THE PATENTS ACT, 1970

Section 15

In the matter of an application for patent No. 924/DELNP/2006 dated the 22nd February, 2006

BOEHRINGER INGELHEIM INTERNATIONAL GMBH. - Applicant

ORDER

1. M/s. Boehringer Ingelheim International GMBH., German Company Of Binger Strasse 173, 55216 Ingelheim, Germany, through their agents M/s. Remfry & Sagar Attorneys-At-Law Remfry House Millennium Plaza, Sector 27, Gurgaon 122 002 filed the application no.924/DELNP/2006 dated 22nd February,2006 for their invention entitled"3-[(2-{4-(Hexyloxycarbonylamino-Imino-Methyl)-PhenylAmino]-Methyl}-1-Methyl-1h-Benzimidazol-5-Carbonyl)-Pyridine-2-Yl-Amino]-Propionic Acid Ethyl Ester Methane Sulphonate and Use Thereof as a Medicament" containing 14 claims. It is derived from PCT international application PCT/EP2004/009432 dated 24th August, 2004 and claims priorities from earlier German application 103 39 862.7 filed on 29th August, 2003. A request for examination of the said application was filed by their agent on 11th September,2006.This application was published under the provisions of Section 11(A) of the Patents Act,1970 as amended in 2005 (hereinafter referred as 'Act') in the Patent Journal No. 32/2007 dated 10th August,2007.
2. This application was examined by the Office and First Examination Report thereof issued on 23rd February, 2009.
3. In response to the objections raised in the said FER the applicant's agent vide their letter dated 27th April, 2009 submitted that the applicant disagreed on the objection under section 3(d) of the Act. The applicant further submitted that the prior art citation Hauel et.al.(J.Med.Chem Vol45,2002,1757-1766) only discloses a method for the preparation of the free base of the compound Ethyl3-[(2-{4-(Hexyloxycarbonylamino-Imino-Methyl)-Phenyl Amino]-Methyl}-1-Methyl-1h-Benzimidazol-5-Carbonyl)-Pyridine-2-

Yl-Amino]-Propionate (Compound code BIBR 1048) which shows a water solubility of 0.003 mg/ml. The claimed invention relates to methansulfonate of the instant compound and the solubility of the mesylate salt in water is 1.8 mg/ml .The claimed invention relates to polymorph II of the methansulfonate of Ethyl3-[(2-{4-(Hexyloxycarbonylamino-Imino-Methyl)-Phenyl Amino]-Methyl}-1-Methyl-1h-Benzimidazol-5-Carbonyl)-Pyridine-2-Yl-Amino]-Propionate.

4. On further examination based on the submissions given, the examiner found that the submissions and the observations given by the agents are not satisfactory to meet the requirements of the Act. This application was further re-examined by the Office and second Examination Report (SER) thereof issued on 23rd February, 2010.
5. In response to the objections raised in the said SER the applicant's agent vide E Mail on 23rd February,2010 request for hearing and their letter dated 30th March,2010 submitted that the bioavailability of as oral dosage form is directly connected to the solubility of the compound. The better the solubility of the compound the higher is its bioavaility .Applicant further submitted that the D1 (WO 03/074056) only discloses polymorph I of the methanesulphate of dabigatran etexilate however the claimed invention relates to polymorph II only and D1 was also not published before the priority date .In reference to D2 & D5 response are same as filed on 27th April, 2009 by the applicant. D3, D4 and D6 to D8 prior art documents have not disclosed the methansulfonate of the compound. Claims 5 & 6 have been deleted by the applicant and four claims maintained.
6. On further examination based on the submissions given, the examiner found that the submissions and the observations given by the agents are again not satisfactory and meet the requirements of the Act .The following objections are maintained:
    1. Claims 1-4 fall within the scope of such clause (d) of section 3 of Patents Act 1970 as the claimed compound is a new form of a known substance with no enhanced therapeutic efficacy.
    2. Subject matter does not constitute an invention u/s2(1)(ja) as the claims lack inventive step in view of cited documents:

       D1: WO03/074056 discloses the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-aminol-propionate methane sulphonate and process of its preparation.

       D2: Hauel N. H. et al: "Structure-based design of novel potent nonpeptide thrombin inhibitors" Journal of Medicinal Chemistry, American Chemical Society. Washington, US, Vol. 45, No.9, 2002, pages 1757 – 1766.

D3: Mungall D.: "BIBR-1048 Boehringer Ingelheim" in Investigational Drugs, Pharmapress, US, Vol. 2002 (2002-06), pages 905 - 907, XPOOl147306 ISSN Current Opinion 3, No. 6 , June 1472-4472 discloses BIBR-1048 MS as well as results from studies with this thrombin inhibitor

D4: Caira M. R.: "Crystalline Polymorphism of Organic Compounds" Topics in Current Chemistry, Springer, Berlin, DE, Vol. 198, 1998, pages 163 - 208.

D5: WO98/37075 discloses BIBR-1048 base having a thrombin-inhibiting effect and a thrombin time prolonging activity.

D6: Collins B. and Hollidge *C.:* "Antithrombotic Drug Market" Nature Reviews Drug Discovery, Nature Publishing Group, 2002, Vol. 2, January 2003, pages 11-12, ISSN: 1474-1776 reports on developmental oral anticoagulants, such as BIBR-1048 MS, which is said to be in phase II trials.

D7: J. M. Stassen: Ex vivo Anticoagulant Activity of BIBR953ZW, A Novel Synthetic Direct Thrombin Inhibitor and of its Prodrug BIBR1048 MS in different animal species, Supplement to the Journal Thrombosis and Haemostasis, July 2001, ISSN: 0340-6245 discloses oral active prodrug BIBR-1048 MS and its antithrombotic potential *in vivo.*

D8: J. Stangier: Pharmacokinetics of BIBR 953 Z, A novel low molecular weight direct thrombin inhibitor in healthy volunteers, Supplement to the journal Thrombosis and Haemostatis, July 2001, ISSN: 0340-6245 discloses administration of BIBR1048MS as oral solution to study pharmacokinetics of BIBR953Z.

7. Before proceeding to dispose of the application in accordance with the provisions hereinafter appearing, and on request from applicant on 23rd February, 2010 and 30th march, 2010 for being given an opportunity to be officially heard by the Controller before any adverse order on the application is passed .Accordingly, a hearing was fixed on 10th November, 2010 Under section 14 of the Act and this matter was heard.

8. The agents for the applicant submitted before hearing that:

8.1 Regarding objection 1 of hearing notice, applicant's agent submitted that the methansulfonate over salts and over free base of the compound dabigartran etexilate. The applicant emphasizes that before the priority date of the instant invention the methansulfonate was not public. The applicant was also shown the inability to provide the efficacy comparison with the prior art references.

8.2 Regarding objection 2, applicant's agent submitted that the present claimed invention is inventive over the cited documents and same response filed against each prior art references.

9. Thus the finally submitted 4 claims, claims 1 for compound, claim 2 for composition and 3 &4 for process for preparation for the same.

10. Findings and conclusions

The issue before me was to decide whether the claims lack inventive step and fall within the scope of section 3(d).

I. I shall now deal with objection that subject matter of claims lack inventive step in view of prior art documents as cited in the examination report. The claimed subject-matter is not novel and does not involve an inventive step. Further, the Claimed invention does not disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

The report mentioned eight documents D1 to D 8 as prior art reference. The claimed compound is derived from ethyl 3-[(2-{[4(hexyloxycarbonylamino -imino-methyl) phenylamino]-methy1}-1methyl-1H-benzimidazole-S-carbonyl)-pyridin-2-yl-amino] propionate. This compound structure is also referred to in the literature as BIBR-1048, or BIBR-1048 base in D2, page 1760.The claimed compound is the methanesulphonate salt of BIBR1048. This methanesulphonate salt is sometimes also referred to in the literature as BIBR-1048 MS. Further, claim 1 does in fact require the methansulphonate to be in crystalline form. Finally, said crystalline form as required in accordance with claim 1 is characterized by a melting point of 190±3°C, as determined by DSC; evaluation by peak maximum; heating rate: 10°C/min. This specific crystalline form characterized by its melting point is also referred to in the claims as form II of BIBR-1048 MS.

In the page 2 of the complete specification, the claimed invention relates to the compound BIBR-1048 MS of formula A and its use as a pharmaceutical composition.

It is also acknowledged that the base of the compound of formula A (i.e. BIBR-1048 base) is originally known from WO 98/037075 (D5). D5 discloses compounds with a thrombin-inhibiting effect and a thrombin time prolonging activity.

The claimed compound of formula A is in fact a double prodrug of the compound of formula B. I.e., the claimed compound of formula A (BIBR-1048 MS) is only converted into the actual effective compound, namely the compound of formula B, in the specification. Compound B, the pharmaceutically active compound, is also referred to in the document D8 as BIBR-953 ZW.

The main fields of application of the claimed compound A (BIBR-I048 MS) are the post-operative prophylaxis of deep vein thrombosis and the prevention of stroke. The specification also refers on page 3 to 4, the requirements of pharmaceutically active

substances, such as stability, low absorption of moisture, solubility etc. Because the claimed invention does not contain any stability, Moisture absorption, or solubility data, let alone any surprising effect in this respect. In fact, the specification already in page 4 states very general technical problem underlying the alleged invention, namely to *"provide* a *pharmaceutically activ*e *substance which is not only characterized by high pharmacological potency but also satisfies the abovementioned physicochemical requirements* as *far* as *possible.*

Present claim 1 relates to a specific crystalline form of BIBR-1048 MS. Crystalline form II is defined by its melting point of 190°C ± 3°C, as *determined by DSC, evaluation by peak maximum, heating rate: 10°C/min.* Document D1, at page 17, describes the preparation of the very compound, BIBR-1048 MS in crystalline state, and page 17, line 18 specifies the melting point to be "178-179°C". The applicant has not provided any evidence that the compound as obtained in accordance with example 3 at page 17 of D1, when having its melting point determined in accordance with the DSC method of the claims, is distinguishable from the claimed crystalline form II having a DSC melting point of 190°C ± 3°C (or *190°C ± 2°C,* compare the specification, page 15, the DSC diagram at the bottom).

Present claim 2 relates to a:

"[a] pharmaceutical composition, containing the salt ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methylJ-phenylamino]-methylj-1-methyl-1H-benzimidazole-S-carbonylJ-pyridin-2-ylaminoJ-propionate-methanesulphonate according to claim 1, optionally together with one or more inert carries and/or diluents"

There is no requirement in this claim that the *"salt according* to *claim* 1" must be contained in the pharmaceutical composition in a crystalline form, let alone specific form II as defined by its melting point. Document D1 discloses such a pharmaceutical composition. Reference is made in this document to page 4, second paragraph, in particular lines 10 to 14 and page 5, line 3 to page 6, tables at the top of pages 8, 9, and 11 of D1.

D2 is therefore state of the art in accordance with Act.D2 discloses the results from studies into the discovery of safe, orally active inhibitors of the serine protein thrombin. A number of prodrugs were synthesized, from which BIBR-1048 (base) exhibited strong and long-lasting anticoagulant effects after oral administration in different animal species. This prodrug was chosen for development, and in accordance with page 1762, was undergoing phase II clinical trials in patients with thromboembolitic disorders. The method

for the preparation of BIBR-I048 is taught in D2 at page 1765. The claimed subject-matter differs from the disclosure of D2 insofar as claim 1 requires the specific methanesulphonate (MS) salt. The applicant argued that the methanesulphonate salt of BIBR-I048 shows good solubility in water. However, this is a phenomenon regularly observed with salts, as compared to the free bases (in this case BIBR-I048 as disclosed in D2), and the search for suitable salts of bases is one of the standard procedures in pharmaceutical chemistry. Hence, this difference cannot give rise to an inventive step. The processes for preparing a pharmaceutical composition according to claim 3, as well as the processes for preparing BIBR-1048 MS polymorph II claim 4 are well within the ambit of the skilled person.

D3 is similar in many respects to document D1 insofar as it discloses BIBR-1048 MS as well as results from studies with this thrombin inhibitor.

Document D6 was reports on developmental oral anticoagulants, such as BIBR-1048 MS, which is said to be in phase II trials.

Document D8 was reports on developmental oral anticoagulants, such as BIBR-I048 MS, which is said to be in phase II trials.

As can be seen from the above, document D1 to D8 discloses in combination all the features defined in independent claim 1 and dependent claims 2-4 .Hence the subject-matter of claim 1 is not new and lack of inventive step under Section 2(1) j of the Act.

Dependent claims 2-4 do not contain any features which, in combination with the features of any claim to which they refer meet the requirements of the Section 2(1) j of the Act. in respect of inventive step.

II. I shall now deal with objection that Claim (s) fall(s) within the scope of section 3 (d).

Section 3 states that following are not inventions within the meaning of this Act. Sub section (d) states that

“the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least a new reactant.”

Explanation.- For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;

I shall now examine the agent contention that claims recite a crystal form II and composition comprising said compound in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers and a process for preparation thereof and also examine the non applicability of section 3(d).

Though the arguments are impressive from the applicant the alleged invention should be judged according to the provisions laid under the Patents Law. Section 3(d) emphasizes that a new form of a known substance is patentable unless the new form shows enhancement in the KNOWN EFFICACY of the known substance. The next question is what is known efficacy? Efficacy of a pharmaceutical, in pharmacology, as defined in Dorland's Illustrated Medical Dictionary is the ability of a drug to produce the desired therapeutic effect and it is independent of potency, which expresses the amount of the drug necessary to achieve the desired effect.

It is stated by the applicant that the claimed compound has got the better solubility compared to its closest prior art compound mentioned in Document D1 to D8.

However the applicant has not provided any argument and experimental proof of any enhancement of the above properties and significant improvement in therapeutic efficacy, i.e. to say no comparative experimental data is available in the specification to prove the improvements are significant and the new form is efficacious than the earlier one. In such circumstances of failure to prove efficacy the compound as claimed is merely a new form of the known substance which is not Patentable U/S 3(d) of the Patent Act. Merely difference in solubility data does not serve the purpose of complying the requirement of section 3(d).

The process claimed in dependent claim 3&4 also not fully supported in the specification.

In the entire description of the invention the new therapeutic effect of the new forms is not disclosed. Hence it is concluded that the new crystalline form II exhibit the same efficacy as the Documents D1 to D8.

Claims 1-4 falls within the scope of sub clause (d) of section 3 as the claimed form is mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance, also the claimed process is a mere use of known process to prepare polymorphic forms of a substance. Therefore the applicant has failed in proving that the alleged invention does not attract the provisions under Section 3(d) of the Patents Act.

My inference from the above arguments with respect to amended claims is as follows:

1) Though the claims 1 to 4 are lack of inventive steps. They fail to meet the requirements under Section 2(1) (j) of the Act.
2) Assuming but not agreeing to the dependent 2-4 claims for composition and process being inventive still they do not satisfy the requirements under Section 3(d) of the Act.

Therefore I conclude that the alleged invention as claimed in the instant applicant do not meet the requirements of Sections viz., 2(1)(j) and 3(d) of the Patents Act 1970 [Amendment Act 2005].

Therefore I hereby order that the grant of patent is hereby refused under the provisions of Section 15 of the Patents Act.

Dated this 12th January, 2011

(Dr.Rajesh Dixit)
Assistant Controller of Patents & Designs

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