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# Datasheet for the decision of 10 January 2007

**Case Number:** T 0417/04 - 3.3.01

**Application Number:** 99930107.0

**Publication Number:** 1095037

**IPC:** C07D 401/12

**Language of the proceedings:** EN

**Title of invention:**
Process of synthesis of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl-1H-benzimidazole

**Patentee:**
Lek, Tovarna Farmacevtskih in Kemicnih Izdelkov

**Opponent:**
AstraZeneca AB

**Headword:**
Omeprazole/LEK, TOVARNA FARMACEVTSKIH

**Relevant legal provisions:**
EPC Art. 54, 56, 64, 69, 84, 123(2)(3)
EPC R. 71a

**Keyword:**
"Amendment: supported by the application as filed (yes) - extending the protection (no) - Article 69 EPC not relevant to the assessement to be made under Article 123(3) EPC"
"Novelty (yes)"
"Inventive step (yes) - non obvious solution"

**Decisions cited:**
G 0010/91, T 0002/80, T 0020/81, T 0442/91, T 0740/96, T 1129/97, T 0412/02

**Catchword:**-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0417/04 - 3.3.01

# D E C I S I O N
**of the Technical Board of Appeal 3.3.01**
**of 10 January 2007**

**Appellant:** (Opponent)
AstraZeneca AB
c/o Global Intellectual Property, Patents
S-151 85 Södertälje (SE)

**Representative:**
-

**Respondent:** (Patent Proprietor)
Lek, Tovarna Farmacevtsikh in Kemicnih Izdelkov, D.D.
Veroskova 57
SI-1526 Ljubljana (SI)

**Representative:**
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**Decision under appeal:**
**Decision of the Opposition Division of the European Patent Office posted 29 January 2004 rejecting the opposition filed against European patent No. 1095037 pursuant to Article 102(2) EPC.**

**Composition of the Board:**

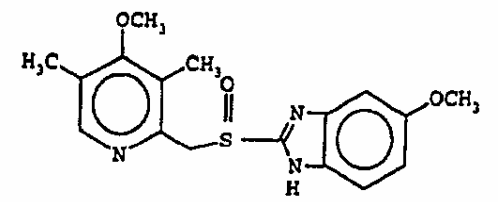
**Chairman:** A. Nuss
**Members:** P. Ranguis
R. Menapace

## Summary of Facts and Submissions

I. The appeal lodged on 18 March 2004 lies from the decision of the Opposition Division posted on 29 January 2004 to reject the opposition filed against the European patent No. 1 095 037 (European patent application No. 99 930 107.0).

II. The sole claim of the patent as granted read as follows:

"1. Process for preparing 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]-sulfinyl-1H-benzimidazole (omeprazole)of the formula



**characterized in that** 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]-benzimidazole is reacted with 3-chloroperoxybenzoic acid in ethyl acetate at a temperature between -10°C and 5°C and the product formed is purified by dissolution in an aqueous solution of methylamine, by precipitation under addition of hydrochloric acid and isolation of the title compound in a pure form".

III. Notice of opposition had been filed by the Appellant (Opponent) requesting revocation of the patent as granted for lack of novelty or inventive step in view of documents

(5) EP-A- 484 265
(6) WO-A-93/06097
(7) EP-A-533 752

(8) WO-A-97/22603

(9) EP-A-5 129

In response to the provisional opinion sent by the Opposition Division pursuant to Rule 71a EPC, the Opponent submitted that the patent claim was not supported by the description and, therefore, contravened Article 83 EPC.

IV. The Opposition Division held in its decision that the subject-matter of the sole Claim as granted was novel in view of documents (5) and (6).

Regarding inventive step, the Opposition Division held that the person skilled in the art would not have found in the whole teaching of document (5) alone or in combination with document (8) any incentive to run the reaction of making omeprazol in the absence of a carboxylic acid which appeared to be an essential feature of document (5). Moreover, none of the documents cited gave any hint to carry out the purification step by using an aqueous solution of methylamine. The Opposition Division also denied that the claim as granted could be construed as not excluding the presence of other constituents *inter alia* a carboxylic acid.

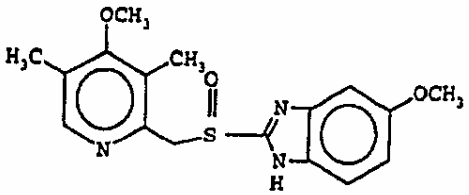
The Opposition Division also rejected the new ground of opposition that the single claim of the patent in suit was too broadly formulated and the skilled person could not reproduce it in its whole scope, for lack of proper substantiation and referred in that respect to the decision of the Enlarged Board of Appeal G 10/91 (OJ EPO 1993, 420).

V. In the communication accompanying the summons to oral proceedings the Board had informed the parties that fresh grounds for opposition might be considered in appeal proceedings only with the approval of the Proprietor of the patent (see G 10/91, Order, point 3). Such an approval was not given and could not be presumed.

VI. Oral proceedings before the Board took place on 10 January 2007.

VII. At the oral proceedings, the Respondent (Proprietor of the patent) defended the maintenance of the patent in suit on the basis of the claim submitted as second auxiliary request with the letter received on 8 December 2006. This claim reads as follows:

"1. Process for preparing 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]-sulfinyl-1H-benzimidazole (omeprazole)of the formula




**characterized in that** 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]-benzimidazole is reacted with 3-chloroperoxybenzoic acid in ethyl acetate at a temperature between -10°C and 5°C and the product formed is purified by dissolution in an aqueous solution of methylamine, to which solution acetone is added and by precipitation under addition of hydrochloric acid and isolation of the title compound in a pure form".

VIII. At the appeal stage, the Appellant did not challenge the decision of the Opposition Division to reject the new ground of opposition under Article 100b) EPC (see point IV, last paragraph).

The Appellant's arguments may be summarized as follows:

The claim as amended contravened the requirement of Article 123(3) EPC since it extended the protection conferred by Claim 1 as granted. Indeed, as recognized by the Opposition Division and supported by the Proprietor of the patent in the opposition proceedings, Claim 1 as granted was "closed" in the sense that the presence of other constituents were excluded (see point 3.2.1 of the reasons). It resulted therefrom that due to the amendment example 1 which was not within the scope of Claim 1 as granted fell within the protection conferred by the subject-matter of this request.

The claim as amended contravened the requirement of Article 84 EPC since something was missing due to the term "and" followed by nothing, whereas the public would have expected that a further feature would follow.

Regarding novelty, no document of the prior art cited anticipated the claimed subject-matter.

Regarding inventive step, as a preliminary remark, a fundamental distinction was to be made depending on the interpretation of the claim in relation to document (5).

That document disclosed like the patent in suit the same oxidation step of 5-methoxy-2-[[(4-methoxy-3,5-

dimethyl-2-pyridyl)methyl]thio]-benzimidazole into omeprazole using the same oxidizing agent (3-chloroperoxybenzoic acid), in the same solvent (ethyl acetate) but in the presence of a carboxylic acid. Document (5) also disclosed an organic base such as triethylamine in the peripheral dissolution and reprecipitation step.

Either the claim was to be understood as "open" which implied that further compound(s) might be added or further step(s) might be taken. In view of document (5), the sole differences laid in the purification step, namely replacement of ethylamine by methylamine, addition of acetone and addition of HCl.

Or, the claim was to be understood as "closed" in excluding the addition of other constituents, then a further difference existed, namely the absence of carboxylic acid in the oxidation step.

Whatever the interpretation was, however, the claim lacked inventive step.

Document (5) might qualify as the closest state of the art. In view of that document no technical effect could be acknowledged in the absence of a proper comparison between this prior art and the claimed subject-matter as required by the Jurisprudence of the Boards of Appeal (see T 20/81, OJ EPO 1982, 217). The technical problem could only be seen, therefore, in the provision of an alternative process for the production of omeprazole. There was in that respect no evidence that the omeprazole be obtained in a pure form or in a purer form than in document (5).

Contrary to the Respondent's contention, the starting material employed in document (5) was the same as that used in the patent in suit. Even though the thio precursor compound might be expected to be protonated to some extent by the added carboxylic acid as taught by document (5), the same protonation occured without the extra addition of an alkyl carboxylic acid since the oxidation agent, i.e. 3-chloroperoxybenzoic acid, usually contained about 10 mol-% of 3-chlorobenzoic acid as a stabilizer. This species was a much stronger acid than e.g. the ethyl hexanoic acid used in example 29 and thus protonated the thio precursor of omeprazole. Consequently the species that would eventually be oxidized in the ethyl acetate would also be the same in document (5) as in the patent in suit. A second reason why it could not be alleged that a different species than in the patent in suit would react in document (5) was that in example 29, the thio precursor was in slight excess over the ethyl hexanoic acid. In other words, there must be necessarily at least some direct reaction of the free thio compound with the oxidizing agent. The type of counter ion was in that respect immaterial to the oxidation process. Therefore, it would have been immediately recognized from document (5) that it was feasible to provide an alternative process for oxidizing the thio intermediate to prepare omeprazole without the addition of further alkyl carboxylic acids.

The sole reason in document (5) for adding an alkyl carboxylic acid was to improve the solubility of the thio compound in the solvent. The insoluble thio compound should partly be transferred to the liquid

phase with the aid of alkyl carboxylic acids which can accelerate the oxidation reaction. However, the person skilled in the art could have expected that the reaction worked without this addition of a carboxylic acid.

Regarding the dissolution and reprecipitation step, the person skilled in the art would have without inventive ingenuity replaced triethylamine cited in document (5) as an example of "organic base" by another organic base such as methylamine. Furthermore, the reprecipitation by acid was obvious from documents (6), (7) and (8). No specific technical effect was achieved by the use of HCl in that respect.

The claimed subject-matter was also objectionable in that the amount of acetone was not defined. Furthermore, the reprecipitation step did not include the dilution with water which was however required according to the patent in suit. The technical problem was, therefore, not solved over the whole claimed area.

IX. The Respondent argued that the added feature related to the addition of acetone was a restricting feature. The subject-matter of Claim 1 did not, therefore, offend against Article 123(3) EPC. The claim was also clear. The Respondent also supported the opinion of the Opposition Division that from document (5) alone or in combination with document (8), the person skilled in the art would not have found any incentive to run the reaction of making omeprazole in the absence of a carboxylic acid. Indeed, in document (5), the presence of a carboxylic acid was necessary to form the pyridinium salt of formula VIII subsequently to be

oxidized to omeprazole. The addition of triethylamine to decompose the omeprazole salt formed by oxidation was further evidence that the reaction involved the carboxylic salt of omeprazole sulphide. In addition, it was pointed out that the process disclosed in document (5) required that the reaction be run at -40°C whereas in the claimed process the reaction took place between -10 and +5°C.

Concerning the dissolution and reprecipitation step, the method disclosed in document (5) was different to that of the claimed process since the function of the triethylamine in the method of document (5) served for stabilization of the omeprazole at elevated temperature whereas in the example of the patent in suit the purification of omeprazole after oxidation consisted of dissolution of the omeprazole at room temperature in an aqueous solution of methylamine to which solution acetone was added and reprecipitation by adding hydrochloric acid to pH 7-8.

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

The Respondent requested that the patent be maintained on the basis of the sole claim as filed with letter dated 8 December 2006.

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

## Reasons for the Decision

1. The appeal is admissible.

2. *Amendments*

2.1 Claim 1 as granted was amended to incorporate the feature "to which solution acetone is added and" (see point VII above). This amendment finds support in the application as filed on page 4, last paragraph which specifies that "the dissolution is carried out in an aqueous solution of methylamine, to which solution acetone is added" and does not give rise, therefore, to objection under Article 123(2) EPC. This was admitted by the Appellant.

2.2 The Appellant submitted that this amendment extended the protection conferred by the patent as granted (see point II above) in contravention of Article 123(3) EPC. He pointed out, in particular, that example 1 of this patent was outside the scope of the claim as granted, whereas, due to the amendment, the claim of this request encompassed the subject-matter of this example.

2.2.1 The Appellant's contention is not convincing however since due to the incorporation of the feature "to which solution acetone is added and", the claimed subject-matter covers a process wherein an additional step is required. Such a feature restricts, therefore, the scope of the claim of this request compared to that of the claim as granted. It results therefrom that Claim 1 as amended does not extend the protection conferred by the patent as granted.

2.2.2 In that context, the question whether or not the patent as amended could be enforceable against the reproduction of example 1, whereas that would not be the case for the patent as granted, is irrelevant to assess the compliance of the amendment with Article 123(3) EPC which concerns the claims as such and not the relationship of the claim with an example of the description. In principle, interpretation of the extent of protection of a patent is not the task of the EPO, but is, according to Articles 64 and 69 EPC, that of the national Courts competent in procedures on infringement cases (see T 442/91 of 23 June 1994, point 3 and T 740/96 of 26 October 2000, point 3.3).

3. *Clarity*

3.1 The Appellant submitted that the added feature (see point 2.1 above) rendered the claim unclear.

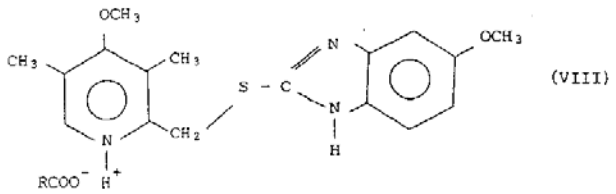
3.2 The clarity requirement of Article 84 EPC relates only to the claims, and consequently, as the EPO's Boards of Appeal have consistently ruled, it demands that these be clear per se for a person skilled in the art with general knowledge of the technical field in question, without the need to refer to the description of the patent in suit (see T 2/80, ibid, point 2). Thus the meaning of the wording of a claim must be fully evident from the actual terms of that claim, so that it is sufficient in itself to provide useful protection and is therefore unambiguous (see T 412/02 of 16 June 2004, point 5.6 and T 1129/97, OJ EPO 2001, 273, point 2.1.2).

3.3 In the present case, the Board does not share the Appellant's view that something is missing after the

term "and". The Board considers that when read as a whole the claimed process as now defined would be clear for the person skilled in the art. The Appellant did not file any evidence to the contrary in that respect. It is, in particular, clear that "the product formed is purified by dissolution in an aqueous solution of methylamine, to which solution acetone is added" (emphasis added by the Board). The objection under Article 84 EPC is, therefore, rejected.

4. *Novelty*

4.1 Document (5) discloses a process for the preparation of omeprazole with a good yield and high purity (see page 22, lines 18 and 28-29), wherein the last but one step involves the treatment of 5-methoxy-2-((3,5-dimethyl-4-methoxy-2-pyridinyl)methylthio)-1H-benzimidazole, i.e. 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]-benzimidazole as defined in the claimed process (see point VII above) with an alkyl carboxylic acid RCOOH, e.g. 2-ethylhexanoic acid, to yield the corresponding 5-methoxy-2-((3,5-dimethyl-4-methoxy-2-pyridinyl)methylthio)-1H-benzimidazoyl carboxylate of formula VIII.



(VIII)

This step is followed by oxidation of the salt formed in a solvent where the compound of formula VIII is partially soluble, preferably ethyl acetate, in the presence of a peracid, preferably m-chloroperbenzoic

acid. When the reaction has terminated, the omeprazol formed is partially precipitated and partially dissolved in the form of the corresponding carboxylate. The salt is destroyed by the addition of an organic base, preferably triethylamine, which insolubilizes the omeprazol. Omeprazol is recrystallized using ethyl acetate or acetone in the presence of an organic base such as triethylamine to give an omeprazol having a 99.7% (HPLC)-99.35% (perchloric acid analysis) purity (see page 11, line 46 to page 12, line 14; page 21, lines 50 to 58; page 22, lines 1 to 29 and example 29).

4.2 The Appellant although recognizing the novelty of the claimed subject-matter due to the purification step, argued however that the step of oxidation might only be considered as different from that of document (5) if the claim was to be seen as a "closed" claim as opposed to an "open" claim.

4.3 The Appellant's view is however at variance with the facts. The oxidation step according to Claim 1 is distinguished as such from that disclosed in document (5) in that the starting product undergoing the oxidation is in the claimed process the 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]-benzimidazole, whereas the starting product in document (5) is the compound of formula (VIII), i.e. 5-methoxy-2-((3,5-dimethyl-4-methoxy-2-pyridinyl)methylthio)-1H-benzimidazoyl carboxylate (see point 4.1 above).

4.4 In view of the above, the question whether or not the claim is "open" or "closed" does not arise since what distinguishes the claimed process from that disclosed in document (5) is, first of all, the nature of the

starting product preceding the oxidation step, namely the sulphide free base in the patent in suit and the compound of formula VIII in the case of document (5). This difference can in no way be related to the issue of whether the claim is "open" or "closed" and the prerequisite question raised by the Appellant is thus irrelevant.

4.5 The Board considers, therefore, that already due to the difference in the starting product of the oxidation step, the subject-matter of Claim 1 is novel in view of document (5). The Board is satisfied that the subject-mater of Claim 1 is also novel in view of the other documents cited. The claimed subject-matter is, therefore, novel in the sense of Article 54 EPC.

5. *Inventive step*

5.1 The Board concurs with the parties that document (5) is the closest state of the art to define the technical problem to be solved. Indeed, this document aims at the same objective as the patent in suit, namely a method for preparing omeprazole with a high purity (see point 4.1 above) and has the most relevant technical features in common, in particular an oxidation step in the presence of 3-chloroperbenzoic acid in ethyl acetate.

5.2 In view of document (5), the least ambitious technical problem may be seen in the provision of a further method of preparing omeprazole in ethyl acetate with a high purity.

5.3 The next step is to verify whether the technical problem is solved by the claimed process within the whole claimed area.

The Appellant contested that with any amount of acetone, even a small amount, the crystallization of omeprazole in a pure form could be achieved. He also argued that the dilution with water was necessary to achieve the desired technical effect. In support thereof he relied upon the description of the patent in suit, in particular paragraph [0012] and example 29.

The Appellant did not however submit any supporting evidence in the form of common general knowledge or experimental results liable to prove that a specific amount of acetone was critical for solving the above defined technical problem. Likewise, one could only argue that a further dilution with water is essential to the claimed process if the Appellant had supported his submission with reliable evidence. That is not the case here.

Under these circumstances and in the absence of concrete evidence or verifiable facts to the contrary, the Appellant's contentions are not properly substantiated.

It derives therefrom that the Board has no reason to doubt that the technical problem as defined above has not been solved within the whole claimed area.

5.4 It remains to be decided whether or not, the claimed solution to the above defined technical problem is obvious in view of the cited prior art. The question

arises, in particular, whether the person skilled in the art would have modified the oxidation step and the dissolution and reprecipitation step as disclosed in document (5) to arrive at a process within the scope of Claim 1.

5.5 As set out above (see points 4.1 to 4.3), the process of document (5) starts from the carboxylate salt of formula VIII. In that respect, the Appellant's arguments that the carboxylate of formula VIII is an hypothetical species and that the mechanism of the oxidation works in the process of document (5) as in the claimed process by the protonation of the 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]-benzimidazole is supported by no evidence and can only be considered as a pure allegation. That line of argumentation is also in contradiction with the fact that in the process of document (5), the addition of a base is necessary to destroy the salt of omeprazole formed (see page 22, lines 8 to 12). From document (5) alone, there is, therefore, no hint which could have led the person skilled in the art to perform the oxidation step in the absence of carboxylic acid, namely on the 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]-benzimidazole. On the contrary, this carboxylic acid is in document (5) necessary to form the corresponding carboxylate salt, such species undergoing afterwards the reaction of oxidation.

5.6 Nor can document (8) also relied upon by the Appellant rebut that finding. Indeed, document (8) prescribes to perform the oxidation step in a different solvent, e.g. methylene chloride or toluene, and in the presence of

an aqueous base, such as sodium or potassium hydrogencarbonate (see page 7, lines 1 to 7).

5.7 The Appellant not relying on further documents in order to object to the absence of an inventive step with respect to the oxidation step of the claimed process, the Board is satisfied that none of the aforementioned documents in the proceedings, either individually or in combination, renders the proposed oxidation step obvious.

5.8 Regarding the second step, namely that of purification, the Board concurs with the Respondent's view that the recrystallization of the omeprazole performed according to document (5) in ethyl acetate or acetone, in the presence of an organic base, such as triethylamine (see page 22, lines 26 to 29), calls on a different procedure not involving HCl for the precipitation step.

Even though in the dissolution and reprecipitation process disclosed in document (8), the precipitation of omeprazole is performed by lowering the pH of the solution of omeprazole through addition of an acid such as HCl, the Board sees no reason why the person skilled in the art would have found in document (8) the relevant information to add HCl in the precipitation step of the process of document (5). Indeed document (8) describes the dilution of omeprazole in an alkaline aqueous phase (see page 7, lines 8 to 12) as opposed to an organic phase containing an organic base used in document (5). The conditions in both documents being thus clearly different, they cannot be combined. Nor would the person skilled in the art have found that information in the other documents cited. Indeed,

document (6) discloses a precipitation of omeprazole in ethyl acetate, without the presence of acid (see example 3), document (7) discloses the precipitation of omeprazole from an aqueous phase due to the adding of an alkyl formate (see col. 1, lines 54 to 58) and document (9) discloses the precipitation of omeprazole in methyl cyanide (see example 1, page 12).

5.9 In conclusion, the subject-matter of Claim 1 represents a non-obvious solution to the technical problem defined above and for this reason Claim 1 involves an inventive step in the sense of Article 56 EPC.

6. *Procedural matters*

Since the Appellant did not challenge the decision of the Opposition Division to reject the new ground of opposition under Article 100b) EPC (see point VIII above) and since the Proprietor of the patent did not give his approval for this ground to be considered and since such an approval cannot be presumed, the Board can only take note that this ground of opposition is not part of the scope of the appeal (see G 10/91, OJ EPO 420, Order, point 3).

## Order

**For these reasons it is decided that:**

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent with the claim filed with the proprietor's letter dated 8 December 2006 and the description as granted.

The Registrar The Chairman

N. Maslin A. Nuss