmaceutically acceptable polymer. Examples of such water-soluble polymers include for example gum arabic or a partially or totally synthetic polymer selected from among the hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, polyvinylpyrrolidone, the copolymers of N-vinylpyrrolidone and vinyl acetate, or combinations of these polymers. Gum arabic or a hydroxypropylmethylcellulose is preferably used. If desired, the coating with the water-soluble, pharmaceutically acceptable polymer may be carried out with the addition of suitable plasticisers, separating agents and pigments, such as for

example triethylcitrate, tributylcitrate, triacetin, polyethyleneglycols (plasticisers), talc, silicic acid (separating agents), titanium dioxide or iron oxide pigments (pigments).

The active substance layer contains the active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate (BIBR 1048) or one of the pharmaceutically acceptable salts thereof as well as binders and optionally separating agents. A preferred salt of the active substance is the mesylate (methanesulphonate) of the compound of formula I. Suitable binders include for example hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, copolymers of *N*-vinylpyrrolidone and vinyl acetate or combinations of these polymers. Preferably, hydroxypropylcellulose or copolymers of *N*-vinylpyrrolidone and vinyl acetate are used. The addition of separating agents such as e.g. talc or silicic acid serves to prevent the particles from aggregating during the process. The active substance content is 5 to 60 %, preferably 10 to 50 % of the pharmaceutical composition.

The optional outermost layer, which serves to reduce any increased abrasion during packing into capsules and/or to increase the shelf life, consists of pharmaceutically conventional film-forming agents, plasticisers and optionally pigments. Suitable film-forming agents include for example hydroxypropyl-cellulose, hydroxypropylmethylcellulose, methylcellulose, polymers and copolymers of acrylic and methacrylic acid and the esters thereof, or combinations of these polymers. Suitable plasticisers include *inter alia* triethylcitrate, tributylcitrate, triacetin or polyethyleneglycols. The pigments used may be e.g. titanium dioxide or iron oxide pigments. Preferably, the outer coating consists of hydroxypropylmethylcellulose and/or methylcellulose, optionally with the addition of polyethyleneglycols as plasticisers.

The pellets may be prepared by the method described hereinafter:

The acid-containing core material consists either of crystals of the particular organic acid used or, more advantageously, of roughly spherical particles of the desired size containing a large amount of organic acid, which can be produced by methods known and established in pharmaceutical technology. The core material may be produced, in particular, by pan methods, on pelleting plates or by extrusion/spheronisation. Then the core material thus obtained may be divided into fractions of the desired diameter by screening. Suitable core material has an average diameter of 0.4 to 1.5 mm, preferably 0.6 to 0.8 mm.

First, the insulating layer is applied to this acid-containing core material. This can be done by conventional methods, e.g. by applying an aqueous dispersion of the water-soluble, pharmaceutically acceptable polymer, optionally with the addition of plasticisers, separating agents and/or pigments, in a fluidised bed, in coating pans or in conventional film coating apparatus. If necessary the product can then be screened again.

Then the active substance is applied from a dispersion containing binder and optionally separating agent. The volatile dispersant is removed during or after the process by drying. Suitable binders in the dispersion may be for example hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, copolymers of N-vinylpyrrolidone and vinyl acetate or combinations of these polymers. Preferably, hydroxypropylcellulose or copolymers of N-vinylpyrrolidone and vinyl acetate are used. Suitable separating agents include e.g. talc or silicic acid; preferably, talc is used. The dispersants may be for example ethanol, 2-propanol, acetone or mixtures of these solvents with one another or with water, preferably 2-propanol. The application of active substance to the core material may be carried out by established methods known in pharmaceutical technology, e.g. in coating



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pans, conventional film coating apparatus or by the fluidised bed method. Then a further screening process may be carried out.

To reduce any increased abrasion during transfer into capsules or to increase the shelf life the system may finally be coated with a coating of a pharmaceutically conventional film forming agent, plasticiser and optionally pigment. This may be done by conventional methods as mentioned earlier in the description of the application of the insulating layer.

When core material with an average diameter of 0.4 – 1.5 mm is used, the process described above produces pellets containing active substance, which can then be packed into hard capsules, for example. To do this, a number of these units corresponding to the required dosage are packed into hard capsules in a standard capsule filling machine. Suitable hard capsules include, for example, hard gelatine capsules or hard capsules of hydroxypropylmethylcellulose (HPMC); HPMC capsules are preferred. The active substance content of the pharmaceutical composition is 5 to 60 %, preferably 10 to 50 %; the content of the pharmaceutically acceptable organic acid is usually between 20 and 90 %, preferably between 20 and 80 %.

Unless otherwise stated, percentages specified are always percent by weight. All the data on the active substance content relate to the active substance base of formula I (not to a specific salt) unless otherwise stated.

Clinical trials

In preliminary tests on test subjects with conventional tablets containing the compound of formula I it had been established that highly variable plasma levels occurred, with individual cases of malabsorption. The variability of the plasma level patterns is significantly lower after the administration of the compound of formula I as an orally administered solution; there were no cases of malabsorption under these circumstances.

Tests have shown that the compound of formula I dissolves relatively well in water at low pH levels, whereas at pH levels above 5 in accordance with the definition of the European Pharmacopoeia it is virtually insoluble. Therefore the volunteers in one branch of the clinical trials were given pantoprazole, which serves to produce an elevated gastric pH.

For example, the pharmaceutical compositions according to Examples 1 and 2 were tested for their bioavailability by comparison with a conventional tablet. To do this, the formulation prepared according to Example 1 containing 50 mg of active substance base per capsule was clinically tested for its bioavailability on a total of 15 volunteers. In one branch of the treatment, the volunteers were given the composition by mouth (= orally) on an empty stomach without any pre-treatment. In another branch of the treatment the same volunteers were pre-treated, prior to the oral administration of the composition, with 40 mg of pantoprazole b.i.d. (= twice a day) for three days by mouth to increase the gastric pH; the treatment with pantoprazole was continued during the administration of the formulation according to the invention.

The degree of absorption was determined by measuring the quantity of active metabolite of formula II excreted in the urine.

The relative bioavailability after pre-treatment with pantoprazole was 94% on average compared with administration without any pre-treatment.

Under comparable conditions of administration, the relative bioavailability (based on the area under the plasma concentration/time curve) of a tablet containing 50 mg of active substance, developed and produced according to the prior art and containing no water-soluble organic acid, after corresponding pre-treatment with pantoprazole, is 18 %. Table I shows the precise composition of the tablet used:



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TABLE I:

| | Ingredient | mg/tablet |
|---|---|---|
| Core | mesylate of the compound of form. I | 57.7 |
| | lactose monohydrate | 58.0 |
| | microcrystalline cellulose | 48.3 |
| | crospovidone | 3.4 |
| | magnesium stearate | 2.6 |
| Film coating | polyethyleneglycol 6000 | 0.56 |
| | titanium dioxide | 0.80 |
| | talc | 0.64 |
| | hydroxypropylmethylcellulose | 1.92 |
| | iron oxide yellow | 0.08 |
| | Total | 174.0 |

The relative bioavailability was thus improved by about a factor of 5 by using the formulation according to the invention.

The formulation prepared according to Example 2 containing 50 mg of active substance base per capsule was also clinically tested for its bioavailability on a total of 15 volunteers. In one branch of the treatment, the volunteers were given the composition by mouth on an empty stomach without any pre-treatment. In another branch of the treatment the same volunteers were pre-treated, prior to the oral administration of the composition, with 40 mg of pantoprazole b.i.d. for three days by mouth to increase the gastric pH; the treatment with pantoprazole was continued during the administration of the formulation according to the invention.

The degree of absorption was determined by measuring the quantity of the active metabolite of formula II excreted in the urine.

The relative bioavailability after pre-treatment with pantoprazole was 76% on average compared with administration without any pre-treatment.

Under comparable conditions of administration, the relative bioavailability (based on the area under the plasma concentration/ time curve) of a tablet containing 50 mg of active substance, developed and produced according to the prior art and

containing no water-soluble organic acid, after corresponding pre-treatment with pantoprazole, is 18%. Table II shows the precise composition of the tablet used:

TABLE II:

| | Ingredient | mg/tablet |
|---|---|---|
| Core | mesylate of the compound of form. I | 57.7 |
| | lactose monohydrate | 58.0 |
| | microcrystalline cellulose | 48.3 |
| | crospovidone | 3.4 |
| | magnesium stearate | 2.6 |
| Film coating | polyethyleneglycol 6000 | 0.56 |
| | titanium dioxide | 0.80 |
| | talc | 0.64 |
| | hydroxypropylmethylcellulose | 1.92 |
| | iron oxide yellow | 0.08 |
| | Total | 174.0 |

The relative bioavailability of the active substance compared with conventional formulations was thus improved by about a factor of 4 by using the formulation according to the invention. The bioavailability of the two formulations according to the invention compared with the tablet described above with and without the simultaneous administration of pantoprazole is graphically illustrated in Figure 2.

The clinical trials show another advantage of the preparation according to the invention containing the compound of formula I, which is that it ensures adequate bioavailability of the active substance, better than that of a conventional pharmaceutical preparation and largely independent of the gastric pH, it reduces fluctuations in the bioavailability of the active substance and it prevents malabsorption. Another advantageous property of the pharmaceutical composition according to the invention is the fact that it is suitable for all patients, i.e. including those in whom the gastric pH is increased by normal physiological variability, by disease or by co-medication with drugs which raise the gastric pH.



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The dosage for oral use is expediently 25 to 300 mg of the active substance base (per capsule), preferably 50 to 200 mg, most preferably 75 to 150 mg of the active substance base, in each case once or twice a day.

The preferred ratio of acid to active substance is about 0.9 : 1 to about 4 : 1, most preferably between about 1:1 and 3:1. Preferably, at least one equivalent of acid is used per mol of the compound of formula I. The upper limit of about 4:1 (acid to active substance) is generally determined by the maximum acceptable size of the preparation in the desired dosages (number of pellets per capsule).

The Examples that follow are intended to illustrate the invention:

Example 1

| | percentage composition | | | | per capsule [mg] | per capsule [mg] |
|---|---|---|---|---|---|---|
| | core material | insulating layer | active substance layer | total | | |
| tartaric acid | 61.3 | - | - | 61.3 | 176.7 | 353.4 |
| gum arabic | 3.1 | 2.8 | | 5.9 | 17.0 | 34.0 |
| talc | - | 5.6 | 3.2 | 8.8 | 25.4 | 50.7 |
| hydroxypropylcellulose | - | - | 4.0 | 4.0 | 11.5 | 23.1 |
| active substance (mesylate of the compound of formula I) | - | - | 20.0 | 20.0 | 57.7* | 115.3** |
| total | | | | 100.0 | 288.3 | 576.5 |

*) corresponds to 50 mg of the compound of formula 1 (active substance base)
**) corresponds to 100 mg of the compound of formula 1 (active substance base)

*a) Production of core material containing tartaric acid*

Composition:

| | |
|---|---|
| gum arabic | 1 part by weight |
| tartaric acid | 20 parts by weight |

1 part by weight of gum arabic is dissolved In 4 parts by weight of purified water at 50°C with stirring. Then 5 parts by weight of tartaric acid are dissolved in this solution with stirring.

8.3 parts by weight of tartaric acid crystals with an average particle size of 0.4 to 0.6 mm are placed in a suitable coating apparatus fitted with an air inlet and exhaust, and the pan is set in rotation. At an air inlet temperature of 60° – 80°C the tartaric acid crystals are sprayed at intervals with the solution of tartaric acid and gum arabic and sprinkled with a total of 6.7 parts by weight of powdered tartaric acid, so that roughly spherical particles are formed.

The spherical tartaric acid core material is then dried in the rotating pan at an air inlet temperature of 60° - 80° C.

The core material is fractionated using a tumbler screening machine with perforated plates with a nominal mesh size of 0.6 and 0.8 mm. The product fraction between 0.6 and 0.8 mm is used in the rest of the process.

*b) Insulation of the core material containing tartaric acid*

Composition:

| | |
|---|---|
| core material containing tartaric acid | 23 parts by weight |
| gum arabic | 1 part by weight |
| talc | 2 parts by weight |



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1 part by weight of gum arabic is dissolved in a mixture of 6.7 parts by weight of 96 % ethanol and 13.5 parts by weight of purified water with stirring. Then 2 parts by weight of talc are dispersed in the solution with stirring.

In a fluidised bed processing apparatus, 23 parts by weight of core material containing tartaric acid are sprayed at an air inlet temperature of 35° – 40° C with the dispersion of gum arabic and talc by the under-bed spraying process.

The insulated core material containing tartaric acid is then dried in the circulating air drier at 40°C for 8 hours.

To remove any lumps the dried insulated core material containing tartaric acid is screened through a screen with a nominal mesh size of 1.0 mm. The fraction of material with a particle size of < 1 mm is further processed.

c) *Production of the active substance layer*

Composition:

| | |
|---|---|
| insulated core material containing tartaric acid | 91 parts by weight |
| hydroxypropylcellulose | 5 parts by weight |
| talc | 4 parts by weight |
| active substance (mesylate of BIBR 1048) | 25 parts by weight |

Hydroxypropylcellulose is dissolved in 168 parts by weight of 2-propanol with stirring and then the active substance and talc are dispersed in this solution with stirring.

In a fluidised bed processing apparatus, 91 parts by weight of insulated core material containing tartaric acid are sprayed at an air inlet temperature of 20° - 30°C with the dispersion containing the active substance by the under-bed spraying process.



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The pellets containing the active substance are then dried in the circulating air drier at 35°C for 8 hours.

To remove any lumps the pellets containing the active substance are screened through a screen with a nominal mesh size of 1.25 mm. The fraction of material with a particle size of < 1.25 mm is further processed.

*d) Packing into capsules*

A quantity of active substance pellets containing in each case 50 or 100 mg of active substance base is packed into size 1 or size 0 elongated hard gelatine capsules or HPMC capsules by means of a capsule filling machine.

Example 2

| | percentage composition | | | | per capsule [mg] | per capsule [mg] |
|---|---|---|---|---|---|---|
| | core material | insulating layer | active substance layer | total | | |
| tartaric acid | 38.5 | - | - | 38.5 | 55.5 | 166.5 |
| gum arabic | 1.9 | 1.7 | | 3.6 | 5.2 | 15.6 |
| talc | - | 3.5 | 6.4 | 9.9 | 14.3 | 42.8 |
| hydroxypropylcellulose | - | - | 8.0 | 8.0 | 11.5 | 34.6 |
| active substance (mesylate of the compound of formula I) | - | - | 40.0 | 40.0 | 57.7* | 173.0** |
| total | | | | 100.0 | 144.2 | 432.5 |

*) corresponds to 50 mg of the compound of formula 1 (active substance base)
**) corresponds to 150 mg of the compound of formula 1 (active substance base)

*a) Production of core material containing tartaric acid*

Composition:

| | |
|---|---|
| gum arabic | 1 part by weight |
| tartaric acid | 20 parts by weight |

1 part by weight of gum arabic is dissolved in 4 parts by weight of purified water at 50°C with stirring. Then 5 parts by weight of tartaric acid are dissolved in this solution with stirring.

8.3 parts by weight of tartaric acid crystals with an average particle size of 0.4 to 0.6 mm are placed in a suitable coating apparatus fitted with an air inlet and exhaust, and the pan is set in rotation. At an air inlet temperature of 60° – 80°C the tartaric acid crystals are sprayed at intervals with the solution of tartaric acid and gum arabic and sprinkled with a total of 6.7 parts by weight of powdered tartaric acid, so that roughly spherical particles are formed.

The spherical tartaric acid core material is then dried in the rotating pan at an air inlet temperature of 60° - 80° C.

The core material is fractionated using a tumbler screening machine with perforated plates with a nominal mesh size of 0.6 and 0.8 mm. The product fraction between 0.6 and 0.8 mm is used in the rest of the process.

*b) Insulation of the core material containing tartaric acid*

Composition:

| | |
|---|---|
| core material containing tartaric acid | 23 parts by weight |
| gum arabic | 1 part by weight |
| talc | 2 parts by weight |



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1 part by weight of gum arabic is dissolved in a mixture of 6.7 parts by weight of 96 % ethanol and 13.5 parts by weight of purified water with stirring. Then 2 parts by weight of talc are dispersed in the solution with stirring.

In a fluidised bed processing apparatus, 23 parts by weight of core material containing tartaric acid are sprayed at an air inlet temperature of 35° – 40°C with the dispersion of gum arabic and talc by the under-bed spraying process.

The insulated core material containing tartaric acid is then dried in the circulating air drier at 40°C for 8 hours.

To remove any lumps the dried insulated core material containing tartaric acid is screened through a screen with a nominal mesh size of 1.0 mm. The fraction of material with a particle size of < 1 mm is further processed.

*c) Production of the active substance layer*

Composition:

| | |
|---|---|
| insulated core material containing tartaric acid | 57 parts by weight |
| hydroxypropylcellulose | 10 parts by weight |
| talc | 8 parts by weight |
| active substance (mesylate of BIBR 1048) | 50 parts by weight |

Hydroxypropylcellulose is dissolved in 335 parts by weight of 2-propanol with stirring and then the active substance and talc are dispersed in this solution with stirring.

In a fluidised bed processing apparatus, 91 parts by weight of insulated core material containing tartaric acid are sprayed at an air inlet temperature of 20° -

30°C with the dispersion containing the active substance by the under-bed spraying process.

The pellets containing the active substance are then dried in the circulating air drier at 35°C for 8 hours.

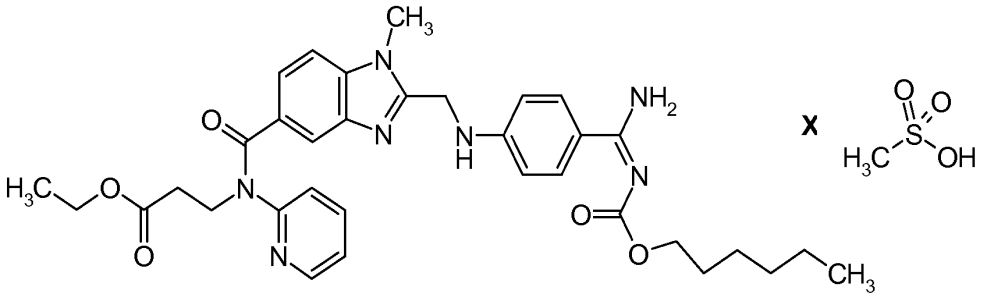
To remove any lumps the pellets containing the active substance are screened through a screen with a nominal mesh size of 1.25 mm. The fraction of material with a particle size of < 1.25 mm is further processed.

*d) Packing into capsules*

A quantity of active substance pellets containing in each case 50 or 150 mg of active substance base is packed into size 2 or size 0 hard gelatine capsules or HPMC capsules by means of a capsule filling machine.

Example 3

Preparation of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate



A solution of 5.0 mmol of methanesulphonic acid in 25 ml ethyl acetate was added dropwise, with stirring, to a solution of 3139 mg (5.0 mmol) of ethyl 3-[(2-{[4-

(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base (prepared as described in WO 98/37075) in 250 ml ethyl acetate, at ambient temperature. After a few minutes the product began to crystallise out. It was stirred for another hour at ambient temperature and then for one more hour while cooling with ice, the precipitate was suction filtered, washed with about 50 ml of ethyl acetate and 50 ml of diethyl ether and dried at 50°C in a circulating air drier.

Yield: 94% of theory

melting point: 178 - 179°C

$C_{34}H_{41}N_7O_5$ x $CH_4SO_3$ (723.86)

| Elemental analysis: | | C | H | N | S |
|---|---|---|---|---|---|
| | calc.: | 58.07% | 6.27% | 13.55% | 4.43% |
| | found: | 58.11% | 6.30% | 13.50% | 4.48% |



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**We Claim:**

1. Pharmaceutical composition for oral administration comprising:
a) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof and
b) one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 ml at 20° C.

2. Pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid or aspartic acid and one of the hydrates or acid salts thereof.

3. Pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, citric acid and succinic acid.

4. Pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable organic acid is tartaric acid.

5. Pharmaceutical composition according to claim 1, wherein the content of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or the salts thereof in the pharmaceutical composition is 5 to 60 %.

6. Pharmaceutical composition according to claim 1, wherein the content of pharmaceutically acceptable organic acid is 20 to 90 %.



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7. Pharmaceutical composition according to claim 1 comprising a substantially spherical core material further comprised of a pharmaceutically acceptable organic acid, and active substance layer comprised of a binder and optionally a separating agent, which encloses said core material.

8. Pharmaceutical composition according to claim 7, wherein said binder is selected from the group consisting of hydroxypropylcelluloses, hydroxypropyl-methylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethyl-celluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone and vinyl acetate or combinations thereof.

9. Pharmaceutical composition according to claim 7, wherein said core material has an average particle size of 0.4 to 1.5 mm.

10. Pharmaceutical composition according to claim 7, wherein said core material and the active substance layer are separated from one another by an insulating layer comprised of a water-soluble polymer, optionally with the addition of suitable plasticisers, separating agents and pigments.

11. Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of gum arabic.

12. Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of a partially or totally synthetic polymer selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethyl-celluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone and vinyl acetate, or a combination thereof.

13. Pharmaceutical composition according to claim 7, wherein the composition containing the active substance is packed into hard capsules.



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14. Pharmaceutical composition according to claim 1, wherein ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate is used as the active substance.

15. Process for preparing a pharmaceutical composition for oral administration containing ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the physiologically acceptable salts thereof, comprising the steps of:

a) forming the core material from one or more pharmaceutically acceptable organic acid(s) with a water solubility of > 1 g / 250 ml at 20° C, optionally with the addition of binders or other technological adjuvants, by pan methods, on pelleting plates or by extrusion / spheronisation,

b) applying to the core material an insulating layer comprised of one or more water-soluble, pharmaceutically acceptable polymers optionally with the addition of plasticisers, separating agents and/or pigments,

c) applying the active substance from a dispersion which contains a binder and optionally separating agents and simultaneously and/or subsequently drying to eliminate the dispersant,

d) optionally applying a coating of film-forming agents, plasticisers and optionally pigments and

e) packing the active substance-containing pellets thus obtained into capsules.



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16. A composition comprised of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate.



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Abstract

The invention relates to a new administration form for the oral application of the active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmacologically acceptable salts thereof.



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Figure 1:

**Schematic structure of the pharmaceutical composition:**

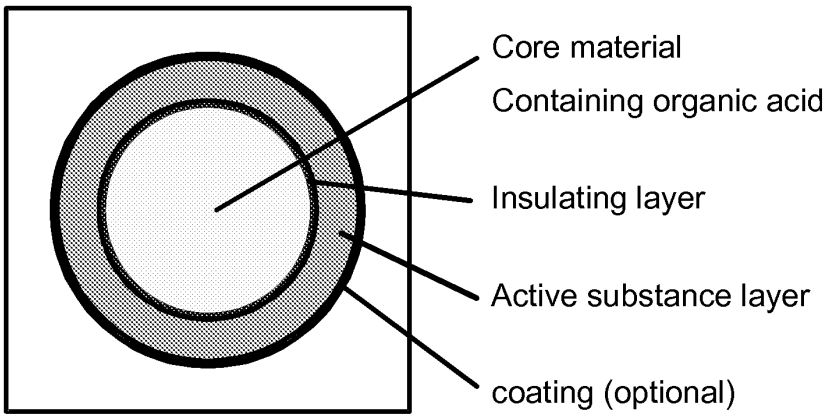
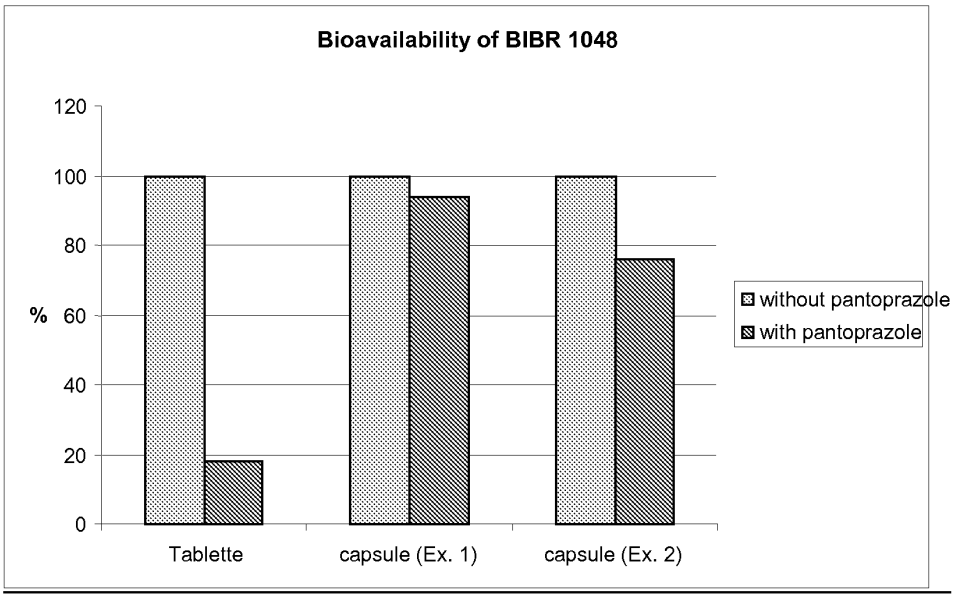



Figure 2:



Please type a plus sign (+) inside this box → [+]

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# DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing **OR** ☑ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

| | |
|---|---|
| **Attorney Docket Number** | 1/1306 |
| **First Named Inventor** | Ulrich BRAUNS |
| ***COMPLETE IF KNOWN*** | |
| Application Number | 10 / 383,198 |
| Filing Date | March 6, 2003 |
| Group Art Unit | to be assigned |
| Examiner Name | to be assigned |

**As a below named inventor, I hereby declare that:**

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-[[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL)-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF

*(Title of the Invention)*

the specification of which
☐ is attached hereto
OR
☑ was filed on (MM/DD/YYYY) 03/06/2003 as United States Application Number or PCT International Application Number 10/383,198 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? YES | Certified Copy Attached? NO |
|---|---|---|---|---|---|
| 10209985.5 | Germany | 03/07/2002 | ☐ | ☐ | ☑ |
| 10245624.0 | Germany | 09/30/2002 | ☐ | ☐ | ☑ |
| | | | ☐ | ☐ | ☐ |
| | | | ☐ | ☐ | ☐ |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

| Application Number(s) | Filing Date (MM/DD/YYYY) |
|---|---|
| 60/409,762 | 9/11/2002 |
| 60/421,896 | 10/29/2002 |

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.



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# DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

| U.S. Parent Application or PCT Parent Number | Parent Filing Date (MM/DD/YYYY) | Parent Patent Number (if applicable) |
|---|---|---|
| | | |

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number 28501 → *Place Customer Number Bar Code Label here*

*OR*

☑ Registered practitioner(s) name/registration number listed below

| Name | Registration Number | Name | Registration Number |
|---|---|---|---|
| Robert P. Raymond | 25,089 | Susan K. Pocchiari | 45,016 |
| Alan R. Stempel | 28,991 | Philip I. Datlow | 41,482 |
| Mary-Ellen M. Devlin | 27,928 | Timothy X. Witkowski | 40,232 |
| Anthony P. Bottino | 41,629 | David A. Dow | 46,124 |

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☑ Customer Number or Bar Code Label 28501 *OR* ☐ Correspondence address below

| | | | | | |
|---|---|---|---|---|---|
| Name | | | | | |
| Address | | | | | |
| Address | | | | | |
| City | | State | | ZIP | |
| Country | | Telephone | | Fax | |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

**Name of Sole or First Inventor:** ☐ A petition has been filed for this unsigned inventor

| Given Name (first and middle [if any]) | Family Name or Surname |
|---|---|
| Ulrich | BRAUNS |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Inventor's Signature | U. Brauns | | | | | Date | 08-06-02 |
| Residence: City | Biberach | State | | Country | Germany | Citizenship | DE |
| Post Office Address | Alleenstrasse 45 | | | | | | |
| Post Office Address | | | | | | | |
| City | Biberach | State | | ZIP | 88400 | Country | Germany |

☑ Additional inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

Please type a plus sign (+) inside this box → [+]

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# DECLARATION

**ADDITIONAL INVENTOR(S)**
**Supplemental Sheet**
Page 1 of 1

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle [if any]) | Family Name or Surname | | |
| Norbert | HAUEL | | |
| **Inventor's Signature** Norbert Hauel | | **Date** 08/08/03 | |
| **Residence: City** Schemmerhofen | **State** | **Country** Germany | **Citizenship** DE |
| **Mailing Address** Marderweg 12 | | | |
| **Mailing Address** | | | |
| **City** Schemmerhofen | **State** | **ZIP** 88433 | **Country** Germany |

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle [if any]) | Family Name or Surname | | |
| | | | |
| **Inventor's Signature** | | **Date** | |
| **Residence: City** | **State** | **Country** | **Citizenship** |
| **Mailing Address** | | | |
| **Mailing Address** | | | |
| **City** | **State** | **ZIP** | **Country** |

| | | | |
|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | ☐ A petition has been filed for this unsigned inventor | | |
| Given Name (first and middle [if any]) | Family Name or Surname | | |
| | | | |
| **Inventor's Signature** | | **Date** | |
| **Residence: City** | **State** | **Country** | **Citizenship** |
| **Mailing Address** | | | |
| **Mailing Address** | | | |
| **City** | **State** | **ZIP** | **Country** |

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Case No. 1/1306

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | |
|---|---|---|---|---|
| Application of | : | U. Brauns, et al. | ) Art Unit | : Not yet assigned |
| Serial No. | : | Not yet assigned | ) Examiner | : Not yet assigned |
| Confirmation No.: | | Not yet assigned | | |
| Filed | : | May 5, 2006 | | |
| Title | : | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1*H*-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF | | |
| Docket No. | : | 1/1306-1-C1 | | |

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

**PRELIMINARY AMENDMENT**

Sir:

Before commencing examination of the above-indentified application, please enter the following amendments:

**Amendments to the Specification** begin on page 2 of this paper.

**Amendments to the Claims** are reflected in the listing of claims which begins on page 3 of this paper.

**Remarks** begin on page 6 of this paper.



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**MSN Exhibit 1008**
**Page 290 of 304**

**Amendments to the Specification:**

Please amend the following paragraph after "Related Applications" and before the "Field of Invention" beginning on page 1, line 10:

**Related Application**

This application is a continuation of pending U.S. Application No. 10/383,198, which claims b[[B]]enefit of U.S. Provisional Application ~~Serial~~ No. 60/421,896, filed on October 29, 2002 and U.S. Provisional Application ~~Serial~~ No. 60/409,762, filed on September 11, 2002, ~~is hereby claimed, and said applications are~~ the contents of which are herein incorporated by reference.



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**Amendments to the Claims:**

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

**Listing of Claims:**

Claim 1 (currently amended): A **[[**P**]]**pharmaceutical composition for oral administration comprising:
a) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof and
b) one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 ml at 20° C.

Claim 2 (original): Pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid or aspartic acid and one of the hydrates or acid salts thereof.

Claim 3 (original): Pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of tartaric acid, fumaric acid, citric acid and succinic acid.

Claim 4 (original): Pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable organic acid is tartaric acid.

Claim 5 (original): Pharmaceutical composition according to claim 1, wherein the content of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or the salts thereof in the pharmaceutical composition is 5 to 60 %.

Claim 6 (original): Pharmaceutical composition according to claim 1, wherein the content of pharmaceutically acceptable organic acid is 20 to 90 %.



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Claim 7 (original): Pharmaceutical composition according to claim 1 comprising a substantially spherical core material further comprised of a pharmaceutically acceptable organic acid, and active substance layer comprised of a binder and optionally a separating agent, which encloses said core material.

Claim 8 (original): Pharmaceutical composition according to claim 7, wherein said binder is selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone and vinyl acetate or combinations thereof.

Claim 9 (original): Pharmaceutical composition according to claim 7, wherein said core material has an average particle size of 0.4 to 1.5 mm.

Claim 10 (original): Pharmaceutical composition according to claim 7, wherein said core material and the active substance layer are separated from one another by an insulating layer comprised of a water-soluble polymer, optionally with the addition of suitable plasticisers, separating agents and pigments.

Claim 11 (original): Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of gum arabic.

Claim 12 (original): Pharmaceutical composition according to claim 10, wherein said water-soluble polymer is comprised of a partially or totally synthetic polymer selected from the group consisting of hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone and vinyl acetate, or a combination thereof.

Claim 13 (original): Pharmaceutical composition according to claim 7, wherein the composition containing the active substance is packed into hard capsules.

Claim 14 (original): Pharmaceutical composition according to claim 1, wherein ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-



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methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate is used as the active substance.

Claim 15 (original): A p[[P]]rocess for preparing a pharmaceutical composition for oral administration containing ethyl 3-[(2-{[4-(hexyloxy-carbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the physiologically acceptable salts thereof, comprising the steps of:

a) forming the core material from one or more pharmaceutically acceptable organic acid(s) with a water solubility of > 1 g / 250 ml at 20° C, optionally with the addition of binders or other technological adjuvants, by pan methods, on pelleting plates or by extrusion / spheronisation,

b) applying to the core material an insulating layer comprised of one or more water-soluble, pharmaceutically acceptable polymers optionally with the addition of plasticisers, separating agents and/or pigments,

c) applying the active substance from a dispersion which contains a binder and optionally separating agents and simultaneously and/or subsequently drying to eliminate the dispersant,

d) optionally applying a coating of film-forming agents, plasticisers and optionally pigments and

e) packing the active substance-containing pellets thus obtained into capsules.

Claim 16 (canceled).



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## REMARKS

Applicants request consideration of the above-identified application in view of the foregoing amendments and the following remarks.

Claims 1-15 are pending in this application.

Applicants have amended the specification to set forth a priority claim under 35 U.S.C. §§ 120 and 119(e).

Applicants have amended claims 1 and 15 to improve the form. Claim 16 has been canceled. This cancellation is made without prejudice and without waiver of applicants' right to pursue the subject matter of this claim in a subsequent application claiming priority herefrom under 35 U.S.C. § 120.

None of the amendments to the specification or claims constitutes new matter.

Applicants respectively request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

/wendy petka/

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**APPLICATION DATA SHEET**

**APPLICATION INFORMATION**

| | |
|---|---|
| **Application Type::** | Regular |
| **Subject Matter::** | Utility |
| **CD-ROM or CD-R?::** | None |
| **Number of CD disks::** | 0 |
| **Number of copies of CDs::** | 0 |
| **Sequence submission?::** | None |
| **Computer Readable Form (CRF)?::** | No |
| **Number of copies of CRF::** | 0 |
| **Title::** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **Attorney Docket Number::** | 1/1306-1-C1 |
| **Request for Early Publication?::** | No |
| **Request for Non-Publication?::** | No |
| **Total Drawing Sheets::** | 1 |
| **Small Entity?::** | No |
| **Petition included?::** | No |
| **Secrecy Order in Parent Appl.?::** | No |

**APPLICANT INFORMATION**

| | |
|---|---|
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| **Primary Citizenship Country::** | Germany |
| **Status::** | Full Capacity |
| **Given Name::** | Ulrich |
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**MSN Exhibit 1008**
**Page 296 of 304**

| | |
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| **Correspondence Customer Number::** | 28501 |

**REPRESENTATIVE INFORMATION**

| | |
|---|---|
| **Representative Customer Number::** | 28501 |

**DOMESTIC PRIORITY INFORMATION**

| Application:: | Continuity Type:: | Parent Application:: | Parent Filing Date:: |
|---|---|---|---|
| This Application | Continuation of | 10/383,198 | 03/06/2003 |
| 10/383,198 | Non-Provisional of | 60/421,896 | 10/29/2002 |
| 10/383,198 | Non-Provisional of | 60/409,762 | 09/11/2002 |

**FOREIGN PRIORITY INFORMATION**

| Country:: | Application Number:: | Filing Date:: | Priority Claimed:: |
|---|---|---|---|
| Germany | 10209985 | 03/07/2002 | Yes |
| Germany | 10245624 | 09/30/2002 | Yes |

**ASSIGNEE INFORMATION**

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| **Country of mailing address::** | Germany |
| **Postal or Zip Code of mailing address::** | 55216 |

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | |
| **Filing Date:** | |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor:** | Ulrich Brauns |
| **Filer:** | Wendy Petka |
| **Attorney Docket Number:** | 1/1306-1-C1 |

Filed as Large Entity

**Utility Filing Fees**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| Utility application filing | 1011 | 1 | 300 | 300 |
| Utility Search Fee | 1111 | 1 | 500 | 500 |
| Utility Examination Fee | 1311 | 1 | 200 | 200 |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Post-Allowance-and-Post-Issuance: | | | | |
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **1000** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 1040075 |
| **Application Number:** | 11381890 |
| **Confirmation Number:** | 5127 |
| **Title of Invention:** | ADMINISTRATION FORM FOR THE ORAL APPLICATION OF 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYL ESTER AND THE SALTS THEREOF |
| **First Named Inventor:** | Ulrich Brauns |
| **Customer Number:** | 28501 |
| **Filer:** | Wendy Petka |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | 1/1306-1-C1 |
| **Receipt Date:** | 05-MAY-2006 |
| **Filing Date:** | |
| **Time Stamp:** | 16:13:01 |
| **Application Type:** | Utility |
| **International Application Number:** | |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment was successfully received in RAM | $1000.0 |
| RAM confirmation Number | 143 |
| Deposit Account | 022955 |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17 | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes) | Multi Part | Pages |
|---|---|---|---|---|---|
| 1 | | 1-1306-1-C1-US-Filing-Text-5-5-06.pdf | 162312 | yes | 23 |
| | **Multipart Description** | | | | |
| | **Doc Desc** | | **Start** | **End** | |
| | Specification | | 1 | 18 | |
| | Claims | | 19 | 22 | |
| | Abstract | | 23 | 23 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Drawings | 1-1306-1-C1-FIGURES-5-5-06.pdf | 102678 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Oath or Declaration filed | 1-1306-1-C1-copy-declaration-5-5-06.pdf | 158539 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Preliminary Amendment | 1-1306-1-C1-Prelim-Amendmt-5-5-06.pdf | 100112 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Application Data Sheet | 1-1306-1-C1-ADS-5-5-06.pdf | 59157 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied ADS fillable form | | | | | |
| 6 | Fee Worksheet (PTO-875) | fee-info.pdf | 8480 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 591278 | | |

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

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

PTO/SB/06 (08-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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# PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number: 11381890

## CLAIMS AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE | SMALL ENTITY FEE | OR | OTHER THAN SMALL ENTITY RATE | OTHER THAN SMALL ENTITY FEE |
|---|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a)) | | | | | $ | OR | | $ 300 |
| TOTAL CLAIMS (37 CFR 1.16(c)) | 15 | minus 20 = | * | X $ = | | OR | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(b)) | 2 | minus 3 = | * | X $ = | | OR | X $ = | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(d)) | | | | + $ = | | OR | + $ = | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | | OR | TOTAL | 300 |

## CLAIMS AS AMENDED – PART II

5/5/06

### AMENDMENT A

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA |
|---|---|---|---|---|
| Total (37 CFR 1.16(c)) | * 15 | Minus | ** 20 | = |
| Independent (37 CFR 1.16(b)) | * 2 | Minus | *** 3 | = |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d)) | | | | |

| SMALL ENTITY RATE | SMALL ENTITY ADDITIONAL FEE | OR | OTHER THAN SMALL ENTITY RATE | OTHER THAN SMALL ENTITY ADDITIONAL FEE |
|---|---|---|---|---|
| X $ = | | OR | X $ = | 0 |
| X $ = | | OR | X $ = | 0 |
| + $ = | | OR | + $ = | |
| TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | 0 |

### AMENDMENT B

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA |
|---|---|---|---|---|
| Total (37 CFR 1.16(c)) | * | Minus | ** | = |
| Independent (37 CFR 1.16(b)) | * | Minus | *** | = |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d)) | | | | |

| SMALL ENTITY RATE | SMALL ENTITY ADDITIONAL FEE | OR | OTHER THAN SMALL ENTITY RATE | OTHER THAN SMALL ENTITY ADDITIONAL FEE |
|---|---|---|---|---|
| X $ = | | OR | X $ = | |
| X $ = | | OR | X $ = | |
| + $ = | | OR | + $ = | |
| TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

### AMENDMENT C

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA |
|---|---|---|---|---|
| Total (37 CFR 1.16(c)) | * | Minus | ** | = |
| Independent (37 CFR 1.16(b)) | * | Minus | *** | = |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d)) | | | | |

| SMALL ENTITY RATE | SMALL ENTITY ADDITIONAL FEE | OR | OTHER THAN SMALL ENTITY RATE | OTHER THAN SMALL ENTITY ADDITIONAL FEE |
|---|---|---|---|---|
| X $ = | | OR | X $ = | |
| X $ = | | OR | X $ = | |
| + $ = | | OR | + $ = | |
| TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest 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.**

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