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D E C I S I O N
of 29 September 1999

Case Number: T 0055/99 - 3.3.2

Application Number: 95306049.8

Publication Number: 0704214

IPC: A61K 31/425

Language of the proceedings: EN

Title of invention:
Process for treating nizatidine

Applicant:
Eli Lilly and Company

Opponent:
-

Headword:
Nizatidine/ELI LILLY

Relevant legal provisions:
EPC Art. 54, 56, 123(2)

Keyword:
"Novelty -yes"
"Inventive step - yes"

Decisions cited:
-

Catchword:
-

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Case Number: T 0055/99 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 29 September 1999

Appellant: Eli Lilly and Company
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 15 September 1998 refusing European patent application No. 95 306 049.8 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: J. Riolo
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent application No. 95 306 049.8 published under No. 0 704 214 was refused by a decision of the Examining Division posted 15 September 1998 on the grounds of lack of novelty.

II. The decision was based on the set of 17 claims as originally filed. Claims 1, 5, 16 and 17 read as follows:

"1. A pharmaceutical composition of nizatidine, in which the nizatidine has been heated in the presence of water to remove N-methyl-1-methylthio-2-nitroethyleneamine.

5. A process for preparing a form of nizatidine, which comprises heating nizatidine containing N-methyl-1-methylthio-2-nitroethyleneamine in the presence of water to remove said N-methyl-1-methylthio-2-nitro-ethyleneamine.

16. The form of nizatidine prepared by the process of Claim 5.

17. A form of nizatidine which contains N,N'-bis[2-[[[2-[2-(dimethylamino)methyl]-4-thiazole]methyl]-thio]ethyl]-2-nitro-1,1-ethenediamine and N,N'-dimethyl-2-nitro-1,1-ethenediamine, but not N-methyl-1-methylthio-2-nitroethyleneamine."

III. The following documents were cited inter alia during the proceedings before the Examining Division and during the written proceedings before the Board of

Appeal:

(6) US-A-4 375 547

(7) Package insert for the drug Axid®, 13 October 1993

(8) US-A-4 904 792

IV. According to the decision under appeal, the Examining Division was of the opinion that the use of the term nizatidine in the claims implied that a pure compound was meant. Accordingly, no attention was paid to any restrictive feature in the product claims for the assessment of novelty. No attention was paid either to the result to be achieved in the process claims. As a result, novelty objections were raised against all the claims, except dependent claims 7 and 8, with respect to documents (4) EP-A-515121 and (5) EP-A-230127. Documents (4) and (5) disclosing nizatidine were regarded as novelty-destroying for the product claims and document (5) was also regarded as novelty-destroying for the process claims as the preparation of nizatidine involved the presence of water.

V. The appellant (applicant) lodged an appeal against this decision and requested that the decision under appeal be set aside and that the patent be granted on the basis of the set of claims as originally filed or alternatively on the basis of three auxiliary requests.

The appellant contested the construction put on the claims by the Examining Division. He argued that as a matter of technical reality drugs were mixtures and that a person skilled in the art of pharmaceutical

product manufacturing would therefore construe the term "nizatidine" used in the claims to mean a real product, not a "pure" chemical compound.

As regards the technical contribution of the invention the appellant argued as follows:

The present application provided a new and non-obvious solution to the problem of the "mild sulfur-like odour" present in the drug named axid®, ie a trade name for nizatidine.

According to the description in the package insert of this drug, which represented the closest state of the art, "nizatidine has a bitter taste and mild sulfur-like odour".

The solution provided to this technical problem comprised heating nizatidine (having a mild sulfur-like odour) in water until the odour has gone.

This solution was not known in the art nor obvious. The reason why nizatidine in axid® has a mild sulfur-like odour was moreover not known. The application also provided an explanation for the mild sulfur-like odour, recognizing that the water degradation of the N-methyl-1-methylthio-2-nitroethyleneamine present in axid® was responsible for the odour.

VI. In a communication of the Board dated 16 February 1999, it was pointed out that, even when constructing the claim as suggested by the appellant, none of the four sets of claims could be regarded as novel because neither the product claims nor the process claims

contained any distinguishing features over the prior art.

VII. With his answer to a further communication of the Board by telephone, the appellant filed on 26 August 1999 a new set of claims 1 to 11 and an adapted description as a single request replacing all the previous ones.

Independent claim 1 reads as follows:

"1. A process for preparing a form of nizatidine, which comprises heating nizatidine containing N-methyl-1-methylthio-2-nitroethyleneamine in an amount up to 5,000 ppm in the presence of water until said N-methyl-1-methylthio-2-nitroethyleneamine has been removed."

VIII. The appellant requested that the decision under appeal be set aside and that the patent be granted on the basis of the set of claims 1 to 11 filed on 26 August 1999 and the adapted description according to the pages filed with his letter on 26 August 1999 and 28 September 1999.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123(2)*

Independent claim 1 corresponds to claim 5 as originally filed in combination with the feature of its dependent claim 12 as originally filed. Moreover the wording "... heated ... to remove said N-methyl-1-

methylthio-2-nitro-ethyleneamine" has been replaced by the equivalent wording "... heated ... until said N-methyl-1-methylthio-2-nitro-ethyleneamine has been removed".

Dependent claims 2 to 10 are respectively identical to claims 6 to 11, 13 to 15 as originally filed.

Claim 11 is based on the disclosure on page 5, line 34 to page 6, line 8 of the description as originally filed.

Consequently the requirements of Article 123(2) EPC are met.

3. *Clarity*

Concerning the interpretation of the term "nizatidine" in claim 1, the Board points out that, for an organic chemist, the meaning of this term is not limited to the conceptual chemical structure named, for instance, N-methyl-N'-[2-(2-dimethylaminomethylthiazole-4-ylmethylthio)-ethyl]-2-nitro-1,1-ethenediamine. It does indeed also encompass the generic name for the drugs which are commercially sold (ie the real products).

Using the term in its fullest sense, claim 1 fulfils the requirements of Article 84 EPC.

4. *State of the art*

In the set of claims under consideration, the original product claims have been deleted. The documents of the state of the art on which the novelty objections

pursuant to the product claims were based have therefore lost most of their relevance.

With respect to the process claims, documents (6) to (8) are the most relevant prior art. Document (6) is referred to in the description of document (5), which was mentioned in the decision of the first instance. It has moreover been cited during the appeal procedure in the first communication of the Board against the previous requests. Document (8) is acknowledged in the description of the application in suit and its relevance has been emphasized by the applicant in his last reply.

5. *Novelty*

In the closest prior art process, which according to the appellant, is used for the preparation of axid® of document (7) and which is disclosed in Example 5 of document (6), 40.7 g of N-methyl-1-methylthio-2-nitro-ethyleneamine (ie 273 mM) are reacted in water and heated for about four hours to produce nizatidine.

From this reaction step, the skilled person will deduce that nizatidine containing N-methyl-1-methylthio-2-nitro-ethyleneamine has already been heated in the presence of water. It is however clear from the reaction conditions that the amount of N-methyl-1-methylthio-2-nitro-ethyleneamine present in the reaction mixture will always be much greater than 5.000 ppm with respect to nizatidine.

As a matter of fact, only 49.5 g of nizatidine are obtained under the working conditions of Example 5 (ie

149 mM). This implies that the amount of unreacted N-methyl-1-methylthio-2-nitro-ethyleneamine present with nizatidine in the water at the end of the reaction is well above 5,000 ppm (273 mM - 149 mM = 124 mM, ie 18.35 g, ie 37%).

Consequently, the process feature of heating nizatidine containing up to 5,000 ppm of N-methyl-1-methylthio-2-nitro-ethyleneamine in the presence of water is not to be found either in the closest prior art process or in the other available documents which are not concerned with the removal of **residual** amounts of N-methyl-1-methylthio-2-nitro-ethyleneamine either.

As none of the cited documents recites this process feature, no novelty objection under Article 54 EPC applies to independent claim 1 and its dependent claims 2 to 11.

6. *Inventive step*

The application concerns a process for purifying nizatidine, a drug used in treatment of duodenal ulcers, according to claim 1.

According to the description of the application, pharmaceutical compositions of nizatidine sold under the trade mark axid® emit a sulfur-like odour (page 2, lines 7 to 15).

Document (7), the package insert for the drug axid®, recites indeed that nizatidine has a mild sulfur-like odour.

The Board agrees with the applicant that document (7) can be regarded as the closest prior art.

For the comfort and the interest of the patient it is, as a rule, always desirable to find out the most effective as well as the most pleasant formulation for a pharmaceutical drug.

Sulfur-like odours are usually very unpleasant, especially in oral formulations such as tablets or capsules.

Accordingly, the present problem can be seen in the provision of a solution to the "mild sulfur-like odour" present in the drug named axid® in order to facilitate its ingestion by sensitive patients.

The problem is solved by the process according to claim 1, and in the light of working Example 1 of the application the Board is satisfied that the problem has been solved.

Thus, the question to be answered is whether the proposed solution, ie heating nizatidine containing up to 5,000 ppm of N-methyl-1-methylthio-2-nitro-ethyleneamine in the presence of water, was obvious for the skilled person in the light of the prior art.

Document (7) does not mention the process for preparation of axid®. With his letter dated 25 August 1999, the appellant therefore informed the Board that the process used for the preparation of axid® was in fact analogous to the one disclosed in Example 5 of document (6), which is moreover identical to Example 5

of document (8) acknowledged in the introduction of the application.

The Board notes that Example 5 of document (6) merely illustrates the use of water as a **reaction solvent**, that the purification step used in the process is based on common recrystallisation techniques and that the document is silent about any sulfur-like odour in the purified product.

As regards the latter point, the appellant pointed out in his letter of 16 April 1999 that the odour problem arose only after the product had been formulated probably due to a degradation reaction between N-methyl-1-methylthio-2-nitro-ethyleneamine and water, and that it did not manifest with the bulk drug.

Under these circumstances, the Board concludes that document (6) cannot give any hint towards the claimed solution since the skilled person would have not been aware of any problem when reading this document.

To end up at the present solution the skilled person is, in fact, faced with two distinct problems. He must first identify among the various impurities and by-products present in axid® the compound which is responsible for the sulfur-like odour and he must then find out a process to selectively remove it in order to prevent its degradation.

Since it is not the product N-methyl-1-methylthio-2-nitro-ethyleneamine itself which has the sulfur-like odour but one of its degradation products, this first step is rendered even more complicated by the fact that

the degradation product might be structurally very different. The question of the chemical structure of this precursor therefore also needs to be solved before looking for any selective purification process.

The available prior art documents do not contain the slightest information about the degradation of N-methyl-1-methylthio-2-nitro-ethyleneamine generating a sulfur-like odour and even less about its selective removal by heating in the presence of water. In the light of the available prior art, N-methyl-1-methylthio-2-nitro-ethyleneamine is only known as a useful reagent for the preparation of nizatidine and the selective purification process used in the application does not appear to be a usual one.

The Board also notes that the drug axid® has been brought to the market despite its unpleasant sulfur-like odour. Having regard to the long period of time which elapses between the formulation of a pharmaceutical compound and its marketing, this can be regarded as a further indication in favour of the presence of an inventive step.

In view of the foregoing the Board judges that the subject-matter of claim 1 and its dependent claims 2 to 11 involves an inventive step as required by Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent with the title "process for treating nizatidine" in the following version:

Claims: 1 to 11 filed on 26 August 1999.

Description: pages 2, 4, 9 to 13 as originally filed.
page 1 filed on 28 September 1999
pages 3, 5 to 8 filed on 26 August 1999.

The Registrar: The Chairman:

E. Görgmaier P. A. M. Lançon