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Application No. / Patent No.	Ref.	Date
00 108 480.5 - 2123 / 1 020 461 /	A1214-2P EP	29.07.2011
Proprietor AstraZeneca AB		

Decision revoking the European Patent (Art. 101(2) and 101(3)(b) EPC)

The Opposition Division - at the oral proceedings dated 09.06.2011 - has decided:

European Patent No. EP-B- 1 020 461 is revoked.

The reasons for the decision are enclosed.

Possibility of appeal
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 and Rules 97 to 98 EPC.

Opposition Division:

Registered letter with advice of delivery

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Enclosure(s): 23 page(s) reasons for the decision (Form 2916)
Wording of Articles 106 - 108 and Rules 97-98 EPC (Form 2019)
Minutes of oral proceedings
Annexes 1 to 3

to EPO postal service: 26.07.11

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I Summary of facts and submissions

1. The present patent EP 1 020 461 B1 is based upon the European patent application 00108480.5 which is a divisional application of EP 94917244.9 (granted as EP 0 652 872 B1).

It has been filed on 27.05.1994 and claims the priority date of 28.05.1993 (SE 9301830).

The title is: Magnesium salts of the (-) enantiomer of omeprazole and its use

The mention of the grant of the patent was published on the 22.07.2009 in EP Patent Bulletin 2009/30.

The proprietor of the patent is Astra Zeneca AB, 151 85 Södertälje (SE), (hereinafter referred to as P).

The patent has 13 claims. Claim 1 relates to the further medical use of the Mg salt of (-) omeprazole with an optical purity superior or equal to 99.8% enantiomeric excess (e.e.) to inhibit gastric acid secretion and claims 2 to 8 depend on it.

Claim 9 is the Mg salt of (-) omeprazole with an optical purity superior or equal to 99.8% e.e. "per se".

Claim 10 is the first medical use claim of the salt of claim 9.

Claims 11 also relates to the further medical use claim of the same Mg salt of (-) omeprazole but is formulated in a different way than claim 1 (i.e. in the so-called "EPC 2000" format).

Claim 12 is dependent on claims 9 to 11.

Claim 13 is a pharmaceutical composition comprising the salt and refers back to claims 9 to 12.

2. Oppositions were filed by:

Hexal AG, Industriestrasse 25, 83607 Holzkirchen (DE) (referred to as O1) with the notice of opposition dated 22.04.2010.

Teva Pharmaceutical Ind. Ltd, 5 Basel Street, PO Box 3190, Petah Tiqva 49131 (IL) (referred to as O2) with the notice of opposition dated 23.07.2009.

Mepha AG, Dornacher Str. 114, 4147 Aesch BL (CH) (referred to as O3) with the notice of opposition dated 31.03.2010.

Stada Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel (DE) (referred to as O4) with the notice of opposition dated 21.04.2010.

Pinewood Lab. Ltd, Ballymacarbry, Clonmel, County Tipperary (IR) (referred to as O5) with the notice of opposition dated 21.04.2010.

Ethypharm, 194 Bureaux de la Colline, 92213 Saint-Cloud Cedex (FR) (referred to as O6) with the notice of opposition, dated 21.04.2010.

Actavis Group hf., Reykjavikurvegi 76-78, 220 Hafnarfjordur (Iceland) (referred to as O7) with the notice of opposition dated 22.04.2010.

Lupin Ltd., 46A/47A Nande, Mulshi Taluke, 411 042 Pune (India) (referred to as O8) with the notice of opposition dated 22.04.2010.

Zentiva k.s., U Kabelovny 130, 102 37 Praha 10 (Czech Republic) (referred to as O9) with the notice of opposition dated 22.04.2010.

Generics (UK) Ltd., Albany Gate, Darkes Lane, Potters Bar, Hertfordshire EN6 1AG (UK) (referred to as O10) with the notice of opposition dated 22.04.2010

Ratiopharm, 89079 Ulm (DE) (referred to as O11) with the notice of opposition dated 21.04.2010.

1A Pharma GmbH and Hexal Pharma GmbH , Stella-Klein-Loew-Weg 17, 1020 Vienna (AT) (both) as joined opponents (referred to as O12) with the notice of opposition dated 22.04.2010.

Dr. Ulrich Hörnchen, Steinenkreuz 28, 53773 Hennef (DE) (referred to as O13) with the notice of opposition dated 22.04.2010.

All opponents requested revocation of the patent in its entirety.

The grounds were the following:

. extension of the granted subject-matter beyond the content of the application as originally filed (A. 100(c) in relation to A. 123(2) and A. 76(1))

. the invention was not sufficiently disclosed (A. 100(b))

. lack of novelty of the granted subject-matter (A. 100(a))

. lack of inventive step of the granted subject-matter (A. 100(a))

. it was also stated that: the granted subject-matter was not entitled to priority

the legal principle of *res judicata* should apply with respect to the fate of the parent patent EP 0 652 872.

the present patent represented a case of double patenting of the subject-matter as claimed in the parent patent EP 0652 872.

All opponents further made subsidiary requests for oral proceedings.

O1, O4, O5, O12 further requested that the proceedings be accelerated.

3. In his reply to the notices of opposition, dated 10.12.2010, the proprietor contested the grounds of opposition, requested maintenance of the patent as granted and presented arguments to this end. It was further requested to join the present opposition procedure with that of patent EP 1 020 460.

A subsidiary request for oral proceedings was also made.

4. Summons to oral proceedings were sent on the 15.02.2011.

The opposition division (OD) expressed a provisional opinion according to which the granted subject-matter: would not extend beyond the content of the application as originally filed (A. 100(c) in relation to A. 76(1)), would be sufficiently disclosed (A. 100 (b)/A. 83) and would be novel with respect to the cited prior art (A. 100(a)/A. 54).

It was also stated that the priority would appear to be valid, that no double patenting would occur and that the principle of *res judicata* would not apply to the patent in suit.

The matter of inventive step was left open.

5. All Os but O8 replied at least once to the P's petition of 10.12.2010, some of them making reference to the OD's provisional opinion of 15.02.2011 as well.

6. With a letter dated 06.04.2011, P filed 4 auxiliary requests (AR1 to AR4, see Annex 2) and extensively debated on all the objections put forward by the Os so far in order to refute them. In doing so P also referred to the OD's preliminary opinion.

7. In a letter dated 15.04.2011, O8 announced that he would not attend the oral proceedings but that his original request to revoke the patent *in toto* was maintained.

8. 1. In a letter dated 28.04.2011, P wrote a direct response to a specific argument (relating to the meaning of "enantiomeric excess" and "enantiomeric purity") presented by O9 in a submission dated 04.04.2011. This submission from O9 was accompanied by two documents D122 and D123 in relation to this point.

P filed a document D156 to support his view and requested, in case the OD would not admit his submission into the proceedings under R. 116, that the submission of O9 concerning this point and including D122 and D123 be also dismissed.

8.2. With a letter dated 05.05.2011, O9 requested that D156 be considered late-filed and thus not admitted into the proceedings.

9. With a letter dated 01.06.2011, on behalf of all opponents that would attend the oral proceedings, O11 suggested that the relevance of D1 be discussed before novelty and inventive step at the hearing.

10. During the written proceedings summarized above, numerous documents and pieces of evidence have been cited and filed by all parties. They are listed in Annex I.

11. Oral proceedings took place on the 07, 08 and 09.06.2011. During these, one additional auxiliary request has been presented (AR5) (see Annex 3).

At the end of the oral proceedings the opposition division announced its decision.

12. The arguments of the parties are summarized as follows:

12.1. Extension of the subject-matter of the patent in suit beyond the content of the application as originally filed (A. 100(c), A. 123(2) and A. 76(1)):

One of the Os' argument is that the subject-matter of claims 1 and 9 of the patent in suit results from a combination of numerous disparate parts of the original description (D23), none of which being described as preferred embodiments. In particular the latter does not **specifically** describe a Mg salt of (-) omeprazole, let alone such a salt with an e.e. greater or equal to 99.8% or its use to inhibit gastric acid secretion.

It is further alleged that since the original application mentions both the (+) and (-) enantiomers of omeprazole without any preference, claiming only one of the two (as in the granted claims) adds technically relevant information which was not originally present.

It is also objected that according to the original description (D23, p.4, l. 4 to 12) an e.e. greater or equal to 99.8% is a feature which is compulsorily linked to a crystalline form of the product. According to a further argument, such an e.e. is also only originally disclosed for Na salts (D23, p. 4, l. 1 to 17).

An additional objection concerns claim 11 and the term "prophylaxis" which is not to be found in the original description.

It is further argued that the original application mentions the disorders of granted claims 3 to 5 only insofar as they occur in mammals and man (D23, p. 4, l. 24-27) and that this is not specified in the granted claims. A similar objection is raised for granted claim 6 because the NSAID therapy is not linked to a treatment of a gastrointestinal disorder as in the original application.

P submits that the original application discloses Mg salts of (-) omeprazole as such (e.g. D23, p. 3) and clearly states that the e.e. greater or equal to 99.8% is obtainable for all salts of both enantiomers of omeprazole, without any compulsory link to either a Na salt or a crystalline form.

He also states that in view of the above, there is no addition of technically relevant information in the granted claims.

Turning to the term "prophylaxis" which is as such not present in the original application, P asserts that since the original application refers to the inhibition of gastric acid secretion (D23, p. 4, l. 22), prophylaxis is encompassed by this inhibiting effect.

Finally, the original application contains embodiments which are not restricted to the use of the compounds in mammals and man (e.g. claims 18, 19 of D23) or which do not link the treatment of a gastrointestinal disorder to and NSAID therapy (D23, p. 4, l. 28-29).

12.2. Observation on the entitlement to priority (A. 87(1)):

O1 states that there is no disclosure in the priority document (D28) of the specific Mg salt of (-) omeprazole with an e.e. greater or equal to 99.8% (subject-matter of claim 9).

P responds by referring to his argumentation with respect to A. 100(c) in relation to A. 76(1).

12.3. Observation on the principle of *res judicata*:

Some Os state that claims 8, 13, 10, 3 and 5 of the patent in suit correspond exactly to claims 1, 8, 9, 10+11 and 15 respectively of the parent patent (D23) except for the feature of an e.e. greater of equal to 99.8%. Using the above reasoning (point 12.3.) for dismissing the e.e., noting that the parent patent has been revoked (T401/04) and further analyzing the criteria of *res judicata*, they allege that T401/04 constitutes *res judicata* in the present case and that the opposed patent should thus be revoked.

P mainly replies that the e.e. is a relevant feature (c.f. point 12.3.) and that evidence has been submitted during examination of the opposed patent which was not available at the time the Board made its decision so that T401/04 has no impact on the claimed subject-matter.

12.4. Observation on the issue of double patenting:

Disregarding the feature relating to enantiomeric excess for the reasons exposed above (point 12.3.) some Os submit that the claims of the patent in suit cover subject-matter which is already present in the claims of the parent patent (D23). Referring to T307/03 it is alleged that the patent in suit constitutes a case of double patenting which should not be allowed.

P retorts that since the parent patent has been revoked, that such revocation is deemed to take effect *ex tunc* and that this occurred before the patent in suit was granted, the two patents have never co-existed and never will co-exist.

12.5. Lack of sufficient disclosure (A. 100(b), A. 83):

Some Os assert that the disclosure provided with the patent in suit is deficient because, in the examples, a specific detection method and parameters therefor are not specified in relation to how enantiomeric excess (e.e.) is determined. For instance, although analytical chiral chromatography is mentioned as a means therefor, no specific processing parameters are given.

Another objection is based on the fact that Ex. 1 of the patent in suit describes that the Mg salt of (-) omeprazole with an e.e. of 99.9% has an optical rotation of -128° whereas D25 discloses an optical rotation between -137 to -155° for a corresponding compound.

It is also alleged that the patent in suit does not disclose how to get the starting material (i.e. the chloromethyl derivative of ex. 2.A of the patent in suit).

Further, it is objected that the patent does not disclose how to arrive at all the embodiments encompassed by the claims, e.g. how to get an Mg salt of (-) omeprazole with an e.e. of 100%.

It is also argued that since it appears that the salt must be crystalline to have an e.e. greater or equal to 99.8%, a method of further purification of the amorphous Mg salts obtained in the patent should be present.

Another objection concerns the lack of clinical data which leads to an insufficient disclosure with respect to the suitability of the claimed product for achieving the claimed therapeutic effect.

P submits that the examples of the patent state that e.e. was determined by column chromatography which was at the priority date a standard, i.e. well-known and documented, determination method for e.e.

He also states that optical rotation is not an absolute determination of e.e., that it can vary and that moreover, D25 which has been cited by the Os, relates to Mg (-) omeprazole **trihydrate** which is not identical to the compound of the claims.

Concerning the starting chloromethyl compound, P retorts that is was routine to find it (and its synthesis) in the prior art, e.g. by consulting the Chemical Abstracts (D84).

P argues that the full scope of the claim is enabled by following the teaching of the patent, e.g. the example describes an e.e. of 99.9%, and that furthermore the Os did not file any evidence to the contrary.

He further submits that there is no requirements for the compound to be crystalline and that the example does provide the claimed e.e.

Finally, the EPC does not require to include clinical data in a patent relating to a pharmaceutical product and anyway the opposed patent discloses the medicinal utility of the compound in a very clear and affirmative way.

12.6. Lack of novelty (A. 100(a), A. 54):

A novelty objection against claims 1, 9, 10 and 13 is raised by some Os in view of D1. The argument is particularly directed to claim 9 and is based on the disclosure of D1 (p. 6, l. 31-42) which provides a list of preferred proton-pump inhibitors (including (-) omeprazole) and then states "and their salts with bases". Concerning the enantiomeric excess feature, Os allege that this term relates to the purity of an organic compound and therefore cannot be used to distinguish the subject invention over the prior art, relying in that respect principally on T990/96.

A further novelty objection is directed against claims 1 to 6 and 9 to 13 in view of D2 which discloses Mg salt of omeprazole in a crystalline form. Based on the alleged teaching of the patent in suit that Mg omeprazole preferentially crystallises in the form of enantiomeric crystals (i.e. any given crystal of Mg omeprazole will contain only a single enantiomer), D2 inherently discloses the claimed Mg salt of (-) omeprazole with the required e.e.

P refutes the first objection by submitting that T990/96 does not apply to the patent in suit, thus the e.e. is a feature relevant to novelty. This feature is not disclosed in D1 and moreover, D1 does not specifically describe an Mg salt of (-) omeprazole.

With respect to D2, P argues that D2 describes how to prepare salts of racemic omeprazole and cannot be regarded as inherently disclosing any enantiomeric form of it.

12.7. Lack of inventive step (A. 100(a), A. 56):

12.7.1. A key issue in that matter concerns D1.

Although the Os use different lines of argumentation based on different documents they all raise an objection based on D1 as closest prior art.

The P's main counter argument is that D1 cannot be the closest prior art because it is a non-enabling disclosure for production of omeprazole enantiomers of any degree of enantiomeric purity. This is denied by all Os.

In order to support their views, a lot of Os as well as P have filed experts' declarations and experimental reports in relation to D1.

12.7.2. One line of argumentation against inventive step considers that, since the enantiomeric excess feature is not a distinguishing one, the subject-matter of the claims of the patent in suit is the same at that of the parent patent D23. Thus, as D23 has been revoked with T401/04 (D22) for lack of inventive step in view of (principally) D1, the same conclusion should apply to the patent in suit.

12.7.3. Another argumentation also considers D1 as closest prior art because it describes compounds closely related in structure (i.e. basic salts of (-) omeprazole among which Mg is mentioned) and used for the same purpose as in the patent in suit (i.e. inhibition of gastric acid secretion) and uses a problem-solution approach on that basis. In particular, it is determined that the differences between the subject-matter of claim 9 of the patent and the disclosure of D1 lie in the fact that the Mg salt of omeprazole is to be used and that it should have a certain optical purity (expressed as a particular e.e.). It is further argued that no technical effect, either therapeutic or related to a physico-chemical property, is provided by these differences. Thus the problem to be solved is the provision of an alternative compound to those disclosed in D1 and the solution consisting in providing the compound of claim 9 is obvious in view of D1 further taking the disclosure of D2 into account (D2 specifically cites Mg as preferred salt for omeprazole). By doing so, the required e.e. is obtained because the patent itself teaches that it is the inevitable result of preparing a basic salt of omeprazole.

Still starting from D1 as closest prior art, a further reasoning considers that the problem with respect to D1 is to improve the optical purity of (-) omeprazole. The solution of the patent in suit is to convert it into its Mg salt so that it can be purified by crystallisation up to an optical purity greater of equal to 99.8% e.e. Since it is common

general knowledge (D120) that improvement of the optical purity of a non-crystalline compound is achieved by converting it into a crystalline salt and then further recrystallizing it and that according to D2 the Mg salt is preferred for omeprazole, providing the compound of claim 9 of the patent is obvious as a solution to the above problem.

12.7.4. A further line of argument starts from D2 as closest prior art. D2 discloses the Mg^{2+} salt of racemic omeprazole, used to inhibit gastric acid secretion. The compound of claim 9 of the opposed patent is the Mg^{2+} salt of the (-) enantiomer of omeprazole with an e.e. greater of equal to 99.8%.

According to the Os, the differences between these compounds do not lead to any technical effect. Thus the problem was the simple provision of alternative compounds to those of D2. Knowing that omeprazole consists of two enantiomers, knowing (from D1 or D3) how to separate them and further knowing how to prepare the Mg salt of (-) omeprazole, the skilled person would have arrived at the compound of claim 9 of the opposed patent without any inventive merit.

Even if it is considered that the differences between D2 and the claimed matter lead to a technical effect in the form of clinical advantages for instance (which is however disputed by the Os), the same conclusion would apply. In this case the problem would be the provision of a PPI which has advantageous properties over the racemic Mg omeprazole of D2 and the solution would be the provision of the Mg salt of (-) omeprazole. Following the conclusion of T296/87 on enantiomers, the skilled person would have been aware that one of the enantiomers of omeprazole might have a better effect than the racemate and would have thus prepared both enantiomers in isolation to test them, thus arriving at the subject-matter of the opposed patent.

In the case a technical advantageous effect is acknowledged, a further argument to refute it relies on the fact that the original application (D23) does not contain any evidence for this technical advantage of the Mg salt of (-) omeprazole. Even if such evidence is provided later in the course of the proceedings it must not be taken into account with respect to T1329/04 and the reasoning is then the one above.

12.7.5. Some Os additionally present a reasoning based on D3 as closest prior art which discloses that (-) omeprazole with an e.e. of 95.6% can be obtained from a chromatographic separation of racemic omeprazole. The fact that the claimed Mg salt leads to a more stable form of the compound is deductible in an obvious manner having regard to the teaching of D2. Then, since according to the patent the act of forming the Mg salt by itself increases the optical purity this represents an inevitable bonus effect devoid of inventive step.

12.7.6. Other objections are put forward, considering D6, D31 or D32 as closest prior art.

12.7.7. P extensively replies to all objections:

A general argument is that at the priority date (i.e. 1993) the skilled person had no motivation whatsoever to develop PPI enantiomers as drugs, let alone omeprazole enantiomers and that the prevailing wisdom at the time actually amounted to a technical prejudice.

Another general consideration concerns the alleged separation techniques of omeprazole enantiomers such as disclosed for instance in D3, D6, D31 or D32 which according to P are mostly analytical techniques which would not have allowed to actually obtain the omeprazole enantiomers, except for D3 however with a low yield and a poor e.e.

Concerning the choice of the closest prior art document, as already mentioned, P asserts that it cannot be D1 because it is a non-enabling disclosure and presents an extensive argumentation to this end, taking also all of the Os' submissions into account.

However for the sake of argument if D1 is taken as closest prior art, then the problem lies in providing an optically stable form of (-) omeprazole or alternatively in providing a (-) omeprazole compound with an e.e. high enough to be of a pharmaceutically acceptable level. If D3 is chosen as closest prior art, then the problem is the same as for D1.

According to P, the skilled person would not consider the formation of a salt but would turn to other, more conventional, techniques such as recrystallisation from different solvents (D1, D20, D13) or chromatographic techniques (e.g. D3). P submits that ultimately these techniques would have failed. Other considerations which would have prevented the skilled person to provide a salt of omeprazole, provided he would have thought about it at all, are that it could not be ascertained beforehand that the salt, particularly the Mg salt, would be crystalline and that this would have meant that optical purity could be enhanced via further purification. Thus the solution consisting in providing the Mg salt of (-) omeprazole to obtain a compound with an enhanced e.e. is not obvious.

If D2 is taken as closest prior art, the problem is to provide an omeprazole compound with improved pharmacokinetic and metabolic properties and/or improved therapeutic profile with respect to the Mg salt of racemic omeprazole (of D2). In relation to this P expresses the view that the clinical advantages filed in D17 indeed represent a technical advantage of the invention of the patent in suit which must be taken into account and are not to be considered as a mere "bonus effect".

P is however of the opinion that, if one follows the criteria developed by the EPO jurisprudence (to be found in the Case Law book p. 164, §3.2.) the closest prior art document is D11. This document represents the "real life" and clearly states that a problem of omeprazole is its variable effect in inhibiting gastric acid secretion. Thus the problem is to provide a compound having an improved effect compared to omeprazole. The solution is to provide an Mg salt of (-) omeprazole with an e.e. greater of equal to 99.8%. The problem has been solved as shown by e.g. D101 or D105. For reasons extensively developed by the P and already referred to above, at the priority date (i.e. 1993) the skilled person had no motivation whatsoever to develop PPI enantiomers as drugs, let alone omeprazole enantiomers. Thus the claimed matter is inventive.

II Grounds for the decision:

1. The oppositions are admissible because they meet all the requirements of Articles 99(1) and 100 EPC and Rules 3(1) and 76(1)(2) EPC.

2. MAIN REQUEST:

2.1. Principle of *res judicata*:

The parent patent EP 652 872 (D21) has been revoked by decision T401/04.

The criteria for a decision becoming *res judicata* are set out in T 167/93, confirmed in T 1099/06 as follows:

The issue must have been:

(a) judicially determined;

(b) in a final manner,

(c) by a tribunal of competent jurisdiction;

(d) where the issues of fact are the same;

(e) the parties (or successors in title) are the same; and

(f) the legal capacities of the parties are the same.

In the present case, it appears that at least criteria (d) is not fulfilled.

As a matter of fact, none of the claims of the parent patent contains the technical feature relating to an optical purity greater or equal to 99.8% e.e.

The presence of this additional feature in the claims of the patent in suit in comparison with the parent patent gave rise to exchange of arguments between the parties concerning different issues (see e.g. points 12.4.2, 12.3 and 12.6).

In the OD's view this demonstrates in itself that the issues of fact in the present proceedings are not the same as in that of the parent patent.

Since at least one of the six criteria listed above is not fulfilled, this is enough to conclude that the principle of *res judicata* does not apply.

2.2. Issue of double patenting:

The above reasoning applies to that matter as well. No double patenting occurs since no identical subject-matter has been claimed by the present patent and the corresponding parent patent.

2.3. Extension of the subject-matter of the patent in suit beyond the content of the application as originally filed (A. 123(2) and A. 76(1)):

The application as originally filed is D23.

The subject-matter of granted claim 9 corresponds to one of the preferred salts described on p. 3, l. 4, 16 and 30 combined with p. 4, l. 10-11 of the original description (D23). A fair reading of the latter statement (p. 4) clearly indicates that the e.e. greater or equal to 99.8% is obtainable for all salts of both enantiomers of omeprazole, without any compulsory link to either a Na salt or to a crystalline form.

This is emphasized by the experimental section, particularly from ex. 5 of D23, which shows that the crystalline Na salt of (-) omeprazole can be converted into the corresponding Mg salt without any need for a crystallization step and without any loss of enantiomeric purity.

In the OD's view, such a reading of the original application is not a combination of several lists. The compound is described per se and the technical feature concerning the optical purity clearly applies to all salts of all enantiomers of omeprazole.

As a consequence, the subject-matter of granted claim 1 corresponds to the above disclosure linked to the statement on p. 4, l. 22-23 (D23) or to claim 19 (D23).

The feature of a crystalline salt (granted claims 2 and 12) is described on p. 4, l. 8 (D23).

The therapeutic uses of claims 3 to 8 are described p. 4, l. 24 to p. 5, l. 7 (D23). They are not restricted to the use of the compounds in mammals and man (D23, claims 18, 19) and do not link the treatment of a gastrointestinal disorder to an NSAID therapy (D23, p. 4, l. 28-29).

The OD is of the opinion that since the original application refers to the inhibition of gastric acid secretion (D23, p. 4, l. 22), prophylaxis is encompassed by this inhibiting effect, thus providing a basis for granted claim 11.

The same holds true for the further technical features of the granted claims. None of this can be seen as extending beyond what was originally disclosed.

Therefore the requirements of A. 123(2) and A. 76(1) are met.

2.4. Entitlement to priority (A. 87(1)):

The priority document is D28.

D28 is very similar to D23, in that the parts relating to the subject-matter of the granted claims are disclosed as follows: p. 3, l. 1, 16, 17 and 30 (Mg salt of (-) omeprazole); p. 4, l. 4 to 7 (crystalline salt; e.e. higher or equal to 99.8%), p. 4 l. 15 to 24 (prophylaxis and therapeutic uses).

Thus, following the reasoning of point 2.3. the OD concludes that the patent in suit is entitled to the priority date of 28.05.1993.

2.5. Sufficiency of disclosure (A. 83):

Example 1 of the patent describes how to obtain the Mg salt of (-) omeprazole with an e.e. of 99.9%.

The synthesis starts in Example 2 with 6-methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)-sulfinyl)-1-(chloromethyl)-1H-benzimidazole, which method of obtention is not described in the patent. However, at the priority date, this compound was easily made available by consulting the Chemical Abstracts (D84). Looking up the Chemical Abstracts is routine for a chemist wishing to find whether a given compound has already been synthesized and how.

Example 1 states that the optical purity has been determined by chromatography on an analytical chiral column. Several documents such as D3 (p. 317), D6 (p. 296, Fig. 1) or D31 (p. 85, Fig. 1 and Table 1) describe the separation of omeprazole enantiomers on different columns under different chromatographic conditions thus proving that at the priority date methods for determining the optical purity of

omeprazole enantiomers were available. As all these methods provide a baseline separation of both enantiomers, the OD has no reason to assume that the result obtained will depend on the method used.

Moreover, both the therapeutic uses (§10) and the galenic forms of the compounds (§18 to 25) are disclosed in the patent in a very clear and affirmative way.

Some Os have argued that the optical rotation given in Ex. 1 is different from that given in the Pharmacopeia for the corresponding compound (D25). This parameter, however, depends on various factors such as the hydration degree of the salt. Therefore the different values cannot substantiate any doubts as to the nature of the product obtained.

Another argument was that it is not known how to provide a Mg salt of (-) omeprazole with an e.e. of 100% but no facts or data have been provided to actually demonstrate that the skilled person would not be able to carry this out.

Hence, in view of the patent as a whole and as detailed above, the invention appears to be sufficiently disclosed.

The requirements of A. 83 are thus met.

2.6. Novelty (A. 54):

D1 relates to the inhibition of gastric acid secretion (p. 2, l. 12-13) and depicts the (-) enantiomer of omeprazole and its salts with bases (p. 6, l. 38 and 42).

D1 however does not specifically describe an Mg salt of (-) omeprazole, let alone such a compound with an optical purity greater or equal to 99.8% e.e. (which is a characterizing technical feature, see point 2.1. above). Mg salts are disclosed in D1 only with the racemic starting material but not with the finally obtained enantiomers (p. 3, l. 51-55).

This holds true for D2 which describes how to prepare salts of **racemic** omeprazole and cannot be regarded as inherently disclosing any enantiomeric form of it.

Therefore, the subject-matter of claims 1 to 13 of the patent in suit is novel.

2.7. Inventive step (A. 56):

2.7.1. Relevance of D1:

As mentioned under point 12.4.1. above, P considers that D1 is a non-enabling disclosure which thus cannot represent the closest prior art whereas Os are of the opposite opinion.

This matter must first be settled.

P bases his arguments on D18, D19 and D20. D19 is a post-published declaration which, in the OD's view, does not contain more information than D20 as far as the present issue is concerned.

D18 is a post-published declaration from a scientist (E.M. Larsson) which comments on attempts (made in February and March 1993 according to the copies of the laboratory notebook attached) to repeat the manufacturing process of (+) omeprazole described in Ex. 6 of D1. Three assays have been made, none of which was successful.

D20 is a post-published declaration from the inventor of D1 (Dr. Kohl). It comments on the scientific work which ultimately led to the filing of D1 and specifies (D20, §50) that only one out of four attempts to produce (+) omeprazole was successful (and has then been described in Ex. 6 of D1). Copies of the laboratory notebook are provided. Reviewing this only successful assay, P notes that although Ex. 6 makes reference to Ex. 2 by stating that the omeprazole is liberated "in accordance with" the procedures described in that example (2) which would require that the pH is adjusted to 7,5 before the CH_2Cl_2 extraction takes place (D1, p. 6, l. 67), the laboratory notebook shows that the pH has actually been adjusted to 9 (D20, §85). This would constitute a discrepancy between D1 and the assay described in D20 and thus could not be considered as a valid attempt proving that Ex. 6 of D1 actually "works".

According to P, this finding, added to the fact that the 3 other assays have failed, demonstrates unequivocally that key information is missing from D1. This is further emphasized by the failed assays commented in D18.

P concludes that D1 is a non-enabling disclosure for production of omeprazole enantiomers of any degree of enantiomeric purity.

Some Os have filed evidence to show that the procedure described in D1 may be reproduced: D27 together with D81, D35 together with D114, D60, D76 together with D115, D77.

Having considered all the evidence it seems to the OD that D114 at least follows the procedure of Ex. 6 of D1 quite strictly to obtain (-) omeprazole.

The fact that according to D20 only one out of 4 assays produced the desired compound does not, in the OD's mind, mean that the procedure is not enabling. Had it been the case, then none of the assays would have produced any (+) omeprazole, Ex. 6 would not be present in D1 and the whole debate concerning the enablement of D1 would be inexistent. Moreover, the methodology applied in the 3 failed attempts of D20 does not completely follow the instructions given in D1.

P argues that the procedure of D1 is too "hit and miss" and thus that it represents undue burden for the skilled person to actually have it succeed. It might well be that more than one assay is necessary to perform this Ex. 6 but this is by no means unusual when trying to reproduce an experiment described in a scientific paper. Moreover, it must be noted that the Os concerned were able to follow the method described therein and to produce some omeprazole enantiomer (e.g. D114). In that respect, the fact that none of the Os mentioned whether they had any failure or that their assays have been done years after the publication date of D1 is not a bar to the validity of their results as long as the procedure of D1 is respected.

Finally, post-published D5 reports the successful obtention of (+)-(R)-omeprazole when cleaving off with H_2SO_4 the fenchylmethylether according to the procedure of D1 (see § "results and discussion" and scheme 1 of D5). Although said hydrolysing step had been identified by the technical expert of the P as leading to a degraded impure product, the inventors of the patent in suit show in D5 that this step indeed provides pure and stable (+)-(R)-omeprazole.

In view of the foregoing, the OD is of the opinion that D1 allows to synthesize (+) omeprazole and, by choosing the adequate starting product and following the procedure of Ex. 6, (-) omeprazole as well. In view of the available evidence, however, the optical purity in terms of a **specific figure** of enantiomeric excess cannot be asserted.

To this extend, it is considered that D1 is an enabling disclosure.

2.7.2. Selection of the closest prior art:

According to the jurisprudence and to the EPO practice, this is normally a prior art document disclosing subject-matter aiming at the same objective as the claimed invention and having the most relevant technical features in common.

Os consider it is best represented by D1 and P by D11.

D1 relates to the inhibition of gastric acid secretion (p. 2, l. 12-13) and describes the (-) enantiomer of omeprazole and its salts with bases (p. 6, l. 38 and 42).

D11 is part of a general textbook and discloses the use of omeprazole as a PPI for the treatment of peptic ulcer and related diseases (p. 104). It also states that omeprazole suffers from disadvantages among which its particularly high acid lability which presumably leads to the variation in the extent of its therapeutic effect (p. 105).

According to the P only D11 mentions the same problem as the patent in suit which is the provision of a compound having an improved effect over omeprazole (§2 of the patent). Because this is an important criteria in selecting the closest prior art, D11 should be chosen.

The OD agrees that the purpose is an important criteria but so are the common technical structural features (see above). In the present case the latter are only found in D1. D11 makes no mention whatsoever of enantiomers of omeprazole or salts thereof. Even if D1 does not specifically state that its goal is to provide "better" gastric acid inhibitors, it deals with such substances and their use as medicaments which is enough as common purpose, particularly as it was a matter of general knowledge that separation of racemic drugs can provide enantiomers with improved pharmacokinetic properties (D12).

D11 might well represent the "real life" situation at the priority date, as argued by P. It is however not the criteria with which the EPO selects the closest prior art document which must be used in assessing inventive step according to the "problem-solution" approach.

Accordingly, the OD is of the opinion that D1 qualifies as closest prior art better than D11.

2.7.3. As concluded from above, D1 is the closest prior art and discloses (-) omeprazole and its salts with bases, together with their inhibiting effect on gastric acid secretion. However, it cannot be ascertained that D1 inherently discloses an optical purity greater or equal to 99.8% e.e. (see point 2.7.1).

Thus the difference with the subject-matter of **claim 9** of the patent in suit lies in the high optical purity of the salt of (-) omeprazole which is greater or equal 99.8% e.e.

It has not been shown that this difference in enantiomeric purity leads to any specific technical effect (see also 5.5.3 below).

Hence the problem with respect to D1 was to provide alternative (-) omeprazole compounds with an improved optical purity.

The solution is to provide the Mg salt of (-) omeprazole, because this salt can be purified by re-crystallization up to the claimed optical purity.

In relation to this problem, D120 must be taken into consideration as part of the general knowledge of the skilled person as it is a textbook dealing with purification of enantiomers. It states (p. 424, §7.6.2) that "the normal procedure for preparing a pure enantiomer ... is recrystallization" and gives hints as how to produce crystals when the enantiomers themselves are not crystalline thereby citing the formation of salts.

It is already known from D1 that salts of (-) omeprazole are available and Mg is cited among the possible basic salts. It is also known from D2 that the Mg salt of omeprazole is particularly stable.

The P argues that the skilled person would not have considered formation of a salt as an obvious solution to enhance the optical purity of (-) omeprazole but would have rather tried chromatographic techniques, such as taught for omeprazole in e.g. D3, D6, D31 or D32.

The OD agrees that chromatographic techniques are part of the means available to purify enantiomers but they are not exclusive of other techniques.

There would have been no reason for the skilled person to concentrate exclusively on chromatographic techniques so that he would also have taken D120 and the crystallization technique into consideration.

The OD agrees with the P's submission that it could not be foreseen that the Mg salt of (-) omeprazole would be crystalline. Still, if the skilled person wanted to get crystals out of a non-crystalline (-) omeprazole compound and was told by D120 that making salts was a possible means of doing it, he would have certainly done so.

Thus in view of the above arguments, the OD considers that it would have been obvious for the skilled person faced with the above problem to provide a salt of (-) omeprazole, more specifically the Mg salt, thus arriving at the compound of claim 9.

Moreover, as far as the feature of crystallinity of the Mg salt of (-) omeprazole is concerned, it is obvious from what has been exposed above that this feature is inherent to this compound, otherwise there would be no means of any further purification via recrystallization. Hence the above reasoning is valid for **claim 12.**

Since D1 discloses the inhibiting effect on gastric acid secretion, the above reasoning extends to the subject-matter of claims 1, 2, 10, 11 and 13 of the patent in suit which thus does not meet the requirements for inventive step.

2.7.4. Should the feature relating to an optical purity greater or equal to 99.8% e.e. be considered inherent to D1, then the reasoning about (lack of) inventive step exposed in the decision T401/04 regarding the parent patent (EP 0 6652 872) applies since it is directed to the subject-matter of claim 15 of this parent patent which is identical to that of claim 5 of the patent in suit except for this only technical feature of optical purity greater or equal to 99.8% e.e.

Thus if it is considered that the subject-matter of dependent claim 5 of the patent in suit does not meet the requirements for inventive step, the same objection applies *a fortiori* to the claims on which claim 5 depends, namely claims 1 to 4. By logical extension this holds true for the subject-matter of claims 10, 11 and 13.

Concerning the compound claim 9, the only difference with D1 would be the selection of the Mg salt among the possible cation of (-) omeprazole cited by D1. Since no technical effect linked to it is shown the problem would consist in providing alternative compounds to those of D1 and is solved as shown in Ex. 1 of the patent in suit. The provision of a Mg salt however is obvious in view of D2 which discloses that salts of omeprazole have a higher storage stability compared to omeprazole in its non-salt form and that this is especially true for Mg salts.

2.7.5. In conclusion whichever position is taken with respect to the feature of optical purity, at least one claim of the main request does not meet the requirements for inventive step (A. 56).

Thus the main request is not allowable.

3. AUXILIARY REQUESTS 1, 2 and 3:

Each of auxiliary requests AR1, AR2 and AR3 contains a claim corresponding exactly to one of the above claims of the main request (patent as granted), namely: claim 1 of AR1 and AR3 is identical to granted claim 1 and claim 1 of AR2 is identical to granted claim 2. Thus the subject-matter of each of these claims does not involve an inventive step for the reasons set out above.

Hence auxiliary requests AR1, AR2 and AR3 are not allowable.

4. AUXILIARY REQUEST 4 (AR4):

Extension of the subject-matter beyond the content of the application as originally filed (A. 123(2) and A. 76(1)):

Claim 1 of AR4 is identical to granted claim 1 with the additional feature of the therapeutic purpose specifying "for the inhibition of gastric acid secretion with a lower degree of interindividual variation than racemic (+ -) omeprazole"

The original application (D23) states on p.1, l. 19 to 20 "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". It is obvious from p. 1, l. 15 that the "properties" should be "improved" over those of "omeprazole and its alkaline salts".

On p. 3, l. 4 to 31 D23 describes the most preferred salts as being the optically pure Na or Mg salts of (+) or (-) omeprazole, i.e. there are 4 preferred salts.

Thus the original teaching does not individualize any of the 4 salts as being particularly efficient or preferred as far as the effect on interindividual variation is concerned and does not provide any data in relation to this effect.

The OD concludes that, since the original application does not disclose which of the enantiomers bears this effect, adding such a feature into the claim amounts to adding technically relevant information which was not originally present.

Hence the subject-matter of claim 1 of AR4 extends beyond the content of the earlier application as filed which is contrary to A. 123(2) and A. 76(1).

AR 4 is not allowable.

5. AUXILIARY REQUEST 5 (AR5):

This request contains 2 claims (see Annex 3).

5.1. Admissibility (R. 80):

The OD is of the opinion that this new request, filed on the third day of the oral proceedings, is a fair attempt to overcome the objections which led to the rejection of all previous requests.

In fact the request contains one single independent claim which scope is restricted by a more specific therapeutic indication in order to address the objection for lack of inventive step raised with the higher ranking requests.

Thus the requirements of R. 80 are met.

5.2. Extension of the subject-matter beyond the content of the application as originally filed (A. 123(2) and A. 76(1)):

The independent claim 1 reads: "A pharmaceutical composition of a Mg salt of (-) omeprazole with an optical purity greater or equal to 99.8% e.e. together with a pharmaceutically acceptable carrier for use in the treatment of reflux esophagitis by the inhibition of gastric acid secretion".

Claim 2 depends on it and specifies that the salt is crystalline.

Compared to the granted claims (which meet the above requirements see point 2.3 above), those claims are as follows:

Claim 1 is in the format of further medical use present in granted claim 11. It is combined with granted claim 13 which describes the composition of a Mg salt of (-) omeprazole with an optical purity greater or equal to 99.8% e.e. together with a pharmaceutically acceptable carrier. The therapeutic use is disclosed in granted claim 5 (reflux esophagitis) in relation with granted claim 1 (inhibition of gastric acid secretion).

The OD is not of the opinion that this claim 1 represents a selection from different lists but considers that it only specifies each technical feature from granted claim 11 with more accuracy thereby using features which were already present in the granted claims.

Thus, since according to the conclusion of point 2.3. above the granted claims meet the requirements of A. 123(2) and A. 76(1) and since it is considered that claim 1 is a combination of features which were present in these granted claims and does not extend beyond their content, claim 1 of AR5 also meet the requirements of A. 123(2) and A. 76(1).

This conclusion also applies to claim 2 of AR5 in view of e.g. granted claim 12.

5.3. Sufficiency of disclosure (A. 83):

Most of the Os maintained the objections raised for the granted claims. These objections were however already considered as not pertinent so that the same conclusion must be drawn for the present AR5.

Independent claim 1 of AR5 is further restricted in that the therapeutic application is specified as being reflux esophagitis. Since a therapeutic effect of omeprazole in reflux esophagitis is already established by the prior art (see e.g. D11) there is no reason to doubt that the claimed medical use can be put into practice.

In conclusion, since according to point 2.5. above the granted claims meet the requirements of A. 83, and since claims 1 and 2 of AR5 are allowable combinations of those, they also meet these requirements.

5.4. Novelty (A. 54):

None of the Os has raised an objection for lack of novelty and the OD sees no reason to differ.

5.5. Inventive step (A. 56):

5.5.1. Selection of the closest prior art:

As for the main request, P regards D11 as being the closest prior art. P notes that D11 is the only document which specifically mentions reflux esophagitis which is the claimed therapeutic use of AR5. D1 only describes gastric acid inhibition and is moreover more focused on stereochemistry aspects. As already argued by P for the main request, the purpose of the invention is an important criteria in the choice of the closest prior art. The latter should thus reflect the real situation that the skilled person was facing at the priority date. In the present case, according to P, it was to provide a compound having an improved effect over omeprazole and had nothing to do with its stereochemistry. Because of this D11 should be chosen.

In relation to the inventive step aspect, P further states that the decision T401/04 concerning the parent patent (D22) is not to be followed at all costs because in the meantime new evidence has been provided to establish the real situation which the Board which issued T401/04 did not have at the time.

The OD agrees that the reflux esophagitis is only mentioned as such in D11.

It considers however that if the skilled person knows that a compound inhibits gastric acid secretion, such as taught by D1, then he would inevitably conclude that this compound has an effect on reflux esophagitis simply because the latter is caused by the former as known from e.g. D11. In fact, effectiveness of omeprazole in reflux esophagitis was a matter of general knowledge (see D38, p. 47; D70).

Therefore, following the reasoning made for the main request (see point 2.7.2 above) the OD considers that D1 which relates to the inhibition of gastric acid secretion (p. 2, l. 12-13) and describes the (-) enantiomer of omeprazole and its salts with bases (p. 6, l. 38 and 42) still represents the closest prior art for AR5.

5.5.2 In view of the reasoning developed under point 2.7.3 above for claims 1 and 2 of the main request in view of D1 and considering that the skilled person knows that a compound which inhibits gastric acid secretion would inevitably have an effect on reflux esophagitis simply because the latter is caused by the former (see 5.5.1. above), the OD is of the opinion that the subject-matter of claim 1 of AR5 does not meet the requirements for inventive step.

5.5.3. Although the following bears no effect on the reasoning on inventive step the OD wishes to comment on some pieces of evidence provided by P and aiming at showing some technical effects linked to the use of the Mg salt of (-) omeprazole in the treatment of diseases linked to gastric acid secretion.

These are D80 and D101 and consist in post-published (i.e. after the priority date) declarations supported by experimental evidence according to which (-) omeprazole (in the form of its Mg salt in D101 and its Na salt in D80) has less interindividual variability than racemic omeprazole and thus can be used to treat patients suffering from gastro-esophageal reflux disease (GERD) who could previously not be successfully treated (D101).

The OD does not dispute the veracity of these declarations and data. However, this technical effect is not present in the application as filed (D23) in that there is no direct link between the diminution of interindividual variability and (-) omeprazole specifically, let alone its Mg salt. D23 rather gives the impression that this effect is shared by all "novel salts of single enantiomers of omeprazole" (D23, p. 1, l. 18-22).

Therefore in accordance with the conclusion of T1329/04 and whatever the other circumstances on inventive step could be, these evidence could not be taken into consideration.

Moreover, the OD emphasizes that these data are anyway not in line with the EPO jurisprudence concerning comparative examples because they compare the claimed matter with racemic omeprazole and not with the closest prior art disclosing (-) omeprazole which is D1.

6. In conclusion, taking account of the amendments made by the patent proprietor during opposition proceedings, European patent EP 1 020 461 is revoked pursuant to Articles 101(2) and 101(3)(b) EPC.