

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-1H-
BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-
PROPIONIC ACID ETHYL ESTER AND THE SALTS
THEREOF
Docket No. : 01-1306-1-C1

DECLARATION UNDER 37 C.F.R. § 1.132

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

Sir:

I, Dr. Ulrich Brauns, being duly warned, declare that:

1. I am a citizen of Germany, residing in Biberach an der Riss, Germany.
2. I have studied Pharmacy at the University of Kiel, Germany and became licensed to practice as a pharmacist in 1982. I continued my studies at the University of Kiel and received a Dr. rer. nat. in Pharmaceutics in 1986. My thesis was entitled "Properties of solubilizing Cyclodextrin Derivatives."
3. From 1986 to 1993, I served as Laboratory Head and then Head of Department of Pharmaceutical Development at Chemische Fabrik Promonta GmbH (ALTANA Group) in Hamburg, Germany. I have been employed by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany since 1993. Between 1993 and 2002, I served as Laboratory Group Leader, Pharmaceutical R&D, Boehringer Ingelheim Pharma GmbH & Co. KG (formerly Dr. Karl Thomae GmbH) in Biberach, Germany. In 1998, Boehringer Ingelheim KG and Dr. Karl Thomae GmbH merged into Boehringer Ingelheim Pharma KG. On February 18, 2003, Boehringer Ingelheim Pharma KG changed its name to Boehringer Ingelheim Pharma GmbH & Co. KG.

From 2002 to 2006, I was Senior Project Leader, Project Management R&D and from 2006 to 2013 I have been a Director of Project Management R&D. Since 2013, I serve as Vice President and Head of Global CMC Project Management in Boehringer Ingelheim Biopharmaceuticals GmbH. My responsibilities include leading a global department with approximately 30 project leaders in the USA, Austria and Germany.

4. I am the sole inventor of the claims of the above-identified application and am knowledgeable about the subject matter of this invention.
5. I am familiar with the grounds for rejection made against the application and have been asked to discuss the inventiveness of the pharmaceutical composition shown in Figure 1 and bioavailability data presented in Figure 2 of the specification.
6. Dabigatran etexilate is a unique acid labile double-prodrug (hereinafter referred to as "prodrug"). Upon exposure to enzymes after absorption, the prodrug is cleaved to form dabigatran, the active metabolite (see compound of formula I in the specification on page 2).
7. Bioavailability requires both solubility and permeability through the GI membranes. Dabigatran, the active moiety, forms a zwitterion at physiological pH but is too polar to pass through the lipophilic membranes in the GI tract via diffusion. Thus, the double prodrug of dabigatran was prepared so that the ester and carbamate ends would increase lipophilicity of the drug so that it may be absorbed in the GI membranes. Although these modifications decreased aqueous solubility, they increased permeability. After absorption through the GI walls, the prodrug is cleaved to the active moiety dabigatran.
8. The prodrug retains some basic properties and can be protonated. However, the prodrug is a weak base so protonation only occurs at rather low pH. A balance between un-protonated species (which is absorbed) and protonated species (which is relevant for aqueous solubility) is decisive for oral bioavailability.

9. The formation of a dabigatran etexilate salt served two purposes: (1) increase aqueous solubility and thus, oral bioavailability and (2) exhibit stability and low hygroscopicity during storage. As pointed out in the parent U.S. application no. 10/383,198 (and proven by comparative data in Declaration form), it was surprising that methanesulfonic acid (“mesylate”) formed a stable dabigatran etexilate salt. One of skill in the art would have expected the opposite to be true, that is, a strong acid, such as methanesulfonic acid, would cleave the double-prodrug and make it less stable during storage. Thus, the methanesulfonic acid salt form of dabigatran etexilate itself is nonobvious due to these unexpected properties. This application’s current claims require the specific methanesulfonic acid salt form of dabigatran etexilate. Therefore, the claims are nonobvious at least on this basis, i.e., for all of the same reasons and evidence provided in the parent U.S. application no. 10/383,198. Additional reasons support the nonobviousness of the particular formulation claims of this application.
10. It was discovered during development that the formation of the prodrug salt alone was not sufficient for providing adequate bioavailability in the entire patient population. An additional acidic environment was preferred to enhance dissolution of the prodrug due to its weakly basic properties to allow for subsequent prodrug absorption.
11. In early clinical trials, dabigatran etexilate mesylate was administered as a conventional tablet. This tablet was prepared according to composition of Table I, page 9, in the specification. It was thought that the gastric juices in the stomach (~ pH 1-2) would be sufficient solubilize the prodrug in the conventional tablet so that it would be absorbed immediately upon entering the small intestine. In other words, availability for absorption would be very high at the beginning of the small intestine. This was an important criterion because the pH of the small intestine is too high to dissolve the prodrug. Page 8, lines 1-3, of the specification discusses solubility of dabigatran etexilate (pH level > 5 results in an insoluble prodrug).

12. The preliminary tests using conventional tablet technology resulted in highly variable plasma levels of dabigatran in healthy volunteers and in some cases, malabsorption. Some volunteers had little to no absorption and thus, little to no bioavailability. However, when the prodrug was administered as an acidic oral solution, the variability of plasma levels of dabigatran decreased significantly. Dabigatran etexilate was shown to dissolve relatively well in water at low pH levels. See bottom of page 7 and top of page 8 of the specification. Thus, a conventional dosage form of dabigatran etexilate mesylate did not give the most desired results for all patient populations.
13. It was hypothesized that some patient stomachs were more basic because of normal variability, by disease, or co-medication with drugs that increase gastric pH. That is, if the gastric environment of the patient is not sufficiently acidic, the prodrug does not dissolve sufficiently to ensure adequate bioavailability. This was not expected but only detected during formulation development. To solve this problem, the formulation itself was re-designed to (a) act as an acidic microenvironment while in the stomach in order to quickly dissolve the majority of the prodrug prior to entering the small intestine; (b) be stable before entering GI tract for storage purposes; and (c) work well for the entire patient population, meaning that bioavailability would be consistent and high for the entire patient population. This solution to the problem was not easy given the unique structure of dabigatran etexilate salt and the resulting solution to the problem, that is providing the particular form of pharmaceutical preparation as claimed, which forms the subject matter of this invention.
14. The current application's claims are thus distinguished from the cited references not only because they are directed to the specific mesylate salt of the prodrug but further because they are directed to a specific pharmaceutical preparation of dabigatran etexilate mesylate (see Figure 1). Figure 1 illustrates a spherical organic acid core, an insulating layer, an active substance layer and optionally, a coating layer of the present invention.

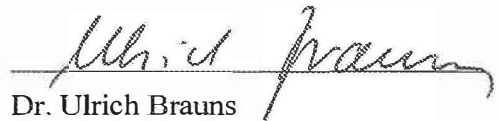
15. In order to test the new oral formulation in high-pH stomach conditions, two sets of 15 volunteers were treated. In the first set, 15 volunteers were given the formulation of Example 1 (in the specification) by mouth on an empty stomach. Bioavailability was measured. The same 15 volunteers were then treated with 40 mg of pantoprazole, a compound that increases the pH of the stomach, twice daily for three days prior to administering formulation of Example 1. Pantoprazole was also continued during administration of formulation of Example 1. The degree of the absorption was determined by measuring the quantity of active metabolite excreted in the urine. The relative bioavailability after pre-treatment with pantoprazole was 94% on average compared with administration without any pre-treatment.
16. In the second set, 15 volunteers were given the formulation of Example 2 (in the specification) by mouth on an empty stomach. Bioavailability was measured. The same 15 volunteers were then treated with 40 mg of pantoprazole twice daily for three days prior to administering formulation of Example 2. Pantoprazole was also continued during administration of formulation of Example 2. The degree of the absorption was determined by measuring the quantity of active metabolite excreted in the urine. The relative bioavailability after pre-treatment with pantoprazole was 76% on average compared with administration without any pre-treatment.
17. The conventional tablet formulation of the prodrug used in the early clinical trials was also tested under comparable conditions to Examples 1 and 2 above. For example, a tablet containing 50 mg of dabigatran etexilate mesylate was prepared according to Table 1, page 9, in the specification. The bioavailability of the conventional tablet after pre-treatment with pantoprazole was 18%.
18. The comparative results are shown in Figure 2 of the specification. Here, the bioavailability (based on the area under the plasma concentration/time curve) of the active metabolite in volunteers treated with and without pantoprazole is shown. The new formulations of Example 1 and 2 provide an improved bioavailability (about a factor of 4 or 5) over that of the tablet formulation in a model simulating a patient population with non-acidic stomachs. This new formulation is advantageous for the

entire patient population and more suitable for administration specifically to a patient population with non-acidic stomachs.

19. The present formulation was designed to accommodate the specific and unique properties of the prodrug, dabigatran etexilate. An acid core layer, an insulating layer and an active substance layer are necessary components of this invention. For example, the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. The insulating layer first acts as a protective layer between the acid core and active substance layer on storage but then permits the diffusion of acid to the active substance layer immediately in passage through the stomach. The active substance layer provides the correct dosage of prodrug. This could not have been obvious in view of the prior art of record in this case because the lack of bioavailability of dabigatran in clinical trial volunteers with elevated gastric pH was not anticipated by those directly involved in the early development of the prodrug.

20. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: March 11, 2014


Dr. Ulrich Brauns