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Datasheet for the decision of 19 December 2006

Case Number: T 0401/04 - 3.3.01

Application Number: 94917244.9

Publication Number: 0652872

IPC: C07D 401/12

Language of the proceedings: EN

Title of invention:
Optically pure magnesium-salt of pyridinylmethyl sulfinyl-1H-benzimidazole compound

Patentee:
AstraZeneca AB

Opponent:
Ratiopharm GmbH

Headword:
Magnesium salt of (-)-omeprazole/ASTRAZENECA

Relevant legal provisions:
EPC Art. 114(2), 56, 100(a)

Keyword:
"Inventive step (no) - obvious solution"
"Late filed documents - not admitted"

Decisions cited:
T 0181/82

Catchword:
-

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Case Number: T 0401/04 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 19 December 2006

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 26 February 2004 concerning maintenance of the European patent No. 0652872 in amended form.

Composition of the Board:

Chairman: A. J. Nuss
Members: C. M. Radke
J. Van Moer

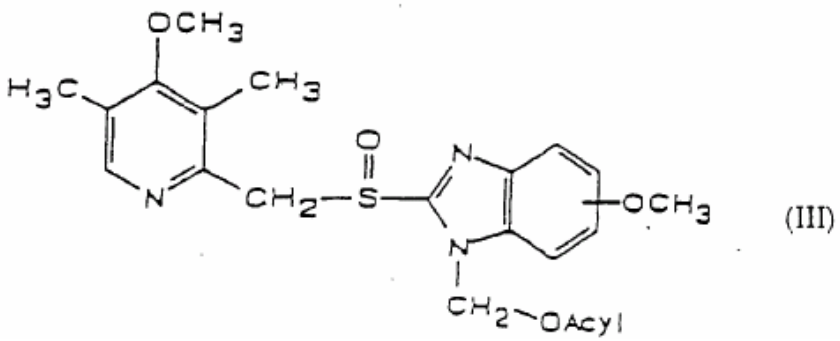
Summary of Facts and Submissions

I. The Opponent lodged an appeal on 12 March 2004 against the interlocutory decision of the Opposition Division posted on 26 February 2004 in which the main request of the Patentee was rejected and which stated that the European patent No. 0 652 872, amended according to the auxiliary request and the invention to which it related met the requirements of the EPC.

II. The decision under appeal was based on claims 1 to 17 as granted as the main request and on claims 1 to 15 as granted as the auxiliary request. The independent claims of the auxiliary request, namely claims 1, 2 and 8 to 15 read as follows:

1. The magnesium salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-lH-benzimidazole (Mg-salt of the (-)-enantiomer of omeprazole).

2. A process for the preparation of the Mg-salt of the (-)-enantiomer of omeprazole characterized in that a diastereomeric mixture of an ester of formula III



(III)

wherein Acyl designates a chiral acyl group having either R or S configuration, is separated, to obtain

the separated diastereomers whereafter the diastereomer comprising the
acyloxymethyl derivative of the (-)-enantiomer of omeprazole is dissolved in an alkaline solution wherein the acyloxymethyl group is hydrolyzed off to give the (-)-enantiomer of omeprazole which is converted to the magnesium salt.

8. A pharmaceutical preparation containing the Mg-salt of the (-)-enantiomer of omeprazole together with a pharmaceutically acceptable carrier.

9. The Mg-salt of the (-)-enantiomer of omeprazole for use in therapy.

10. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation for the treatment of gastric acid related diseases by inhibition of gastric acid secretion.

11. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.

12. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation having improved pharmacokinetic and metabolic properties.

13. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation

with a lower degree of interindividual variation in plasma levels when treating gastric acid related diseases.

14. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation with an improved therapeutic profile when treating gastric acid related diseases.

15. The use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation for the treatment of reflux esophagitis.

III. Inter alia, the following documents were cited during the opposition and/or appeal proceedings:

(D2) EP-A-0 124 495
(D3) DE-A-40 35 455
(D9) Comparative tests filed by the Respondent on 23 April 1999, eight pages
(D10) EP-B-0 166 287
(D13) P. Lindberg et al., Medicinal Research Reviews, vol. 10, no. 1 (1990), 1-54
(D14) P. Erlandsson et al., Journal of Chromatography, vol. 532 (1990), 305-319
(D24) C. Hansch et al., Comprehensive Medicinal Chemistry, 1st edn. (1990), vol. 2, Pergamon Press, Oxford/GB, 204-205
(D29) Expert opinion of Prof. Ammon dated 13 June 2005, 51 pages, with 46 printed references in support
(D30) M. Tanaka et al., Clinical Pharmacology & Therapeutics, vol. 69 (2001), no. 3, 108-113

(D31) K.-A. Kim et al., Clinical Pharmacology & Therapeutics, vol. 72 (2002), no. 1, 90-99

(D32) M. Miura et al., Xenobiotica, vol. 35 (5) (May 2005), 479-486

(D33) A. Äbelö et al., Drug Metabolism and Disposition, vol 28 (2000), no. 8, 966-972

(D34) T. Andersson et al., Gastroenterology, vol. 118 (2000), no. 4, Suppl.2, 1210, Abstract 5551

(D35) M. Hassan-Alin et al., Eur. J. Clin. Pharamacol., vol. 56 (2000), 665-670

(D36) T. Andersson, Clin. Pharmacokinet., vol 40 (6) (2001), 411-426

(D37) T. Lind et al., Aliment. Pharmacol. Ther., vol. 14 (2000), 861-867

(D38) K. Röhss et al., Digestive Diseases and Sciences, vol. 47 no. 5 (May 2002), 954-958

(D39) P. J. Kahrilas et al., Aliment. Pharmacol. Ther., vol. 14 (2000), 1249-1258

(D40) C. Wilder-Smith et al., 8th United European Gastroenterology Week, 25-30 November 2000, abstract P.51

(D41) C. H. Wilder-Smith et al., Digestion, vol. 68 (2003), 184-188

(D42) K. Röhss et al., Clin. Drug Invest., vol. 24 (1) (2004), 1-7

(D43) C. Wilder-Smith et al., 8th United European Gastroenterology Week, 25-30 November 2000, abstract P.49

(D44) C. Nilsson-Pieschl et al., Abstract P3, publication date and source not identified

(D45) K. Röhss et al., Abstract No. 61, publication date and source not identified

(D46) C. Wilder-Smith et al., AGA Abstracts, page A-200, Abstract S1293, without printed publication date

(D47) C. Wilder-Smith et al., AGA Abstracts, pages A-22-A-23, Abstract 352, Gastroenterology, vol. 118, no. 4, (April 2000)

(D48) C. Röhss et al. "Esomeprazole 40 mg Provides Faster and More Effective Acid Control ...", 1 page, publication date and source not identified

(D49) P. Miner et al., The American Journal of Gastroenterology, vol. 98, no. 12 (2003), 2616-2620

(D50) P. Miner et al., AGA Abstracts, page A-229, abstract 51 599, publication date not identified

(D51) C. Wilder-Smith et al., Digestion, vol 68 (2003), 184-188

(D52) D. O. Castell et al., The American Journal of Gastro-enterology, vol. 97, no. 3 (2002), 575-583

(D53) J. Labenz et al. , Aliment. Pharmacol. Ther., vol. 21 (2005), 739-746

(D54) Expert Opinion of Prof. Levy, 37 pages with 13 references in support, filed with the letter dated 19 May 2006.

IV. The opposition division was of the opinion that the patent could not be maintained unamended, as claims 16 and 17 were not inventive in view of document (D3).

The subject-matter of the claims of the auxiliary request, namely claims 1 to 15 as granted, were deemed to be novel in view of document (D3). This document disclosed the (-)-enantiomer of omeprazole but not the Mg-salt thereof.

Document (D2) which disclosed the racemate of the magnesium salt of omeprazole was considered to represent the closest prior art. It was apparent from document (D9) that the objective problem solved in view of document (D2) was to reduce the interindividual variation, namely the variation of the area under the plasma concentration versus time curve (AUC) of the drug within a group of patients. When trying to solve this problem, the person skilled in the art would not have consulted document (D3) as this document was completely silent on this problem. The opposition division thus deemed the subject-matter of the claims of the auxiliary request to be based on an inventive step.

V. Oral proceedings before the Board were held on 19 December 2006.

VI. The Appellant argued, inter alia, that the subject-matter of claim 8 of the Main Request was not novel in view of document (D2). This document disclosed a pharmaceutical preparation containing the magnesium salt of the racemate of omeprazole, which in turn contained the (-)-enantiomer of said salt. During the oral proceedings he confirmed that he no more considered the subject-matter of the claims on file to lack novelty in view of document (D3). He considered document (D3) as the closest prior art for the assessment of inventive step. This document disclosed the (-)-enantiomer of omeprazole and its salts with bases. The problem to be solved in view of (D3) could not be the decrease in interindividual variation as the free form of the (-)-enantiomer of omeprazole as

disclosed in document (D3) was bioequivalent to the respective magnesium salt (see document (D9), the bottom paragraph on page 8).

He deemed that the objective technical problem to be solved could be considered as to provide the (-)-enantiomer of omeprazole in a form in which it is easier to handle and to process. To solve this problem by forming the respective magnesium salt was obvious in view of document (D2) as this document taught that the magnesium salt of omeprazole was easier to handle than omeprazole in its free form.

Moreover, he did not deem the subject-matter of the claims directed to second medical uses, namely claims 10 to 15 of the Main, claims 2 to 6 of the First Auxiliary, claims 1 to 5 of the Second Auxiliary, claims 1 to 3 of the Third Auxiliary and the only claim of the Fourth Auxiliary Requests, to be based on an inventive step as the use of omeprazole for these purposes was known from documents (D10), (D2), (D13), and (D24).

VII. The Respondent (Proprietor of the patent) considered document (D2) to represent the closest prior art, said document disclosing the magnesium salt of the racemate of omeprazole. He argued that the objective technical problem to be solved was to decrease the interindividual variation. This problem was solved as was evident from document (D9). Document (D3), so he argued, did not address the problem of interindividual variation nor did it give any indication that the (-)-enantiomer of omeprazole showed any advantages over the respective (+)-enantiomer. He concluded that the

subject-matter of the claim was based on an inventive step.

VIII. The Appellant requested that the decision under appeal be set aside and the patent be revoked.

The Respondent requested that the appeal be dismissed or that the patent be maintained on the basis of the claims of any one of the four auxiliary requests filed with the letter dated 17 November 2006.

The claims of these auxiliary requests correspond to the following claims as granted (see point II above):
- claims 9-11 and 13-15 (First Auxiliary Request);
- claims 10, 11 and 13-15(Second Auxiliary Request);
- claims 13-15 (Third Auxiliary Request); and
- claim 15 (Fourth Auxiliary Request).

IX. At the end of the oral proceedings the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123(2) and (3) EPC and novelty*

Since the Board came to the conclusion that the subject-matter of claim 15 of the Main Request and of the respective claims of the Auxiliary Requests is not based on an inventive step, it is not necessary to give reasons as to whether the requirements of Article 123

EPC are met or as to whether the subject-matter of claim 8 of the Main Request is novel.

3. *Main Request*

3.1 Patentability of claim 15

Claim 15 of the Main Request concerns the use of the Mg-salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical formulation for the treatment of reflux esophagitis.

3.1.1 Novelty

The novelty of the subject-matter of this claim was not under dispute and resides from the fact that neither document (D2) nor (D3) discloses the use for the manufacture of a pharmaceutical formulation for the treatment of reflux esophagitis.

3.1.2 Inventive step

(a) Closest prior art

(i) In accordance with the "problem-solution" approach consistently applied by the Boards of Appeal, it is necessary, as a first step, to establish the closest prior art which is normally a prior art document disclosing subject-matter aiming at the same objective as the claimed invention and having the most relevant technical features in common.

(ii) The Appellant considered document (D3) to represent the closest prior art, whereas the Respondent deemed document (D2) to be closer.

(iii) The Respondent stressed in particular that the patent in suit aimed at an improvement of omeprazole so that document (D3) was not a realistic starting point for the skilled person as it did not indicate that any of the enantiomers of omeprazole showed a benefit. Moreover, the person skilled in the art would not have expected such a benefit as (-)-omeprazole was considered to be equal in potency with the racemate and was likely to racemise (see document (D14), page 318 and the second paragraph on page 311).

(iv) The Board has come to a different conclusion for the following reasons:

Both documents (D2) and (D3) relate to the inhibition of gastric acid secretion (see document (D2), page 1, lines 21-30; and (D3), page 2, lines 12-13 ("... die magensäuresekretionshemmende Eigenschaften besitzen.")). So, both documents aim at the same objective.

Document (D2) discloses the magnesium salt of omeprazole (see examples 5 and 6). It is silent on the fact that the product is a racemate, i.e. a mixture of two enantiomers, and that the enantiomers may be separated therefrom. Therefore, document (D2) cannot

give any guidance concerning separating the magnesium salt of omeprazole into its enantiomers and using the (-)-enantiomer for the purpose indicated in claim 15 of the Main Request.

Document (D3) discloses the (-)-enantiomer of omeprazole and its salts with bases (see page 6, lines 38 and 42). As document (D3) does not specify the cation of the (-)-omeprazole salt, it directs the skilled reader to look for a suitable cation. The teaching of document (D3) thus appears to be the better springboard for the skilled person for making the claimed invention, namely using the magnesium salt of the (-)-enantiomer for the manufacture of a pharmaceutical formulation for the treatment of reflux esophagitis.

The fact that document (D3) does not indicate that the (-)-enantiomer of omeprazole shows a beneficial effect is of secondary importance in view of the fact that document (D2) does not even disclose that omeprazole exists in two enantiomeric forms.

Consequently, document (D3) is considered to represent the closest prior art.

(b) Once it is established which document is the closest prior art, the next steps to be made when assessing inventive step in accordance with the

"problem-solution" approach are to determine the problem to be solved in view of said closest prior art, and to examine whether that problem is solved over the whole claimed area.

The Respondent referred to the problem mentioned in paragraph [0002] of the patent in suit, the respective sentence reading as follows: "It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.". He argued that this problem had indeed been solved, as was apparent from the comparative tests (D9).

However, these tests compare the magnesium salt of the (-)-enantiomer of omeprazole (i.e. the product to be used according to present claim 15) with omeprazole as the racemate, i.e. as a mixture of its (+)- and (-)-enantiomers. This is clearly not a comparison with the closest prior art document (D3) which discloses the (-)-enantiomer of omeprazole.

According to the established jurisprudence of the Boards of Appeal, comparative examples in which comparison is not made with the compound of the closest prior art having the maximum structural similarity with the one(s) specified in the invention claimed cannot render the presence of an inventive step sufficiently plausible (see, e.g., decision T 181/82, published in OJ EPO 1984, 401, especially point 5 of the reasons and headnote I).

Moreover, without evidence to the contrary, there is no reason to believe that the claimed use of the magnesium salt of the (-)-enantiomer of omeprazole could give rise to less interindividual variation with respect to the non-salt form disclosed in document (D3), as the comparative tests (D9) indicate that these two compounds are "bioequivalent" and give rise to comparable interindividual variation (see the bottom paragraph on page 8).

Consequently, this problem cannot be considered to be solved in view of document (D3).

The Respondent has not provided any evidence that any other specific technical problem is indeed solved in view of document (D3).

Hence, the problem to be solved by the subject-matter of claim 15 can only be considered as how to provide an alternative use for a compound alternative to those disclosed in document (D3).

This problem has indeed been solved by the subject-matter of claim 15 as is apparent from examples 1 to 3 and paragraph [0009] of the patent in suit.

(c) Finally, it has to be determined if the solution of this problem as described in claim 15 of the Main request is obvious in view of the prior art.

On the one hand, in the judgment of the Board, the use of the magnesium salt of the (-)-enantiomer of

omeprazole for the manufacture of a pharmaceutical formulation is obvious in view of the teaching of document (D2). This document discloses that salts of omeprazole show a higher storage stability against degradation as compared to omeprazole in its non-salt form (see page 2, lines 3-15 and the test report bridging pages 13 and 14). This is especially true for the magnesium salt which is most preferred (see page 3, line 8 and claim 4).

On the other hand, the use of such a pharmaceutical formulation for the treatment of reflux esophagitis is obvious in view of document (D24) which forms part of a general text book on "Comprehensive Medicinal Chemistry" and discloses the use of omeprazole for that purpose (see page 204, bottom paragraph).

The Respondent argued that it was expensive to separate omeprazole into its enantiomers and that the prior art taught that no difference in therapeutical effect had to be expected by using the (-)-enantiomer instead of the racemate. So, he argued, the person skilled in the art would not have used the magnesium salt of (-)-omeprazole.

These arguments are not convincing as (-)-omeprazole as a salt is already disclosed in the closest prior art document (D3) (see point (iv) above).

Consequently, it is an obvious measure for the skilled person in charge of solving the problem mentioned above to choose the magnesium salt of

(-)-omeprazole for the manufacture of a pharmaceutical formulation for the treatment of reflux esophagitis.

Hence, the subject-matter of claim 15 of the Main Request is not based on an inventive step.

3.2 The Board can only judge on a request as a whole. As the subject-matter of claim 15 does not involve an inventive step within the meaning of Article 56 EPC, the Main Request as a whole is rejected.

4. *Auxiliary Requests*

Each of the Auxiliary Requests contains a claim exactly corresponding to claim 15 of the Main Request, namely claim 6 of the First, claim 5 of the Second, claim 3 of the Third and the only claim of the Fourth Auxiliary Requests. Thus, the subject-matter of each of these claims does not involve an inventive step for the reasons set out above in respect to claim 15 of the Main Request.

Hence, the four Auxiliary Requests are also rejected.

5. Consequently, grounds under Article 100(a) EPC prejudice the maintenance of the patent based on either the Main or any of the Auxiliary Requests.

6. *Late-filed documents*

6.1 According to the Rules of Procedures of the Boards of Appeal (RPBA), the statement of grounds of appeal and the reply thereto shall contain a party's complete case

including all the facts, arguments and evidence relied on (see Article 10a, paragraph (2), of the RPBA in the version of 12 December 2002, published in OJ EPO 2003, 62).

The Appellant filed document (D29) with the letter dated 12 July 2005, i.e. more than one year after he had submitted the grounds for appeal. The Respondent filed in turn documents (D30) to (D53) with the letter dated 26 April 2006 and document (D54) with the letter dated 19 May 2006, i.e. more than one year after his first response to the grounds for appeal.

Consequently, all these documents are not considered to be filed in due time and thus may be disregarded by the Board under Article 114(2) EPC in the exercise of the Board's discretion.

6.2 When considering whether such late-filed documents are to be admitted, their complexity and the need for procedural economy is to be taken into account (see Article 10b, paragraph (1), RPBA in the version of 12 December 2002, published in OJ EPO 2003, 62).

In the present case, the late-filed documents referred to above concern a particular aspect in the context of only some of the independent claims, namely whether or not the magnesium salt of the (-)-enantiomer of omeprazole provides for a lower degree of interindividual variation in plasma levels when treating gastric acid related diseases or other effects shown with respect to the racemate of omeprazole or other gastric acid secretion inhibitors, i.e. not with respect to the closest prior art, said effects thus

being of no relevance for all of the independent claims and in particular not for claim 15 of the Main Request.

In view of the fact that expert opinion (D29) includes 51 pages and 46 printed references, whereas the 24 references (D30) to (D53) were filed by the Respondent with the letter dated 26 April 2006 in support of counter-arguments against this expert opinion, and, finally, the expert opinion (D54) contains 37 pages and thirteen printed references, the late filed documents (D29) to (D54) as a whole represent a body of evidence of unusually high complexity.

Moreover, the findings in documents (D29) and (D54) were strongly contested by the other party (see the Appellant's submission by fax on 21 November 2006 and the Respondent's submission by fax on 8 December 2006). Hence, the relevance of those late-filed documents remains unclear. Their admission would therefore have unduly delayed the proceedings before the Board.

Finally, all the documents (D29) to (D54) relate to a comparison of the pharmaceutical effects of the magnesium salt of the (-)-enantiomer of omeprazole with respect to those of omeprazole racemate or with respect to those of other compounds not representing the closest prior art. Therefore, these documents are not relevant for deciding whether claim 15 of the Main Request meets the requirements of the EPC.

For these reasons, the Board decided not to admit late filed documents (D29) to (D54) to the proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

A. Townend A. Nuss