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Datasheet for the decision of 27 November 2012

Case Number: T 1677/11 - 3.3.01

Application Number: 00108479.7

Publication Number: 1020460

IPC: C07D 401/12, A61K 31/44, A61P 1/04

Language of the proceedings: EN

Title of invention:
The sodium salt of the (-)-enantiomer of omeprazole

Patentee:
AstraZeneca AB

Opponent:
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Wittkopp, Alexander
Teva Pharmaceutical Industries Ltd.
Actavis Group hf.
LEK Pharmaceuticals d.d.
Hörnchen, Ulrich, Dr.

Headword:
(-)-Omeprazole Na/ASTRAZENECA

Relevant legal provisions:
EPC Art. 24(3), 54, 56, 87, 100(b), 100(c)
EPC R. 115(2)
RPBA Art. 15(3)
BDS Art. 7

Keyword:
"Admissibility of partiality objections (no)"
"Main request, allowable"
"Added matter (no)"
"Sufficiency (yes), starting material retrievable from Chemical Abstracts"
"Novelty (yes), specific salt"
"Inventive step (yes), post-published evidence (yes), unexpected advantage"

Decisions cited:
G 0005/91, T 0206/83, T 0296/87, T 0292/92, T 0990/96, T 1028/96, T 0967/97, T 0609/02, T 0401/04, T 0591/04, T 1329/04, T 0021/08, T 1760/11

Catchword:
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Case Number: T 1677/11 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 27 November 2012

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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 14 July 2011 revoking European patent No. 1020460 pursuant to Article 101(2)(3)(b) EPC.

Composition of the Board:

Chairman: P. Ranguis
Members: L. Seymour
L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 020 460 was filed as patent application number 00 108 479.7. It is a divisional application of the parent application EP-A-0 652 872, based on international application WO 94/27988 (document (23)), filed on 27 May 1994 and claiming priority of 28 May 1993 from the Swedish patent application number 9301830-7 (document (28)). It was granted on the basis of sixteen claims.

Independent claim 1 as granted reads as follows:

"1. The sodium salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Na-salt of the (-)-enantiomer of omeprazole) with an optical purity of ≥ 99.8% enantiomeric excess (e.e.)."

Claims 2 and 9 relate to "the Na-salt as defined in Claim 1" "in crystalline form" and "for use in therapy", respectively. Claims 3 to 7 are process claims, and claim 8 is directed to a pharmaceutical preparation. Claims 10 to 16 are formulated as "Swiss-type" claims; in claim 13, the disease to be treated is specified to be "reflux esophagitis".

II. Oppositions were filed and revocation of the patent in its entirety requested pursuant to Articles 100(c), 100(b) and 100(a) EPC (lack of novelty and inventive step).

III. The following documents were cited *inter alia* during the opposition/appeal proceedings (note: where

documents are numbered in the format (*x*-*y*), this designates annex *y* attached to document *x*):

(1) DE-A-40 35 455

(1A) Translation of document (1), received 16 December 2010

(2) EP-A-0 124 495

(3) P Erlandsson et al., J. Chromatogr., 1990, 532, 305 - 319

(7) B Kohl et al., Poster, 4th International Symposium of Chiral Discrimination, Sept. 19-22, 1993, Montreal, Quebec, Canada, Abstract No. 35

(8) T Uematsu et al., J. Pharm. Sci., 1994, 83(10), 1407 - 1411

(9) WO 94/24867

(11) Comprehensive Medicinal Chemistry, Ed. C Hansch, Pergamon Press, Oxford, 1990, 198-205

(12) Chirality, 1992, 4, 338 - 340

(14) H Nagaya et al., Biochem. Pharmacol. 1991, 42(10), 1875 - 1878

(17-6) E Carlsson et al., Chem. Brit., May 2002, 42 - 45

(18) Declaration of E. Magnus Larsson and Exhibits

(originally received 27 November 2008, as cited in "Table of Cited Documents" filed with letter of 28 April 2011)

(20) Declaration of Dr Bernhard Kohl and Exhibits (originally received 27 November 2008, as cited in "Table of Cited Documents" filed with letter of 28 April 2011)

(21) EP-B-0 652 872

(23) WO 94/27988

(28) SE 9301830-7 (priority document of patent in suit)

(33) K M Williams, "Molecular Asymmetry and Its Pharmacological Consequences", in Advances in Pharmacology, 1991, Vol. 22, pages 57 - 135

(34) T Andersson et al., Ther. Drug Monit., 1990, 12, 415 - 416

(36) EP-A-0 005 129

(37) EP-B-0 166 287

(38) P Lindberg et al., Med. Res. Rev., 1990, 10(1), 1 - 54

(42) W H De Camp, Chirality, 1989, 1, 2 - 6

(47) (= document (101-14)), P J Kahrilas et al., Aliment. Pharmacol. Ther., 2000, 14, 1249 - 1258

(80) Declaration of Tommy Andersson and Exhibits (submitted with patentee's letter dated 14 December 2010, received 16 December 2010)

(83) WO 88/03921

(84) Chemical Abstracts reference to document (83) (submitted with patentee's letter dated 14 December 2010, received 16 December 2010)

(87) Swedish MPA Monograph for Lansoprazole (published June 1993, submitted with patentee's letter dated 14 December 2010, received 16 December 2010)

(101) Declaration of Dr Nimish Vakil and Exhibits (submitted with patentee's letter dated 28 April 2011, received 29 April 2011)

(101-12) K Röhss et al., Digest. Dis. Sci., 2002, 47(5), 954 - 958

(101-16) C J Lightdale et al., Digest. Dis. Sci., 2006, 51, 852 - 857

(104) Second Declaration of Tommy Andersson and Exhibits (submitted with patentee's letter dated 28 April 2011, received 29 April 2011)

(105) Declaration of Professor Ernst Kuipers and Exhibits (submitted with patentee's letter dated 28 April 2011, received 29 April 2011)

(105-3) M Hassan-Alin et al., Eur. J. Clin. Pharmacol., 2005, 60, 779 - 784

(120) Enantiomers, Racemates, and Resolutions, Krieger Publishing Company, 1991, 423 - 434

(146) (= document (101-6)) T Lind et al., Aliment. Pharmacol. Ther., 2000, 14, 861 - 867

(147) T Andersson et al., Clin. Pharmacokinet., 2001, 40(6), 411 - 426

(148) T Andersson et al., Pharmacogenetics, 1992, 2, 25 - 31

(149) Auterhoff, Knabe, Höltje, Lehrbuch der Pharmazeutischen Chemie, 1991, 10 - 11

(150) E Mutschler, Arzneimittelwirkungen, 1991, 48 - 49

(151) R H Levy et al., Pharm. Res., 1991, 8(5), 551 - 556

(152) W R Crom, Am. J. Hosp. Pharm., 1992, 49(Suppl. 1), S9 - S14

(153) C G Regårdh et al., Ther. Drug Monit., 1990, 12, 163 - 172

(154) P N Maton, New Engl. J. Med., 1991, 324(14), 965 - 975

(164) B Kohl et al., J. Med. Chem., 1992, 35, 1049 - 1057

(168) I M Gralnek et al., Clin. Gastroenterol. Hepatol.,

2006, *4*, 1452-1458

(174A) K Miwa et al., Jpn. Pharmacol. Ther., **1990**, *18*, 3413-3435

(174B) English translation of document (174A) received 23 May 2012

(179) Second declaration of Sverker von Unge, dated 29 August 2012, and Exhibits, filed by the appellant with letter dated 25 September 2012

(180) Third declaration of Marcus F Brackeen, dated 20 October 2012, and Exhibits, filed by respondent 3

IV. The appeal lies from the decision of the opposition division revoking the patent under Article 101(2),(3)(b) EPC, based on a main request, namely, the claims as granted, auxiliary requests 1 to 4 filed with letter dated 28 April 2011 (whereby auxiliary request 3 was corrected during oral proceedings before the opposition division), and auxiliary request 5 filed at oral proceedings before the opposition division.

With respect to the main request, the opposition division found in favour of the appellant on all issues raised (namely, Article 100(c) EPC, entitlement to priority date, Article 100(b) EPC, and novelty), apart from the question of inventive step. In its analysis of inventive step, the opposition division identified document (1) as representing the closest prior art, and defined the problem to be solved as lying in the provision of an alternative compound for the same use

as in document (1). The solution as proposed in claim 1 was considered to be obvious in view of the teachings of documents (2) and (120).

V. The appellant (patentee) lodged an appeal against this decision and filed grounds of appeal. Accelerated processing of the appeal was requested in view of ongoing litigation in several countries in respect of the related patent EP 1 020 461. It was argued that, although the litigation did not directly involve the present patent in suit, it was evident that the issues in the two cases were closely related, and that, if the proceedings concerning EP 1 020 461 were accelerated, it would be appropriate to also accelerate the present proceedings.

VI. In a communication dated 19 December 2011, the board informed the parties that it had decided to grant the appellant's request for accelerated processing and set out a procedural timetable.

VII. Responses to the grounds of appeal were received from respondents 1, 3, 5 and 6 (opponents 1, 3, 5 and 6).

VIII. In a communication sent as annex to the summons to oral proceedings dated 6 July 2012, the issues to be discussed at oral proceedings were summarised. Reference was made to appeal case T 1760/11, which concerns European patent No. 1 020 461 stemming from the same parent application as the patent in suit (cf. above points I and V). It was noted that a particularly contentious point was the choice of closest prior art.

IX. With letter dated 25 September 2012, the appellant filed an annex containing further submissions and a declaration numbered as document (179).

X. In reply, respondent 3 filed a declaration numbered as document (180) with letter of 26 October 2012, and requested that document (179) not be admitted into the proceedings.

XI. With letter dated 22 November 2012, respondent 5 announced that it would not be represented at oral proceedings scheduled for 27 to 29 November 2012. This was followed by corresponding announcements from respondent 3, with letter dated 23 November 2012, and from respondents 1 and 6 with letters dated 26 November 2012. In their letters, respondents 1, 3 and 6 also raised an objection of partiality under Article 24(3) EPC with respect to all board members. The same objection was raised by respondent 4 with letter of 23 November 2012.

XII. Oral proceedings were held before the board on 27 November 2012, in the absence of all respondents.

XIII. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The appellant submitted that the allegation of partiality under Article 24(3) EPC against all board member was inadmissible. The constitution of the boards for the present proceedings and the related appeal T 1760/11 had been announced in October 2011. If the respondents' concerns were valid, they should have objected at that point.

In connection with the ground of opposition raised under Article 100(c) EPC, the appellant argued that the sodium salt of (-)-omeprazole was individualised as compound Ib on page 3 of document (23). The limitation of ≥ 99.8% e.e. clearly applied to all salts disclosed, including compound Ib, and did not apply only to crystalline products.

The appellant further submitted that the objections under Article 100(b) EPC were unfounded. At the priority date of the opposed patent, appropriate analytical chromatographic techniques had been readily available for the routine measurement of optical purity. Moreover, the *N*-chloromethylated starting material was disclosed in the document (83) and abstracted in Chemical Abstracts (document (84)).

Turning to the issue of inventive step, the appellant argued that document (11) or alternatively document (2) represented more appropriate closest prior art documents than document (1) under the problem-solution approach, since they were reflective of the real world situation that all those working in the field faced at the priority date of the patent in suit, namely, improving on omeprazole. This problem was also addressed in more detail in paragraph [0002] of the patent in suit. More specifically, the problem of interindividual variation referred to therein related to the phenomenon observed to affect 30 to 50% of the patient population, for which omeprazole had proved to be ineffective or less effective than in other patients at clinical doses. That this was a well recognised

problem in the art was confirmed *inter alia* by documents (11), (104), and (105).

In contrast, the choice of document (1) as the closest prior art was based on hindsight, since this document was focused on the resolution of pyridylmethyl-benzimidazole sulfoxides into their enantiomers, and did not look into their therapeutic properties, let alone any benefit associated therewith. The skilled person would therefore not have regarded document (1) to be a suitable starting point for drug development. This would also go against the prevailing state of the art, in which the efforts to provide improved proton pump inhibitors (PPIs) had exclusively been focused on modifying the structural scaffold of omeprazole.

In any case, document (1) should not be taken as the closest prior art since it was non-enabling. In other words, the skilled person would not have been able to use the process disclosed therein to separate the enantiomers of omeprazole in a satisfactory way, reproducibly and without undue burden, or in any form that could be considered to be worth taking further. Whilst accepting that the first step, the reaction of the racemate with the chiral auxiliary, was capable of leading to some enrichment, up to a diastereomeric excess of 92% at best, the appellant submitted that the second hydrolysis/work-up step was intrinsically non-reproducible because the conditions were too severe for a highly acid-labile molecule like omeprazole. The scant description provided in document (1) was insufficient to allow the skilled person to successfully reproduce this step without undue burden. This was confirmed by the contemporaneous report

document (18) describing the attempts by the patentee to reproduce document (1). Further confirmation could be derived from document (20) and the attached laboratory notebook pages recording the experimental results on which document (1) was based. It could be derived therefrom that, at very best, an enantiomer of omeprazole had been obtained with 90% e.e., at low yields and as an unpurifiable material. The respondents' evidence in this respect should be disregarded since it had been produced with the benefit of intervening knowledge and could moreover not be regarded as an accurate reproduction of the process according to document (1). In fact, in example 6 of document (1), (+)-omeprazole had only been obtained as an amorphous material which could not be purified by conventional means. Contrary to assertions by the respondents, salt formation and recrystallisation were not part of the resolution process disclosed in document (1). Furthermore, the methods disclosed in document (120) did not represent common general knowledge in the relevant field, and such a method could not be viewed as an obvious choice.

The appellant defined the problem to be solved, starting from document (2) as the closest prior art, as lying in the provision of a PPI having an improved therapeutic profile, in particular with a lower degree of interindividual variation of therapeutic effect. Copious amounts of evidence had been filed to demonstrate that the subject-matter claimed in claim 1 successfully solved the problem posed, such as documents (101) and (105), and their attachments, and documents (80) and (147).

The solution claimed was not rendered obvious by any of the documents in the proceedings. According to document (3), the enantiomers of omeprazole were equipotent. This was to be expected given the fact that PPIs were known to be prodrugs that were chemically converted at their site of action to achiral sulfenamides. A similar teaching could be derived from document (11). Document (1) also did not offer any prospect of a therapeutic improvement for single PPI enantiomers. Confirmation of this was provided by documents (164) and (7) for pantoprazole, and by document (87) for lansoprazole. There was therefore no pointer towards developing a single enantiomer of any PPI as a drug in the expectation of obtaining a superior product.

XIV. The respondents' arguments submitted in writing, insofar as they are relevant to the present decision, may be summarised as follows:

Respondents 1, 3, 4 and 6 justified their objection of partiality under Article 24(3) EPC with respect to all board members as follows:

On 16 November 2012, European patent No. 1 020 461 had been maintained in appeal proceedings T 1760/11 before a board of identical composition to that of the present board. This patent and the patent in suit were both divisionals of same parent application EP-A-0 652 872, and the only difference between the subject-matter of these two patents lay in the nature of the counter ion (magnesium vs. sodium). As was apparent from the prosecution history, the relevant issues in terms of patentability were substantially identical in both

cases, and the parties common to both proceedings had filed practically identical submissions, supported by the same documents. Thus, in view of their decision rendered on 16 November 2012, the members of the board clearly must be expected to have a preconceived mind as to how the present case was to be decided. The situation was analogous to that set out in decision T 1028/96, in particular under point 6.1. Respondent 4 additionally drew attention to the fact that it had not taken a procedural step in the present case, prior to filing its objection under Article 24(3) EPC.

The respondents disputed the appellant's submissions with respect to Article 100(c) EPC.

From a comparison of the subject-matter of claim 1 of the main request with the disclosure of document (23) it could be seen that several selections were required, namely, a selection from a list of various salts, the selection of the (-)-enantiomer of omeprazole over the (+)-enantiomer, and the combination thereof with the specific optical purity of ≥ 99.8% e.e.

In particular, from the first paragraph on page 4 of document (23), it was clear that the feature relating to the degree of optical purity of ≥ 99.8% e.e. was only disclosed in connection with production of crystalline salts.

In addition, the claimed subject-matter was based on further selections with respect to the specific medical uses, such as "reflux esophagitis" (claim 13).

These combinations of features from several originally disclosed lists were not directly and unambiguously derivable from document (23).

Furthermore, the claimed subject-matter already added new technically relevant information to the original application due to the selection the (-)-enantiomer of omeprazole as the enantiomer that allegedly led to the claimed effect.

Several objections under Article 100(b) EPC were raised by the respondents.

It was firstly argued, with reference to decision T 609/02, that the claimed subject-matter was insufficiently disclosed because the original application did not contain any evidence that (-)-omeprazole was the enantiomer leading to the alleged effect of reduced interindividual variation.

A further objection raised related to the fact that the preparation of the claimed salt described in the patent in suit started from an *N*-chloromethylated omeprazole. However, no method for its preparation was disclosed therein, and it would be an undue burden for the skilled person to prepare this compound based on common general knowledge alone. Reliance on the contents of the Chemical Abstract database could not remedy this deficiency, as confirmed by decision T 206/83.

Finally, the patent in suit did not contain any information that would allow the skilled person to reliably determine the claimed parameter relating to the optical purity of ≥ 99.8% e.e. In the absence of

such a method, the skilled person therefore faced an undue burden when trying to determine this parameter.

Regarding the issue of inventive step, the respondents considered document (1) to be the closest prior art, rather than document (2) or (11). All these documents aimed at the same objective of providing inhibitors of gastric acid secretion for therapeutic use, namely, the treatment of gastrointestinal diseases. In terms of structural features, document (11) did not disclose (-)-omeprazole or a sodium salt thereof; document (2) disclosed the sodium salt of racemic omeprazole, but did not provide any suggestion as to the presence of enantiomers or the separation thereof. In contrast, document (1) not only specifically disclosed the (-)-enantiomer of omeprazole, which was the active ingredient of the patent in suit, but also taught the formation of salts thereof with bases. The degree of optical purity of ≥ 99.8% e.e could not be considered to be a feature distinguishing the claimed subject-matter from that of document (1), in view of established case law of the boards of appeal. In particular, according to decision T 990/96, if conventional methods existed for purifying a low molecular compound, said compound was made available in all grades of purity. There was no reason to assume an extraordinary situation in the present case. Hence, document (1) made both enantiomers of omeprazole and its salts with bases available in all degrees of purity, including the level of ≥ 99.8% e.e. now claimed. The only difference between the claimed subject-matter and the disclosure of document (1) was thus the selection of the specific sodium counter ion.

In this context, the respondents submitted that, contrary to the view of the appellant, the disclosure of document (1) was to be regarded as being enabling. Since it was the appellant who was now alleging the contrary, it was also the appellant who carried the burden of proof in this respect. Neither documents (18) nor (20) met the required standard of proof to demonstrate that the clear technical teaching of document (1) was non-enabling. Thus, document (18) was of little value in this respect, since the experiments described therein did not implement the teaching of document (1), in particular, that the pH should be raised as rapidly as possible in the work-up step, a measure that was aimed at avoiding the mildly acidic conditions in which omeprazole was known to be unstable. Moreover, by the appellant's own admission, at least one of the experiments discussed in document (20) had been successful in synthesising (+)-omeprazole with an optically purity of about 90% e.e. Thus, if anything, this evidence confirmed the workability of the procedure according to example 6 of document (1). Moreover, a number of respondents had independently provided experimental evidence demonstrating that document (1) was enabling.

Therefore, the respondents were of the opinion that document (1) was to be regarded as the closest prior art since it had the most relevant technical features in common with the subject-matter claimed.

The respondents further disputed that the "real world situation" would favour document (2) as closest prior art. This was not an objective criterion, and the appellant had painted a completely misleading picture

in this respect. In fact, at the priority date of the patent in suit, it was a realistic and even promising approach to consider the isolated enantiomers as candidates for drug development.

The conclusion that document (1) constituted the more promising springboard was in accordance decision T 401/04, which had led to the revocation of the parent patent, relating to the magnesium salt (document (21)). The reasoning given therein clearly also applied to the present case. Apart from the difference in the cation, the only additional feature in the present claims was that defining the optical purity to be ≥ 99.8% e.e. However, since document (2) did not mention any special degree of optical purity, while document (1) was directed to "optically pure" enantiomers, this additional feature rather strengthened the selection of document (1) as closest prior art.

In any case, it was clear that document (1) must at least be regarded as a promising starting point, in view of the fact that this had been considered as the closest prior art in the parent case T 401/04 and in the decision under appeal. Therefore, an inventive step would also have to be demonstrated relative to this route before a positive conclusion could be reached. In this context, the respondents highlighted a number of decisions, in particular T 21/08, but also *inter alia* T 967/97 and T 591/04. According to these decisions, if there was a choice of several workable routes which might lead to the invention, the rationale of the problem-solution approach required that the invention be assessed relative to all these possible routes, before an inventive step could be acknowledged.

However, even were document (2) to be considered the closest prior art, the respondents submitted that the subject-matter of the patent in suit would not based on an inventive step. [Note by board: In the submissions of respondent 3 dated 1 June 2012 (see point 7.7), specific reference is made to the arguments presented in sections 6.2.4 and 6.3 of DYC 101(a), which is said to correspond to "O2's submission of 7 April 2011 filed during opposition proceedings". However, a file inspection reveals that DYC 101(a) must in fact designate "O3's submission of 21 April 2011 filed during opposition proceedings"].

The respondents criticised the evidence relied on by the appellant in support of an alleged advantage on several levels.

Firstly, there was absolutely no evidence provided in the patent in suit that the effects alleged in paragraph [0002] had actually been achieved. In fact, it was evident from document (17-6) that the pharmacokinetic properties of the two enantiomers had not even been studied in humans until 1994, and it must therefore be concluded that the alleged invention had not yet been completed at the claimed priority date. Since the patent in suit did not make the alleged effect plausible, in accordance with decision T 1329/04, any post-published evidence should not be taken into consideration when assessing whether the problem had been solved. The appellant could not have it both ways: if it were to be argued that the alleged effect was plausible, then the subject-matter claimed could not be based on an inventive step.

It was further noted that the statistical significance of the findings with respect to interpatient variability had not been indicated in document (146).

Even if differences in bioavailability, gastric acid suppression and interpatient variability were to be accepted as having been demonstrated, the clinical relevance of these results would be questionable, in view of the contradictory results obtained in documents (47), (101-16) and (168).

Furthermore, even were it to be accepted that the problem defined in the patent in suit had been successfully solved, the subject-matter claimed would nevertheless not be based on an inventive step over document (2) as closest prior art document. A skilled person would namely have expected that one of the two enantiomers of omeprazole would have advantageous properties over the other and thus over the racemate, as had been confirmed in decision T 296/87. An inventive step could not be recognised on the basis of any effect to have emerged from obvious and routine tests. This assessment was not altered by the fact that, in the case of omeprazole, the species responsible for activity was achiral, since decision T 296/87 did not make a distinction between advantages resulting from pharmacodynamic or pharmacokinetic effects.

Indeed, the skilled person was well aware at the date of priority of the patent in suit that enantiomers may differ in their pharmacokinetic properties, that is, in their absorption, distribution, metabolism, and excretion (ADME) profiles, as could be seen from the

textbook knowledge and reviews cited as documents (33) and (149) to (152). This general knowledge was also reflected in the recommendations of regulatory authorities that single enantiomers of racemic drugs should be investigated in this respect, as illustrated *inter alia* by documents (12) and (42); in document (42), it was stated to be "both good science and good sense to explore the potential for in vivo differences between these forms".

The skilled person would therefore have regarded it to be a real possibility that differences in pharmacokinetic properties would result in a better activity for one of the omeprazole enantiomers.

It was further noted that interindividual variation had been known to exist for omeprazole before the priority date of the patent in suit, in relation to pharmacokinetics and acid secretion (documents (153) and (154)). More specifically, it was also known, for example from documents (34) and (148), that there were poor and extensive metabolisers of omeprazole and that these groups co-segregated with polymorphic hydroxylation of *S*-mephenytoin. Furthermore, interindividual variation in the metabolism of racemic mephenytoin was known to result from the fact that the (*S*)-enantiomer of mephenytoin was metabolised differently in poor and extensive hydroxylators, whereas this was not the case for the corresponding (*R*)-enantiomer (see e.g. document (33), section III.B). The skilled person would therefore have had at least a reasonable expectation that enantioselective metabolism would also be the reason for variation amongst patients treated with racemic omeprazole. This knowledge

provided a further incentive for a skilled person to investigate the single enantiomers of omeprazole in order to reduce variations between poor and extensive metabolisers of omeprazole.

Moreover, document (3) suggested possible differences between the enantiomers in the degree of plasma protein binding. The skilled person would expect this to lead to different effects of the enantiomers.

Finally, the significance of differing pharmacokinetic properties of enantiomers had also already been recognised in the field of PPIs, as illustrated by documents (14) and (174) for lansoprazole, and further confirmed by documents (8) and (9). The lack of stereochemical difference in activity discussed in documents (3), (14) and (164) was based on experiments conducted *in vitro*, and none of these documents uttered an expectation that there would not be a difference between the two enantiomers *in vivo*.

The respondents therefore submitted that, starting from document (2), it would have been obvious to the skilled person to isolate the enantiomers of the sodium salt of omeprazole, for example, according to the process of document (1), or by means of methods according to document (3) and related commercially available HPLC technology, and test these in order to identify the one having the better properties.

XV. The appellant requested that the decision under appeal be set aside and, as its main request, that the patent be maintained as granted, or, alternatively, that the patent be maintained on the basis of one of the

auxiliary requests 1 to 4 filed with the letter dated 28 April 2011, whereby auxiliary request 3 was corrected during oral proceedings before the opposition division on 1 July 2011, or on the basis of auxiliary request 5 submitted during oral proceedings before the opposition division on 1 July 2011. The appellant further requested that the respondents' requests for replacement of the board be rejected.

Respondents 1 and 3 to 6 requested in writing that the appeal be dismissed. Respondent 3 further requested in writing that document (179) not be admitted into the appeal proceedings. Respondents 1, 3, 4 and 6 raised an objection of partiality under Article 24(3) EPC with respect to all board members and requested their replacement. Additionally, postponement of oral proceedings was requested until such time as a new board be appointed.

XVI. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. The oral proceedings before the board took place in the absence of the respondents who were duly summoned but chose not to attend. According to Article 15(3) of the Rules of Procedure of the Boards of Appeal (see Supplement to OJ EPO 1/2012, 38 to 49), the board shall not be obliged to delay any step in the proceedings, including its decision, by reason only of the absence

at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case (see also Rule 115(2) EPC).

3. *Admissibility of partiality objections (Article 24(3) EPC)*

Partiality objections were raised by respondents 1, 3, 4 and 6 against all board members under Article 24(3) EPC. It was argued that, since the substantively identical parallel appeal case T 1760/11 had been decided by a board in identical composition one week previously, the present board would not bring an open mind to the present appeal.

As a first step, it is to be decided by the present board whether the said objections are admissible (cf. decision T 1028/96, reasons point 1).

According to Article 24(3) EPC, second sentence, "an objection shall not be admissible if, while being aware of a reason for objection, the party has taken a procedural step". The principle underlying this provision is that an objection should be "raised immediately after the party concerned has become aware of the reason for the objection", since "otherwise, the system could be open to abuse" (see decision G 5/91 (OJ EPO 1992, 617), reasons point 4).

In the present case, the statement of grounds of appeal dated 22 November 2011 already contained a reference to the parallel appeal concerning to the closely related patent EP 1 020 461 (cf. above point V). In addition, present respondents 3, 4 and 6 were also respondents in

the corresponding appeal case T 1760/11 (as respondents 2, 7 and 13, respectively), and although respondent 1 was not a party in appeal T 1760/11, its representative was the same as that acting for respondent 6. Therefore, respondents 1, 3, 4 and 6 would have been aware of the closely related parallel appeal T 1760/11 right from the beginning of the present appeal proceedings.

A communication of the board was sent on 19 December 2011 granting the request for accelerated processing of the appeal, and informing the parties that the board then envisaged issuing an invitation to oral proceedings by August 2012 to attend oral proceedings from 27 to 29 November 2012 (cf. above point VI). On the same day, an identically worded communication was sent out in appeal case T 1760/11, except that the date foreseen for oral proceedings was stated to be 13 to 15 November 2012. Both communications were signed by the same rapporteur.

At this stage in the proceeding, present respondents 1, 3, 4 and 6 would therefore have been aware that the boards had been constituted in both cases, that the rapporteur was the same, and that appeal T 1760/11 was likely to be decided prior to the present appeal. Moreover, the information would have been readily available by online file inspection (entry from 20 October 2011) that the boards were identical in both cases, as foreseen in Article 7 of the business distribution scheme, which stipulates that, where appeals pending before the board are closely linked, in particular by involving similar legal or factual questions, the chairman may order that the board

decides in the same composition (see Supplement to OJ EPO 1/2012, 12 to 25).

Replies to the statement of grounds of appeal were *inter alia* received from respondents 1, 3 and 6, but not from respondent 4 (cf. above point VII). However, it is to be noted that respondent 4 did file a response in case T 1760/11 (as respondent 7), as did respondents 3 and 6 (as respondents 2, and 13, respectively). No concerns were voiced by said parties in either case with respect to the identical compositions of the boards.

Thereafter, summons were sent out on 6 July 2012 to attend oral proceedings on 27 to 29 November 2012, as previously announced. Corresponding summons were sent out on the same day in appeal case T 1760/11 to attend oral proceedings on 13 to 16 November 2012. The board's composition appearing on the these summons was identical in both cases and had not changed with respect to that previously available by online file inspection.

These summons therefore provided confirmation to the parties that the boards were to be identically constituted in both cases and that oral proceedings for T 1760/11 would take place two weeks prior to those for T 1677/11. Again no concerns were voiced by any of the parties in this respect, and the representatives of present respondents 1, 3, 4 and 6 all attended the oral proceedings in case T 1760/11 from 13 to 16 November 2012.

It was only after an adverse decision in that case had been announced that said respondents raised their objections of suspected partiality in the present case. However, as outlined above, the reasons for said objections, namely, the close link between the cases and the identical compositions of the boards, had been known to the parties long before the date of the first oral proceedings. Therefore, regardless of whether the respondents, notably respondent 4, took a specific procedural step in the present appeal proceedings, it is undoubtedly the case that they did not submit their objection immediately after becoming aware of the reasons therefore. Moreover, in view of the fact that the objections raised are linked to both appeals, attendance of oral proceedings for T 1760/11 must be regarded as a procedural step within the factual context of the present case, in the sense of Article 24(3) EPC.

Consequently, in view of their timing, the objections under Article 24(3) EPC are rejected as inadmissible.

4. *Admissibility of document (179)*

Since document (179) is not relevant for the outcome of the present appeal, there was no need to decide on its admissibility.

Main request

5. *Article 100(c) EPC*

5.1 The patent in suit was filed as a divisional application of the parent application EP-A-0 652 872,

which was published as the international application designated in the present procedure as document (23). It is noted that pages 1 to 26 of document (23) are identical to the corresponding pages of the present application as originally filed, apart from the fact that the claims in the former (page 22, line 1) are now labelled as being preferred embodiments in the latter (page 21, lines 28, 29). In the following, reference is therefore only made to document (23).

5.2 The question to be decided is whether a direct and unambiguous basis can be found in document (23) for that which is now claimed.

Under the heading "Field of the invention" it is stated that "the present invention is directed to new compounds with **high optical purity**, their use in medicine ..." (page 1, lines 5, 6, emphasis added). Claim 1 relates to **optically pure** salts of (+)- and (-)-omeprazole whereby Na^+ is listed as one of six possible counter ions. In dependent claim 3, four salts are explicitly listed, namely, the sodium and magnesium salts of each enantiomer, and these are also specifically depicted as most preferred salts in the corresponding passage of the description, including the optically pure sodium salt of (-)-omeprazole Ib (see page 3, lines 4 to 30).

It is further disclosed on page 4, lines 1 to 4, that:

"With the expression "optically pure Na^+ salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (-)-enantiomer of

omeprazole Na-salt and the (-)-enantiomer essentially free of the (+)-enantiomer, respectively".

Therefore, by way of this example, a general definition of the expression "optically pure salt" can be derived as being a salt that is "essentially free" of the other enantiomer.

The paragraph on page 4 goes on to state the following (page 4, lines 4 to 12; emphasis added):

"Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. By means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole, the salts defined by the present invention are easy to obtain. In addition, the salts, however not the neutral forms, are obtained as crystalline products. Because it is possible to purify optically impure salts of the enantiomers of omeprazole by crystallisation, they can be obtained in **very high optical purity, namely ≥99.8% enantiomeric excess (e.e.)** even from an optically contaminated preparation".

This is the only passage of document (23) to provide a specific definition of optical purity, and it is directly and unambiguously derivable therefrom that the level obtainable for the salts defined by the invention by means of the disclosed purification process is ≥ 99.8% e.e. Therefore, the limitation of the expression "optically pure" to this level of enantiomeric excess for the salts specifically disclosed in document (23) does not contravene Article 123(2) EPC. The passages referred to above are

thus considered to provide a proper basis for the sodium salt according to present claim 1.

The basis for the crystalline form as claimed in claim 2 can be found in on page 4, lines 7 to 12 and claim 5 of document (23).

The process claims 3 to 7 are based on page 5, line 24 to page 7, line 1, and claims 7 to 9 of document (23).

The basis for a pharmaceutical composition of the claimed salt, and for the use thereof in therapy, as claimed in claims 8 and 9 can be found in the following passages of document (23): page 7, lines 25 to 27, and claim 17; and page 1, lines 5, 6, and claim 18.

The specific uses appearing in the claims are disclosed in document (23) on page 4, line 23 to page 5, line 2; on page 5, line 7; and in claims 19 and 20. Therefore, present claims 10 to 16 are also not open to objection.

5.3 The respondents' arguments are not considered to be persuasive for the following reasons:

As explained above under point 5.2, the optically pure sodium salt of (-)-omeprazole is disclosed in individualised form in document (23), on page 3, lines 4 to 15 and in claim 3. Therefore, it cannot be accepted that a selection is already to be seen in the choice of the sodium counter ion in combination with the (-)-enantiomer of omeprazole.

Moreover, in the last sentence of the paragraph from page 4 of document (23) reproduced above under

point 5.2, the pronoun "they" in the clause "they can be obtained in very high optical purity, namely ≥99.8% enantiomeric excess (e.e.)" refers back to the subject of the preceding clause, namely, said "optically impure salts". Thus, although the process described proceeds via a crystalline product, the defined level of purity is not forcibly linked to crystallinity, and this is to be seen as an optional feature. Confirmation is also provided by the following paragraph of document (23) (page 4, lines 19 to 21) wherein it is disclosed, with reference to said method, that "it can be used to obtain the single enantiomers of omeprazole in neutral from as well as the salts thereof", without any mention of crystallinity.

Concerning the specific medical uses listed in document (23), these are disclosed as belonging to a single class of condition, namely, which are treatable by the inhibition of gastric acid secretion. Moreover, the salts of (+)- and (-)-omeprazole are disclosed in document (23) as being equivalent in displaying this activity (see page 4, lines 23, 24 and claim 19), and therefore as being suitable for the use in the treatment of the conditions listed. Under these circumstances, it cannot be accepted that the present claims referring to specific medical uses, such as claim 13, present the skilled person with any new information which was not directly and unambiguously derivable from document (23).

Finally, it is disclosed in document (23), on page 1, lines 12 to 22, that the effect linked with the "novel salts of single enantiomers of omeprazole" resides in "improved pharmacokinetic and metabolic properties

which will give an improved therapeutic profile such as a lower degree of interindividual variation". It is noted that no amendments have been undertaken with respect to the corresponding paragraph of the patent in suit, namely, paragraph [0002]. The point of reference for the alleged improvement can be found in the first sentence of the paragraph, namely, "omeprazole, and therapeutically acceptable alkaline salts thereof". The claims have now been limited to a specific salt of (-)-omeprazole. However, it cannot be inferred from document (23) that the information that this specific embodiment exhibits an advantage with respect to the racemic mixture necessarily implies that other embodiments, which are now no longer claimed, do not, as suggested by the respondents. Therefore, the limitation of the patent in suit to one of the preferred embodiments disclosed in document (23) is not considered to lead to the provision of any additional information extending beyond the content of the latter.

5.4 Consequently, the subject-matter of the main request does not extend beyond the content of the application as filed, or of the content of the parent application as filed (Article 100(c) EPC).

6. *Entitlement to priority (Article 87 EPC)*

The respondents did not advance any additional objections to those raised under Article 100(c) EPC.

Passages corresponding to the decisive passages of document (23) discussed under point 5.2 above are to be found in the present priority document (28), apart from page 5, line 7 of document (23), which is the line

referring to the treatment of *Helicobacter* infections (cf. document (28), page 1, lines 5, 6; page 3, line 1 to page 4, line 7; page 4, lines 15 to 24; page 7, lines 10 to 12; claims 1, 3, 5, and 15 to 18).

The patent in suit is therefore entitled to the priority date claimed, apart from claim 16, which relates to the treatment of *Helicobacter* infections.

7. *Sufficiency of disclosure (Article 100(b) EPC)*

7.1 As outlined above under point I, the claims under consideration relate to a specific sodium salt (claim 1) and a crystalline form thereof (claim 2), and processes, pharmaceutical compositions and first and second medical uses thereof.

The patent in suit provides methods for the synthesis of compounds of claims 1 and 2 (see page 2, line 57 to page 3, line 3; paragraphs [0012] to [0016]; and example 1). Pharmaceutical formulations thereof are disclosed in paragraphs [0017] to [0024] and [0040] to [0045].

The board is therefore of the opinion that the requirements of sufficiency of disclosure are fulfilled, since the skilled person, having regard to the general guidance and examples provided in the patent in suit, would have been in a position to provide the claimed salts and employ them in therapy, and specifically in the treatment of medical conditions of the type claimed.

7.2 The respondents' arguments with respect to sufficiency of disclosure are not considered to be convincing for the following reasons:

It is firstly noted that decision T 609/02 relates to a claim in which the effect in question is expressed as a functional feature thereof (see points VII and 9). In contrast, in the present case, the effect of reduced interindividual variation is part of the problem to be solved (see point 9.4 below). The principles established in decision T 609/02 are therefore not relevant for the present case.

Moreover, the fact that a synthesis of the *N*-chloromethylated starting material used in example 2 is not provided in the patent in suit is not considered to be detrimental to sufficiency of disclosure. The skilled person in search of a synthesis of said compound would certainly have consulted the Chemical Abstracts database, as a standard source of chemical information in the field. Thus, following standard procedures for retrieving information from Chemical Abstracts, the skilled person would first establish the molecular formula of the compound of interest and check the collective formula index to see if there was a corresponding entry citing the chemical name and abstract number. Document (84) includes the relevant excerpts, available at the priority date of the patent in suit, from the print version of Chemical Abstracts. As can be seen from the last page of document (84), the standard procedure outlined above would have led the skilled person directly to the relevant abstract(i.e. molecular formula $C_{18}H_{20}ClN_3O_3S$; compound name 1*H*-benzimidazole 1-(chloromethyl)-6-methoxy-2-[[(4-

methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-; abstract number 110: 57664p), and to the cross-reference to document (83), in which the desired synthesis is to be found (page 35). Thus, in the present case, the information sought was retrievable in a direct and straightforward manner, without necessitating a comprehensive search. Therefore, since the starting material of example 2 was readily available to the skilled person, the synthesis disclosed therein is considered to be sufficiently disclosed.

The present situation is not comparable with that underlying the decision T 206/83 (see OJ EPO 1987, 5). In that decision, it is apparent that the compounds in question were not traceable through the index of Chemical Abstracts (see point V.b), and it was held under the circumstances that "reliance on the **contents of Chemical Abstracts** to rectify insufficiency might be tantamount to leave the skilled reader to carry out a **search in the whole state of the art**, which would be an unacceptable burden on the public" (see point 6, emphasis added). It is further noted that in decision T 206/83, the board went on to analyse in detail why none of the required compounds were available to the skilled person through common general knowledge (points 7 to 11). This step has been omitted from the respondents' argumentation in the present case.

Finally, lack of sufficiency was alleged based on the method used for measuring enantiomeric excess was not disclosed in the patent in suit. However, no convincing case was made by the respondents as to why the available methods for performing analytical chiral

chromatography would not have yielded reliable results. It is further noted that this argument is inconsistent with the submission of the respondents that preparative HPLC columns had been commercially available at the present priority date that were suitable for separating the enantiomers of omeprazole. This objection is therefore to be rejected as being unsubstantiated in the absence of evidence to the contrary.

7.3 Consequently, the requirement of sufficiency of disclosure is considered to be met, and the objection under Article 100(b) EPC is to be rejected.

8. *Novelty (Articles 52(1) and 54 EPC)*

The respondents did not raise any novelty objections, and the board sees no reason to differ.

Indeed, the passage on page 6, lines 31 to 42 of document (1) discloses six enantiomers, including (-)-omeprazole (line 38), and their salts with bases (line 42). However, no specific salt of the compounds listed is disclosed. The sodium salt according to present claim 1 is therefore considered to be novel over this disclosure. Thus, the subject-matter of claim 1, and consequently that of the remaining claims of the main request, are novel over document (1).

None of the remaining cited prior art documents disclose the salt of present claim 1.

Accordingly, the subject-matter of the main request meets the requirements of novelty.

9. *Inventive step (Articles 52(1) and 56 EPC)*

9.1 In accordance with the problem-solution approach applied by the boards of appeal to assess inventive step, it is first necessary to identify the closest prior art, then to determine in the light thereof the technical problem which the claimed invention addresses and successfully solves, and finally to examine whether or not the claimed solution to this problem is obvious for the skilled person in view of the state of the art.

As explained in "Case Law of the Boards of Appeal of the EPO", 6th edition 2010, chapter I, section D, under point 2, the problem-solution approach was primarily developed to ensure an objective assessment of inventive step.

As further outlined under points 3.1 to 3.4, the aim with regard to the choice of closest prior art is to identify a starting point which the skilled person would have realistically taken under the circumstances of the claimed invention. Therefore, the first consideration in this selection is whether a prior art document discloses subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention. A further consideration is the structural similarity with the claimed invention, in terms of common relevant technical features. In cases of doubt as to the choice of closest prior art, the problem-solution approach should be repeated taking possible alternative starting points.

9.2 In the present case, it is explained in paragraph [0002] of the patent in suit, in the section entitled

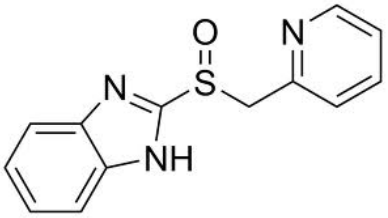
"Background of the invention", with reference to documents (36) and (2), that omeprazole and its alkaline salts are known to be effective gastric acid secretion inhibitors, and are useful as antiulcer agents. It is further disclosed that these compounds exist as two optical isomers (enantiomers). Paragraph [0002] then goes on to state that "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", and that "the present invention provides such compounds, which are novel salts of single enantiomers of omeprazole".

Thus, the patent in suit relates to the field of gastric acid secretion inhibitors and aims at providing compounds having an improved therapeutic profile.

The subject-matter of present claim 1 is directed to the sodium salt of (-)-omeprazole with an optical purity of ≥ 99.8% e.e.

9.3 In the light of the foregoing, it must now be decided whether, as argued by the appellant, document (11) or (2) is to be seen as the closest prior art, or whether, as argued by the respondents, document (1) represents a more appropriate starting point.

9.3.1 Document (11) provides an overview over the class of gastric acid secretion inhibitors, otherwise known as proton pump inhibitors (PPIs), based on the following pyridylmethylbenzimidazole sulfoxide template, also known as timoprazole:



Details are provided of their mode of action, and the effect on activity of various structural modifications to this template (pages 198 to 204). Under point 6.4.2.6.4 (page 204), it is stated that, "more than 40 companies have now patented in this area", but that "relatively few compounds had reached the clinic". The next section 6.4.2.6.5 focuses on omeprazole itself and states under the heading "clinical profile" that "omeprazole (Losec) is the first therapeutically proven proton pump blocker and is clearly emerging as a significant advance in the treatment of peptic ulcer and related diseases". This is followed on page 205 by a section dealing with "limitations of omeprazole should be considered by the medicinal chemist designing new proton pump blockers with advantages over omeprazole", whereby the main disadvantage of omeprazole is stated to be "its ready activation at mildly acidic pH", as a result of which the drug has to be administered as an enterically coated formulation to prevent its destruction in the stomach (see page 205, point (ii)(5)).

9.3.2 Document (2) takes omeprazole at its starting point (see page 1, lines 6 to 30) and provides new forms thereof which exhibit improved storage stability (page 2, lines 1 to 15), namely, specific alkaline salts (claim 1). The sodium salt is particularly preferred, especially for the preparation of liquid pharmaceutical formulations (claim 3, and page 3,

lines 5 to 7). Pharmaceutical compositions and the uses thereof related to the inhibition of gastric acid secretion are disclosed on page 5, line 29 to page 8, line 8 and in claims 8 to 11. The sodium salt is prepared in examples 1 and 2, and incorporated into a solution in example 13.

9.3.3 Document (1) is entitled "Enantiomerentrennung" ("Separation of Enantiomers") and starts with a paragraph describing the field of the invention (page 2, lines 4 to 9), which is translated in document (1A) as follows (emphasis added by the board):

"**The invention relates to a process for the resolution** of chiral pyridylmethylsulphinyl-1H-benzimidazoles into their enantiomers. The enantiomers are used in the pharmaceutical industry for the production of medicaments."

In the introduction (page 2, lines 10 to 23), it is pointed out that, despite the large number of patent applications in the field of gastric acid secretion inhibitors based on the timoprazole template, no process had been described for separation thereof into their enantiomers, and consequently the latter have not as yet been isolated and characterised.

In the following description of the invention (page 2, line 24 to page 4, line 14), a process is disclosed for the resolution of timoprazole-based compounds of formula (I) into their optically pure enantiomers wherein the racemate is reacted with a chiral auxiliary of formula (II) to form a regio- and diasteromeric mixture of formula (III). The diastereomers are then

separated, and converted into the optically pure compound by solvolysis in a strongly acidic medium, followed by a work-up procedure.

On page 4, lines 15 to 17, it is stated that the compounds of formula (III) and the optically pure compounds of formula (I) are novel and therefore a subject of the invention. There then follows a table listing specific exemplary combinations of substituents for these compounds obtainable according to the process of the invention (page 4, line 18 to page 6, line 30), whereby six enantiomers, and their salts with bases, are then listed as being particularly preferred (page 6, lines 31 to 42). The chemical names in this list correspond to (+)- and (-)-pantoprazole, (+)- and (-)-omeprazole, and (+)- and (-)-lansoprazole.

In the following examples, (+)- and (-)-pantoprazole, and (+)-omeprazole are prepared (page 6, line 43 to page 7, line 37).

The description ends with a section entitled "Gewerbliche Anwendbarkeit" ("Commercial Utility") (page 7, lines 39 to 49), which has been translated in document (1A) as follows:

"Pyridylmethylsulphinyl-1H-benzimidazoles can be resolved into their optical antipodes for the first time by the process according to the invention. The fact to be judged as particularly surprising here is that the liberation of the optically pure compounds from the diastereomers is carried out with the aid of highly concentrated mineral acids, although it is known

that the pyridylmethylsulphinyl-1H-benzimidazoles are very acid-labile compounds.

The compounds prepared according to the invention are employed as active ingredients in medicaments for the treatment of gastric and intestinal disorders. Reference is made, for example, to European Patent 166 287 with respect to the manner of use and dosage of the active ingredients."

Finally, the claims of document (1) are directed to optically pure compounds of formula (I) (claims 1, 2), a process for their preparation (claims 3, 4), and intermediates of formula (III) (claims 5, 6).

9.3.4 Thus, as outlined above under points 9.3.1 and 9.3.2, both documents (11) and (2) relate to the active pharmaceutical ingredient omeprazole, the therapeutic properties of which had been extensively investigated and were well understood. Therefore, both documents represent realistic starting points for the skilled person in the field of pharmaceutical drug research and development, seeking improved drug candidates.

The board considers, however, that document (2) constitutes a closer prior art than document (11), since it is directed to a related objective to that specified in the patent in suit, namely, that of providing improved drug forms of omeprazole. Moreover, the sodium salt disclosed in document (2) only differs from that claimed in the fact that the omeprazole molecule in the salt is racemic rather than a single enantiomer, and is therefore structurally closer to the

subject-matter claimed than the free base disclosed in document (11).

9.3.5 In contrast, the board does not regard document (1) to be a realistic starting point for the assessment of inventive step.

As summarised above under point 9.3.3, the invention according to document (1) mainly relates to a process for the enantiomeric resolution of the class timoprazole-based PPIs of formula (I).

It is stated that the optically pure compounds obtained are a subject of the invention because they are novel (see page 4, lines 16, 17). Although it is implied that the isolation of these compounds would allow their characterisation (see page 2, lines 20 to 22), the properties that are of interest in this respect are not specified. Indeed, the only characterisation provided for the (+)-omeprazole obtained as an amorphous solid in example 6 is its optical rotation value.

Although the use "in the pharmaceutical industry for the production of medicaments" is mentioned (page 2, lines 7, 8), none of the claims relate to medical uses, and there is only one paragraph in document (1) referring to a concrete medical use of the compounds prepared according to the invention, namely, for the treatment of gastrointestinal disorders (page 7, lines 46 to 48). With regard to their manner of use and dosage, reference is made to the basic patent disclosing racemic pantoprazole (see document (37), in particular, page 12, line 47). This paragraph of document (1) can therefore only be said to provide a

general statement of field of activity by reference to that of the unresolved starting materials of the process disclosed.

In summary, the overwhelming focus of document (1) is on providing a process for resolution, and it is in no way concerned with investigating any particular pharmaceutical properties of the resolved enantiomers, let alone with providing any improvement in this respect. Under these circumstances, the board concludes that this document cannot be regarded as a realistic starting point for a skilled person seeking improved drug candidates.

9.3.6 The further arguments of the respondents in favour of document (1) as closest prior art are not considered to be convincing for the following reasons:

It is true that documents (1), (2) and (11) all relate to the same general technical field of gastric acid secretion inhibitors. Indeed, at the priority date, the basic mode of action of this class of pyridylmethyl-benzimidazole sulfoxides was well understood (see e.g. document (11), sections 6.4.2.6.1 and 6.4.2.6.2). However, as explained under point 9.2 above, the problem that the patent in suit sought to solve was not simply to provide further compounds having this basic activity, but to provide PPIs having an improved therapeutic profile. Therefore, in order to ensure an objective assessment of inventive step, the board considers that it is not only necessary to determine the closest state of the art by reference to the general field of activity and the chemical structure of the compounds disclosed, but also to consider whether,

taking into account the purpose of the claimed invention, a person skilled in the art would have had any reason to select a particular piece of prior art as a basis for further development. For the reasons set forth in point 9.3.5, the board has come to the conclusion that the skilled person would not have selected document (1) for this purpose.

On a structural level, the board agrees with the respondents that document (1) can be considered to be enabling, in the sense that the process described therein allows the disclosed enantiomers of omeprazole to be obtained. The patent in suit acknowledges as much, and the evidence submitted by the appellant cannot throw doubt on this fact, since the laboratory notebook pages attached to document (20) include an experiment in which an enantiomer of omeprazole was successfully synthesised by means of a method within the teaching of document (1) (see Exhibits J, K and L to document (20)). There was considerable dispute between the parties as to what levels of optical purity were achievable by means of the process of document (1) and as to what conventional methods of resolution were available at the priority date of the patent in suit. However, since these questions are not decisive for the present decision, they need not be discussed further.

Therefore, it can be accepted, as argued by the respondents, that the (-)-enantiomer of omeprazole disclosed in document (1) essentially differs from the subject-matter claimed in present claim 1 in that it is present as the free base. However, the sodium salt of document (2) is structurally just as close since it also characterised by a single distinguishing feature,

namely, in the fact that it is racemic. More importantly, a structural analysis cannot detract from the primary consideration, as outlined above under point 9.3.5, that the absence of an identifiable objective related to that derivable in the patent in suit disqualifies document (1) as a starting point for further modification. Under these circumstances, secondary considerations, such as the fact that document (2) is silent on the subject of enantiomers whereas document (1) discloses salts with bases, cannot be decisive in determining the choice of closest prior art.

Finally, concerning the feature defining "an optical purity of ≥ 99.8% enantiomeric excess", it was argued, with reference to decision T 401/04, that this would strengthen the selection of document (1) over document (2) as closest prior art. The board does not consider this argument to be persuasive, since the respective single structural features distinguishing the claimed subject-matter from documents (1) and (2), as outlined in the previous paragraph, remain the same, regardless of whether the degree of optical purity is specified or not. The board therefore considers that said feature defining a very high optical purity can be viewed as reflecting the intended objective set out in paragraph [0002] of the patent in suit, since the greater the degree of optical purity, the more marked will be any improvement in therapeutic profile. As explained above under points 9.3.4 and 9.3.5, it is the consideration of this objective that is decisive in the choice of document (2) as closest prior art.

9.3.7 The board also does not agree with the final line of argument of the respondents according to which inventive step would in any case have to be assessed starting from document (1) since it was to be regarded as a "feasible" starting point.

The board is aware of decisions T 21/08, T 967/97 and T 591/04 that were *inter alia* cited in this context, and in particular of the conclusion arrived at in decision T 967/97 (see point 3.2), which was cited in decision T 21/08 as follows (see point 1.2.3): "If the skilled person has a choice of several workable routes, i.e. routes starting from different documents, which might lead to the invention, the rationale of the problem-solution approach required that the invention be assessed relative to all these possible routes, before an inventive step could be acknowledged". The board in T 21/08 decided, after consideration of the facts of the case, that document E13 was considered to be a "feasible starting point" for the assessment of inventive step (see points 1.2.4 to 1.2.6). In decision T 591/04, three documents were regarded as "equally legitimate starting points" and "more or less equally promising" (see point 4.2). However, the rationale behind these decisions is not applicable to the present case, since, as explained in detail in above points 9.3.5 and 9.3.6, the present board does not regard document (1) to be a "realistic, feasible or legitimate" starting point for the assessment of inventive step in view of the problem posed in the patent in suit. In other words, in the opinion of the board, taking document (1) as a starting point for the analysis of inventive step relies on a hindsight knowledge of what is claimed and is therefore

inappropriate for an objective assessment of inventive step.

The fact that the opposition division decided otherwise in the decision under appeal cannot change this conclusion. After all, it is a primary purpose of an appeal to give the losing party the possibility to challenge the appealed decision on its merits. Furthermore, as explained in the last paragraph under point 9.3.6 above, the claims under consideration in decision T 401/04, differed from the present claims not only in that they related to a magnesium salt, but also in the feature defining "an optical purity of ≥ 99.8% enantiomeric excess". Since the factual situation is not the same in the two cases, the conclusions reached in decision T 401/04 are not considered to be of consequence for the present decision.

9.3.8 Consequently, the board sees no reason to deviate from the starting point indicated in patent in suit for the assessment of inventive step. Document (2) is therefore considered to represent the closest state of the art.

9.4 The problem to be solved in the light of the closest prior art, as submitted by the appellant and derivable from the patent in suit, can be seen as lying in the provision of a PPI having an improved therapeutic profile, in particular with a lower degree of interindividual variation of therapeutic effect.

It is noted in this context that the problem to be solved has been formulated without reference to "improved pharmacokinetic and metabolic properties" (cf. paragraph [0002] of the patent in suit), since the

inclusion thereof would result in inadmissible pointers to the solution (cf. "Case Law of the Boards of Appeal of the EPO", 6th edition 2010, chapter I, section D, point 4.3.1).

The solution as defined in claim 1 relates to a salt characterised by the fact that omeprazole is present as its (-)-enantiomer with an optical purity of ≥ 99.8% e.e.

9.5 As a next step, it has to be decided whether it has been rendered plausible that the problem defined under point 9.4 has been successfully solved with respect to the closest prior art.

9.5.1 In order to demonstrate that this was the case, the appellant has submitted a number of documents containing comparative data. The respondents contested that this post-published evidence should be taken into account, since there was no evidence in the patent in suit to render the alleged effect plausible, citing decision T 1329/04 in support of their case.

However, the facts of the present case differ substantially from those underlying decision T 1329/04.

Thus, in decision T 1329/04, the problem to be solved was defined as isolating a further member of the TGF-β superfamily, and the solution proposed was a specific polynucleotide sequence encoding the polypeptide denoted as GDF-9 (Reasons, points 4 and 5). However, GDF-9 was not found to exhibit the most striking structural feature which would serve to establish it as belonging to the TGF-β family, and lacked sufficient

sequence homology with other family members (Reasons, points 7 and 8). In addition, no evidence had been provided in the application as filed that GDF-9 played a role similar to that of the transforming factor-β (Reasons, point 9). In the face of these doubts, it was concluded that the application did not sufficiently identify said factor as a member of said family (Reasons, points 6 and 11). Under these circumstances, it was decided that post-published evidence could not be considered in order establish that a solution had indeed been provided to the problem posed (Reasons, point 12).

In contrast, in the present case, the structure of the claimed sodium salt of (-)-omeprazole is fully consistent with that of the known class of gastric acid secretion inhibitors. This clearly differs from the situation in T 1329/04 where the structural features of the polypeptide were found to be inconsistent with that expected of the superfamily. Moreover, the patent in suit discloses a synthesis of the claimed salt (Example 1), and provides a clear statement that it provides "an improved therapeutic profile such as a lower degree of interindividual variation" (paragraph [0002]). When presented with this information, the board can see no reason *a priori* for the skilled person to regard it as being implausible, and no arguments were advanced to this effect. Therefore, this situation again differs from that dealt with in T 1329/04 where a concrete technical basis was given for the reservations expressed. It is noted in this context that the evaluation of information provided in the patent in suit for consistency cannot be equated with an assessment as to whether, without hindsight knowledge,

the state of the art would render the claimed solution to the problem posed obvious.

In the patent in suit, a consistent and verifiable disclosure is provided of the essential elements of a specific structure and corresponding therapeutic benefit. Under these circumstances, the board considers it to be appropriate to take into account the post-published evidence submitted for the purpose of assessing whether or not the effect identified is indeed observed.

9.5.2 The appellant relied on a number of documents disclosing comparative studies in humans on administration of the same oral dose of (-)-omeprazole and omeprazole.

In a first category of experiments, the area under the plasma concentration-time curves (AUC) was examined as a measure of bioavailability. The results thereof may be summarised as follows:

- In Study A of document (80) (pages 6 to 9), the sodium salts of omeprazole and its optical isomers were administered in the form of oral solutions. The AUC values were measured on days 1 and 7 of daily treatment for two groups of healthy subjects, one of which was made up of extensive metabolisers (EMs) (dose 15 mg) and one of poor metabolisers (PMs) (dose 60 mg). In the EMs, the AUC of (-)-omeprazole at steady state (day 7) was approximately two-fold higher than for omeprazole. In the PMs, the pattern was reversed.

- The study discussed in document (147), section 2.1.2, appears to be based on the same data as that outlined in the previous paragraph (cf. e.g. number of patients, duration, dosage). It is additionally reported therein that, in the EMs, the increase in AUC from days 1 to 7 was more pronounced for esomeprazole ((-)-omeprazole) than for omeprazole (page 416, left-hand column). An explanation offered in document (147) for this observation is that the lower metabolic rate of esomeprazole than omeprazole is reinforced with repeated doses owing to the fact that one of the metabolites of esomeprazole, the sulfone, inhibits the major esomeprazole metabolising enzyme, CYP2C19 (see page 424, right-hand column, second complete paragraph).

- In document (105-3), the AUC values in healthy EMs at days 1 and 5 were compared for doses of 20 and 40 mg of omeprazole and its optical isomers, all administered as solutions of the sodium salts (cf. page 780, right-hand column, "Study drugs"). The results obtained were in line with those of document (147) (cf. page 784, left-hand column, first complete paragraph).

- In Study B of document (80) (pages 9 to 12), patients with gastroesophageal reflux disease were given enteric-coated pellets within gelatine capsules comprising the magnesium salt of (—)-omeprazole corresponding to 20 mg of neutral compound, or 20 mg of racemic omeprazole in the non-salt form. After five days of treatment, the AUC for the former was almost two-fold higher than for the latter, with less interindividual variation (see page 11, last paragraph, coefficient of variation for the mean AUC 59 vs. 88%, $P < 0.0001$).

- The AUC values reported in document (146) appear to correspond to those of Study B in document (80) (cf. e.g. Table 2 of document (80) with the first row of Table 3 of document (146)).

A second category of studies related to effectiveness in controlling gastric acid secretion. The results thereof may be summarised as follows:

- In Study B of document (80), additionally to the AUC data mentioned above, the effect on 24-hour intragastric acidity was measured on day 5. It was found that (-)-omeprazole, at a dose of 20 mg once daily, maintained an intragastric pH above 4 for 2.2 hours longer than omeprazole at the same dose (mean percentage of time 53 vs. 44%, $P < 0.0001$).

- Again, document (146) appears to report the same study in more detail (cf. e.g. Table 1 of document (80) with the second row of Table 2 of document (146)). It is additionally disclosed therein that the interpatient variability (as expressed by standard deviation) in the percentage of time for which intragastric acidity exceeded pH 4 was 19.7% for esomeprazole 20 mg and 22.8% for omeprazole 20 mg (see page 864, left-hand column).

- Document (101-12) reports a study in which patients with symptoms of gastroesophageal reflux disease (GERD) received esomeprazole or omeprazole in the form of 40 mg capsules once-daily for five days. The mean percentage of the 24-hr period with intragastric pH > 4 was found to be significantly greater ($P < 0.001$) with

the former than with the latter on days 1 (48.6 vs. 40.6%) and 5 (68.4 vs. 62.0%), and interpatient variability significantly less (see page 956, right-hand column).

Thirdly, two documents were cited relating to randomised clinical trials comparing healing and symptom resolution in larger populations of GERD patients:

- In document (47), significantly more patients were healed at week 8 with esomeprazole 20 mg (89.9%, *n* = 656) vs. omeprazole 20 mg (86.9%, *n* = 650) (see Table 3 and Summary, $P < 0.05$). Moreover, a significantly higher percentage of heartburn-free nights were observed (see Table 4 and page 1253, right-hand column, last paragraph).

- In the study disclosed in document (101-16), the 20 mg esomeprazole group had a higher healing rate than 20 mg omeprazole group at 8 weeks (see Table 2: 90.6%, *n* = 587 vs. 88.3%, *n* = 588), but the difference was not significant ($P = 0.621$).

9.5.3 The first question that arises with respect to the comparative tests outlined under point 9.5.2 is whether they were properly designed to demonstrate that any effect observed has its origin in the distinguishing feature of the invention (see e.g. T 292/92, point 4.3.3).

In all the studies listed, identical doses were used, based on the amount of neutral compound, and identical oral dosage forms, either as enteric-coated

formulations or as a buffered solutions, in order to protect the drug from acid degradation in the stomach (see point 9.6.1 below and document (153), page 164, left-hand column, first complete paragraph).

It is further noted that, in Study A of document (80) and in document (105-3), sodium salts (-)-omeprazole and omeprazole are compared, which accurately reflects the distinguishing feature of the invention over document (2). Moreover, it can be seen from Study B of document (80) that analogous trends in bioavailability were obtained when comparing the magnesium salt of (—)-omeprazole with racemic omeprazole.

The board therefore concludes that the results summarised under point 9.5.2 can be regarded as being pertinent since they reflect the impact of the distinguishing feature of the invention.

9.5.4 Turning now to said data, the board notes the following:

The first category of data relates to AUC values, which are known to correlate with inhibitory effect on gastric acid secretion (see point 9.6.1 below). The comparative studies demonstrate that in EMs, which make up the majority of the population (about 97% of Caucasians, see document (80), page 5), higher and less variable AUC values are observed for (-)-omeprazole than for omeprazole. In addition, with repeated doses, the increase is more pronounced for the former than for the latter. At the same time, the difference in AUC values with respect to PMs is reduced.

In the second set of data, (-)-omeprazole was shown to produce a greater duration than omperazole at an intragastric pH exceeding 4. This is the threshold used to differentiate between aggressive and nonaggressive reflux (see e.g. document (146), Introduction). Less interpatient variability was also observed.

Finally, document (47) reported that (-)-omeprazole was more effective than omeprazole in healing and symptom resolution in GERD patients with reflux oesophagitis. Although the study disclosed in document (101-16) did not confirm these results, it is reported therein that in a pooled analysis of both studies, superiority was confirmed (see paragraph bridging pages 855 and 856).

In view of the above results, the board is convinced that the weight of evidence confirms that the (-)-enantiomer of omeprazole provides an improved therapeutic profile and a lower degree of interindividual variation of therapeutic effect with respect to the racemate.

9.5.5 The additional arguments of the respondents challenging the pertinence of this data are not considered to be convincing:

Although it is true that statistical significance of the findings with respect to interpatient variability was not specified in document (146), other studies do provide this information (see above point 9.5.2 and document (80), page 11, last paragraph; document (101-12), page 956, right-hand column).

With respect to the Sierra study cited as reference [23] in document (168), it is stated in the first complete sentence on page 1454 that the authors were unable to assess methodological quality on the basis of the published abstract. Therefore, the information provided in Figures 3 and 4 of document (168) cannot be regarded as being sufficiently reliable to cast doubt on the conclusion reached in the previous section.

9.5.6 Having regard to the considerations outlined above, the board is therefore satisfied that the problem as defined under point 9.4 has been credibly solved by the salt defined in claim 1.

9.6 It remains to be investigated whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

9.6.1 The skilled person starting from the sodium salt of omeprazole as disclosed in document (2) would have been aware of the body of knowledge relating to the properties, pharmacology and pharmacokinetics of omeprazole and its analogues, as has for example been reviewed in documents (11), (38) and (154), which can be summarised as follows:

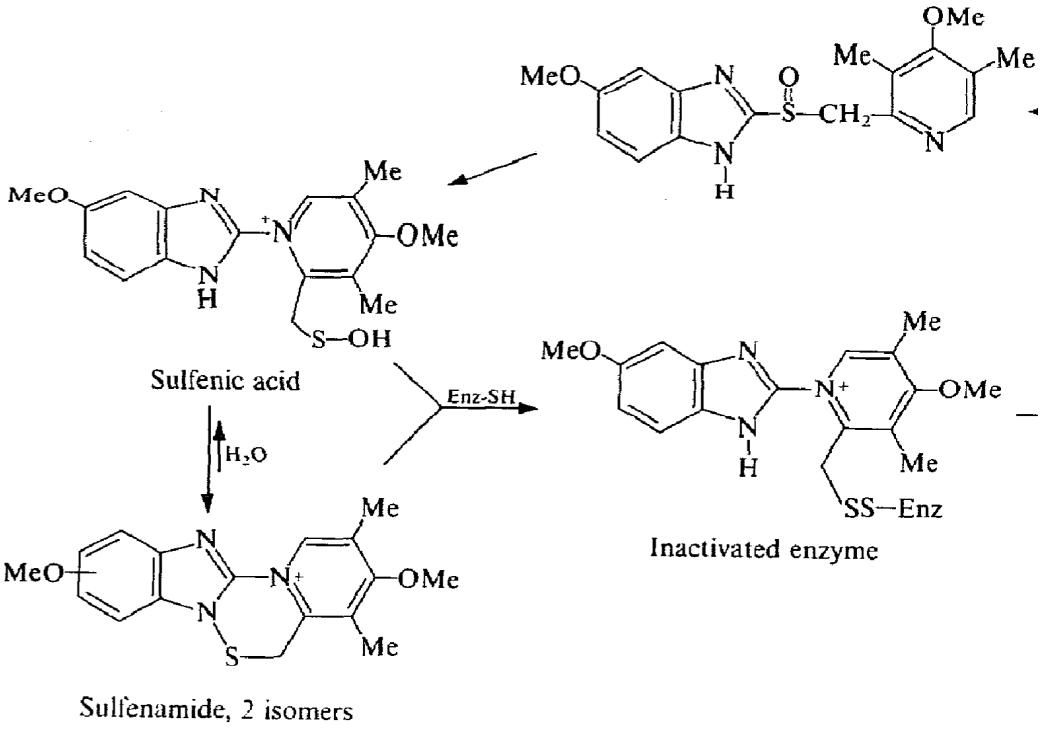
Omeprazole is essentially stable at neutral pH, but undergoes rapid decomposition at mildly acidic pH, and therefore needs to be formulated so as to protect it from destruction in the stomach (see document (11), page 205, point (ii)(5); document (38), section V.A; document (154), page 965, "Pharmacokinetics and Pharmacodynamics", first two sentences).

Once it is absorbed in the intestine, omeprazole undergoes extensive first-pass metabolism (document (38), section IX). Omeprazole interacts with the cytochrome P-450 system in the liver, and interactions with other drugs may thus occur (document (154), page 966, "Metabolism"; document (11), page 205, point (ii)(5)).

Its mode of action is summarised in document (154) as follows (page 965, right-hand column, first complete paragraph; see also document (38), section IV; document (11), sections 6.4.2.6.1 and 6.4.2.6.2):

"It ... reaches the parietal cells of the stomach through the bloodstream. At a pH of approximately 7 omeprazole is not charged and can cross cell membranes (Fig. 1). However, in the secretory canaliculus of actively secreting gastric parietal cells, where the drug is exposed to a pH of less than 2.0, omeprazole becomes protonated. It therefore ceases to be lipophilic and is trapped and concentrated. Omeprazole itself is inactive, but under acidic conditions it is converted to the active form, a sulfenamide[11,12] that reacts covalently with the sulfhydryl groups of cysteine residues on the extracellular surface of the α subunit H^+/K^+—ATPase and inhibits the activity of the enzyme (Fig. 1)."

The conversion of omeprazole to the sulfenamide and its subsequent reaction with the enzyme are depicted in document (11) as follows (page 200):



It is further explained in document (154) under the heading "Pharmacokinetics and Pharmacodynamics" (see also document (38), point VIII, in particular on page 41):

"Peak plasma concentrations occur two to four hours after oral administration[15] and tend to increase during the first few days of treatment, probably because the increasing inhibition of gastric acid secretion results in less degradation of omeprazole in the gastric lumen. The plasma half-life of omeprazole is about 60 minutes,[16] but because it is linked covalently to H^+/K^+—ATPase, the duration of action of a single dose exceeds 24 hours.[17] The degree of inhibition of acid secretion thus does not correlate with the plasma concentration of the drug, but it does correlate with the area under the plasma concentration—time curve.[18] A single 20-mg dose of omeprazole inhibits acid secretion by 65 percent after 4 to 6 hours and by 25 percent

after 24 hours,[18] but with subsequent doses inhibition increases, reaching a plateau after four doses.[18] This increased activity is due both to increased bioavailability and to inhibition of more H^+/K^+—ATPase molecules."

Omeprazole is well tolerated and "has proved to be remarkably free of side effects" (see document (154), page 971, "Side Effects and Toxicity"; also document (38), sections X, XI.E).

9.6.2 Reviewing documents (11), (38) and (154), the board notes that, although the sulfoxides described were known to be optically active compounds, there is only a single reference therein to stereochemistry, namely, on page 204 of document (11) where the following is stated:

"There is no evidence supporting a stereochemical requirement for activity. This is not surprising in the light of the covalent nature of the drug-receptor interaction".

This appears to be a reference to the fact that the affinity for the site of action, i.e. pharmacodynamics, would not be expected to depend on stereochemistry since the sulfenamide active species is achiral.

The observation that a steady state is reached on repeated administration is suggested to be caused by less degradation of omeprazole in the stomach and long duration of action of omeprazole, owing to the covalent bonding of the sulfenamide species to the enzyme that it inhibits. In both these cases, chirality would not be expected to play a role.

Moreover, it is apparent from documents (11) and (38) that there was active research by a number companies in the area of PPIs, but that this was concentrated on structural modifications to the timoprazole template as a means for modifying pH stability and activity (see document (11), sections 6.4.2.6.3 and 6.4.2.6.4 research in document (38), sections V.B, V.C, VI and VII).

The issue of interindividual variation in the steady-state inhibition of acid secretion is addressed in document (154) (sentence bridging pages 965 and 966). However, the only solution proposed to this problem is an increase in dose (page 966, top; also document (11), page 205, last sentence of point (ii)(5)).

Consequently, no teaching can be found in the review documents (11), (38) and (154) pointing to the present solution to the problem posed.

9.6.3 The skilled person would have further been aware of the primary literature cited by the parties relating to omeprazole and its analogues, and enantiomers thereof.

Two documents were cited in this context that were published between the priority and filing date of the patent in suit, namely, documents (7) and (87). In view of the conclusion on the validity of the present priority for the relevant parts of the main request (cf. above point 6), these documents cannot be considered to belong to the state of the art as defined in Article 54(2) EPC. The same is true of documents (8) and (9) published after the present filing date. It is

further noted that all these documents disclose very specific information and data relating to particular PPIs, and cannot therefore provide a legitimate basis for evidence of the common general knowledge or thinking of the skilled person at the priority date of the patent in suit. Consequently, documents (7) to (9) and (87) cannot be relied on in the assessment of inventive step.

The respondents further referred to a series of papers by T Andersson et al. numbered, in order of publication, as documents (153), (34) and (148). In document (153), it was observed that, following oral administration, two of the eight subjects examined showed significantly higher concentrations of omeprazole (page 169, left-hand column, first complete paragraph), and slower formation of hydroxyomeprazole (page 170, left-hand column, second complete paragraph). In the sentence bridging pages 170 and 171, it is suggested that "the hydroxylation of omeprazole and possibly some other metabolic reaction in the elimination of this drug is subjected to a genetic influence, as has been reported for several other drugs, e.g., debrisoquine, some β-blockers, and mephenytoin". This suggestion is confirmed in documents (34) and (148), which disclose that a few Caucasian individuals (<5%) exhibit a slower metabolism of omeprazole, with significantly higher plasma levels than the average subjects, and that these subjects are also poor metabolisers of diazepam and *S*-mephenytoin (see documents (34) and (148), introductions). It is therefore hypothesised that the metabolism of omeprazole and diazepam is associated with the *S*-mephenytoin hydroxylation polymorphism, and that the enzyme *S*-mephenytoin hydroxylase is either

lacking or functionally altered in the poor hydroxylators (see document (34), left-hand column, last two sentences, and document (148), paragraph bridging pages 28 and 29).

Thus, these studies may be summarised as postulating that the enzyme *S*-mephenytoin hydroxylase is associated with the metabolism of omeprazole in Caucasians and that this enzyme is lacking or functionally altered in PMs. These documents are totally silent on the subject of the chirality of omeprazole, despite the fact that the enantioselectivity with respect to the metabolism of mephenytoin observed with this enzyme was well understood at the time, as can be deduced from the fact that the *S*/*R* enantiomeric ratio of mephenytoin is used to phenotype subjects as PMs and EMs in documents (34) and (148) (see document (34), left-hand column, second paragraph; document (148), paragraph bridging pages 26 and 27). Contrary to the contention of the respondents, the board can therefore see no basis for the respondents assertion that documents (153), (34) and (148) would lead to an expectation of significant enantioselective metabolism of omeprazole and thus provide an incentive to investigate the enantiomers thereof. Moreover, all three documents emphasise that the findings would be expected to have few clinical implications, in view *inter alia* of the fact that omeprazole had been found to be well tolerated and no dose-related side effects had been reported (see last paragraphs of each of these documents). Indeed, the existence of PMs implies that a small subpopulation of individuals would be given a dose that is higher than necessary. The skilled person would therefore have no reason to regard this issue to be of significance in

addressing the issue of variability in therapeutic effect in the population as a whole.

Document (3) indicates in its introduction that successful resolutions of omeprazole have been achieved on an analytical scale by means of chromatography using human and bovine serum albumin, and discloses that this may indicate a difference in the degree of plasma protein binding of the two enantiomeric forms. However, no information whatsoever is provided as to whether any differences are actually observed and as to any expected clinical consequences thereof. Moreover, document (3) then goes on to disclose a chromatographic method for the separation of racemic omeprazole, yielding (+)- and (-)-omeprazole in quantities of 3 and 4 mg and enantiomeric purities of 82 and 95.6%, respectively (page 317). From *in vitro* tests with isolated gastric glands, the conclusion is reached that omeprazole was equal in potency to the (-)-enantiomer, and that the inhibitory effect of the racemate should be ascribed to the inhibitory action of both of its enantiomers (page 318). Based on this information, the skilled person would not expect to achieve any benefit from the use of a single enantiomer.

Furthermore, as outlined above under points 9.3.3 and 9.3.5, document (1) discloses a method of resolution of timoprazole-based PPIs, but does not provide any guidance as to the particular behaviour of the isolated enantiomers. Indeed, subsequent to the filing date of document (1), the inventors thereof authored document (164) describing the process leading up to the selection of pantoprazole as a clinical candidate. This paper details how structural modifications were

undertaken in order to obtain inhibitors possessing a combination of high potency, similar to omeprazole and lansoprazole, but increased stability at neutral pH (cf. abstract and Table II); it is further disclosed that pantoprazole was selected for further evaluation over another candidate owing to its greater water solubility and low global lipophilicity, believed to be of benefit with respect to potential cytochrome P450 system interaction (see page 1054, left-hand column, first paragraph). Under the heading "Implications of the Mechanism of Action on Sulfoxide Stereochemistry", the achiral sulfenamide intermediate derived from pantoprazole (**1a**) is discussed with respect to its preparation, properties and reaction with thiols. It is further stated that, "due to their unique mechanism of action, therefore, the in vitro inhibitory activity of the enantiomers of **1a** is anticipated to be identical as has been shown for omeprazole[24] and Ro 185364.[25]" Therefore, document (164) once again emphasises the energies directed towards structural modifications in the search for improved PPIs around the priority date of the patent in suit, and the expectation of equipotence of the enantiomers.

Finally, two documents were cited pertaining to lansoprazole. Document (174A) relates to studies into the metabolic fate in rats and dogs of racemic ^{14}C-tagged material. One set of experiments reports differences in enantiomer concentrations following oral and intravenous doses thereof (see translation (174B), "Results and Discussion", point 2). However, no data is provided for the resolved enantiomers. In a subsequent publication, document (14), originating from the same company, Takeda Chemical Industries Ltd., the

properties of the resolved enantiomers of lansoprazole were examined. In particular, acid formation in isolated canine parietal cells and H^+/K^+-ATPase activity in canine gastric microsomes were investigated, and similar conclusions were reached as in documents (3) and (164), as summarised in the last paragraph on page 1878 as follows:

"From these results it is suggested that both enantiomers of lansoprazole have antisecretory action due to the inhibition of $(H^+ + K^+)$-ATPase and that the inhibitory effects of the two enantiomers are almost the same, at least in isolated parietal cells. Differences in pharmacodynamics and pharmacokinetics of the enantiomers remain to be studied."

In summary, from the documents dealt with in this section, the board concludes that the consensus at the priority date of the patent in suit, derivable from documents (3), (14) and (164), and reviewed in document (11), was that the activity of omeprazole and its analogues was to be ascribed to both enantiomers, and that these had the same effect at the site of action, owing to their conversion to the achiral sulfenamide species. Although the possibility of pharmacokinetic differences is not excluded, the only one of the cited documents to actually mention the pharmacokinetics of the resolved enantiomers states that they "remain to be studied". Based on this statement alone, the skilled person would have had no expectation that an improvement in therapeutic profile would result from the use of the resolved enantiomers, and would therefore have no reason to explore this avenue.

9.6.4 Finally, the respondents attacked inventive step based on decision T 296/87 coupled with the general literature on the role of chirality in pharmacokinetics (documents (33), (149) to (152)), and corresponding recommendations of regulatory authorities (e.g. documents (12) and (42)).

In decision T 296/87, the following is stated in paragraph 8.4.1 under the heading "Inventive step" (emphasis added):

"Long before the contested patent's priority date, it was generally known to specialists that, in physiologically active substances (e.g. herbicides, fungicides, insecticides and growth regulators, but also pharmaceuticals and foodstuffs) with an asymmetrical carbon atom enabling them to occur in the form of a racemate or one of two enantiomers, one of the latter **frequently** has a quantitatively greater effect than the other or than the racemate. If - as here - the aim is therefore to develop agents with increased physiological activity from a physiologically active racemate the **obvious first step** - before any thought is given, say, to synthesising structurally modified products - is to produce the two enantiomers in isolation and test whether one or the other is more active than the racemate. Such **tests are routine**. Under established Board case law, an enhanced effect cannot be adduced as evidence of inventive step if it emerges from obvious tests."

As pointed out by the respondents, this passage does not make a distinction between pharmacokinetic and

pharmacodynamic effects. This is not surprising since the board deciding case T 296/87 was not confronted with this issue. However, in the following paragraph 8.4.2, it was noted that the conclusion reproduced above could be generalised only to a limited extent, and several situations were listed where a different outcome could be envisaged, for example, "if the basic racemate were indeed known but not in line with the general technical trend".

Therefore, it must be decided whether the rationale underlying the above conclusion of decision T 296/87 applies equally to the present situation where no difference in pharmacodynamic effect of the enantiomers was to be expected (cf. above point 9.6.3). For this purpose, it is appropriate to examine the textbook knowledge and reviews numbered as documents (33) and (149) to (152).

In the most general of these citations, textbook excerpt cited as document (149), the following is listed as points to be considered with respect to the interaction of enantiomers in biological systems (emphasis in bold added by the board):

"1. Enantiomere besitzen **in den meisten Fällen** eine *quantitativ* unterschiedliche Wirkung, in manchen Fällen wirken sie *qualitativ* unterschiedlich, im Extremfall können die pharmacodynamischen Eigenschaften der Enantiomere sogar einander *entgegengesetzt* sein.
2. Enantiomere **können** sich in der Gewebeverteilung und in ihrer Eiweißbindung unterscheiden.
3. Enantiomere **können** Unterschiede in der

Metabolisierungsgeschwindigkeit und im Metabolitenmuster aufweisen."

This passage may be translated as follows (board's translation):

"1. **In most cases**, enantiomers exhibit *quantitatively* different activities, in some cases, their activities are *qualitatively* distinct, in extreme cases, the enantiomers may even have *opposing* pharmacodynamic properties.
2. Enantiomers **may** differ in their tissue distribution and protein binding.
3. Enantiomers **may** display differences in their rate of metabolism and metabolite pattern."

The first statement under point 1, which relates to pharmacodynamic effects, closely reflects that in paragraph 8.4.1 of decision T 296/87. However, when it comes to pharmacokinetic properties (points 2 and 3), document (149) is much more cautious, and only refers to the possibility of differences therein, without commenting on any consequences thereof in terms of activity.

Documents (33) and (150) to (152) provide detailed accounts of the pharmacokinetic consequences of chirality in terms of absorption, distribution, metabolism, and excretion (ADME) effects. In document (33), it is explained that most drugs are absorbed across the intestinal epithelium entirely by passive mechanisms following oral drug ingestion, and that the importance of the lipophilicity of a drug far exceeds the effect of chiral interactions (see section

II.A, page 64, first paragraph, and section II.B.1, pages 67, 68). The binding of enantiomers to plasma proteins can occur enantioselectively and may determine the relative concentrations of the enantiomers which are available for interaction with receptors or for metabolic modification (see paragraph bridging pages 64 and 65 and section II.B.2, pages 68 to 72). Finally, it is set out that "enantioselectivity may be displayed in the clearance of drugs, whether this is by direct renal excretion or secretion or whether by metabolism" (see section II.B.3, pages 72 to 81). Similar, analyses are presented in documents (150) to (152). Certain trends are emphasised in these documents, such as the fact that the most marked differences between enantiomers are to be found with regard to parameters that reflect interactions between drug molecules and metabolic enzymes (see document (150), page 48, right-hand column; document (151), page 552, first paragraph), or that intersubject variability in the ratio of plasma concentrations of enantiomers can result from differences in first-pass metabolism (document (152), page S10, left-hand column). However, all these documents also emphasise the multiplicity and complexity of the processes involved in the pharmacokinetics of chiral drugs. This is graphically illustrated in document (151) (Figure 1), in which a method is presented for classifying the various relevant pharmacokinetic parameters involved in the processes outlined above according to the level of organisation in the body, as a means for accounting for stereoselectivity in drug distribution and elimination (see Abstract).

Consequently, the board concludes that, in view of the background knowledge disclosed in documents (33) and (149) to (152) as summarised above, the skilled person would have appreciated that the enantiomers of omeprazole might differ in any one of the relevant pharmacokinetic parameters. However, in the absence of any relevant teaching in the available prior art relating to the field of PPIs (see above points 9.6.1 to 9.6.3), the skilled person would not have had any reasonable expectation that any such differences would translate into a therapeutic benefit on administering only one of the enantiomers of omeprazole. The present circumstances are therefore not comparable to those considered in decision T 296/87.

It is further noted in this context that there was considerable dispute between the parties as to whether the means of resolution of the enantiomers of omeprazole available at the priority date of the patent in suit (e.g. the process of document (1), or methods according to document (3) and related commercially available HPLC technology) would have allowed (-)-omeprazole to be obtained in sufficient quantity and quality in a routine manner. However, the board does not regard the answer to this question to be decisive. The fact remains that, in order to demonstrate the present therapeutic benefit relying solely on pharmacokinetic processes, clinical studies were required on a statistically relevant number of individuals (cf. point 9.5.2 above). In view of the considerable complexity and effort involved in such tests, the skilled person would not have embarked on such an avenue, in the absence of any reasonable expectation of success. In this respect, the situation

also differs from that underlying decision T 296/87, where the tests required were considered to be routine.

Moreover, in contrast to the statement in paragraph 8.4.1 of decision T 296/87, where the "obvious first step" was considered to be to isolate and test the enantiomers, it is apparent that in the area of PPIs, as outlined under point 9.6.2 above, energies in the field were directed to "synthesising structurally modified products".

Finally, the documents cited by the respondents relating to regulatory considerations would also not provide the skilled person, starting from the racemic salt of document (2), with a motivation to resolve its enantiomers and investigate their pharmacokinetic properties. For example, in the last column of document (12), situations are described where the development of a single enantiomer should be considered. One example given is "where one enantiomer has a toxic or undesirable pharmacologic effect and the other does not", whereby it is cautioned that these "might reside not in the parent isomer, but in an isomer-specific metabolite". Another example is "when both enantiomers are pharmacologically active but differ significantly in potency, specificity, or maximum effect". However, neither of these situations apply in the present case. As outlined above under point 9.6.1, omeprazole and its metabolites were not thought to associated with any significant toxicological issues at the priority date of the patent in suit; in addition, differences in potency were not to be expected, since both enantiomers were known to rearrange to give the same active species. Moreover, in a general sense, it might theoretically be

"good science and good sense" (cf. document (42)) to obtain as much information as possible on the individual enantiomers of a racemate. However, whether there was motivation to do so in any particular case must be based on the specific relevant circumstances. As outlined above, such a motivation could not be found in the present case.

9.7 In view of the above considerations, the board concludes that the subject-matter of claim 1 of the main request involves an inventive step. The same applies to the remaining claims, relating to a crystalline form, and processes, pharmaceutical compositions and first and second medical uses thereof.

10. Accordingly, the subject-matter of the claim set according to the main request meets the requirements of Articles 52(1) and 56 EPC.

Since this request is considered to be allowable, it is not necessary to comment on the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained unamended.

3. The objections under Article 24(3) EPC are rejected as inadmissible.

The Registrar: The Chairman:

M. Schalow P. Ranguis