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D E C I S I O N
of 10 February 2004

Case Number: T 0524/00 - 3.3.2

Application Number: 91500066.5

Publication Number: 0519144

IPC: A61K 9/54

Language of the proceedings: EN

Title of invention:

New galenic process for omeprazole containing pellets

Patentee:

ILSAN ILAC VE HAMMADELERI SANAYI A.S.

Opponent:

AstraZeneca AB
ETHYPHARM

Headword:

Process for Omeprazole pellets/ILSAN ILAC VE HAMMADELERI A.S.

Relevant legal provisions:

EPC Art. 56

Keyword:

"Inventive step - no: obvious combination of prior art teachings"

Decisions cited:

-

Catchword:

-



Case Number: T 0524/00 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 10 February 2004

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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 7 April 2000
revoking European patent No. 0519144 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
P. Mühlens

Summary of Facts and Submissions

- I. European patent No. 0 519 144 based on international application No. 91 500 066.5 was granted on the basis of three claims.

Independent claim 1 as granted read as follows:

"1. A production method for pellets containing Omeprazole, wherein the pellets are finally filled into a gelatine capsule, characterized in that the process consists of the following steps:

- preparation of an inert core including 65-85% of saccharose, 15-25% of starch and 2-66% of glucose, being sieved through a mesh within 0.71 and 0.85 mm,
- micronizing and sieving the active substance containing Omeprazole through a 150 mesh sieve and dispersing it in a buffered aqueous dispersion at pH = 7.1 +/- 0.1% with the addition of an anionic surface active agent,
- spraying said dispersion comprising the active substance onto the inert core pellets in the cabin of a rotary type fluidized machine,
- protective coating with HPMC in the cabin of a rotary type fluidized bed machine,
- enteric coating with HPMC phthalate, diethyl phthalate, acetone and ethyl alcohol by using a rotary type fluidized bed,
- drying to obtain a water content of less than 1 %."

- II. Oppositions were filed against the granted patent by respondent 1 (opponent O1) and respondent 2 (opponent O2). The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step.

The following documents were cited *inter alia* during the proceedings before the Opposition Division and the Board of Appeal:

(1) GB-A-2 189 698

(5) EP-A- 277 741

(6) Pharma International, n° 2/84 (1984), pages 1, 70-77

(14) L.S.C. Wan et al., Int. J. of Pharmaceutics 88 (1992), pages 159-163.

III. By its decision pronounced on 1 March 2000, the Opposition Division revoked the patent under Article 102(1) EPC.

The Opposition Division refused a main request containing an amended claim 1 as inadmissible within the meaning of Rule 57a EPC. As regards the first auxiliary request (patent as granted) and the second auxiliary request (combination of claims 1 and 2 as granted), the reasons may be summarised as follows:

The Opposition Division had no objection with respect to Article 123 EPC.

Moreover, the Opposition Division held that novelty objections were not maintained by the opponents during the oral proceedings and also considered that the patent as granted was novel over the available prior art.

As for inventive step, the Opposition Division regarded document (1) as the closest prior art and saw the problem underlying the patent in suit in a simple and economic process for providing a stable Omeprazole preparation.

It concluded however that the subject-matter of the patent in suit was obvious over the combination of document (1) with document (6).

In its view, the only essential difference to be seen in document (1) over the subject-matter of the process according to the patent in suit lay in the fact that in this document the drug was dispersed in a core comprising additives usually used in pellets, whereas in the contested patent the drug together with said additives was coated on an inert core (nonpareil), and that in the contested patent all coating steps were carried out in a rotary type fluidized bed machine.

As, in the Opposition Division's opinion, the skilled person would have regarded the "nonpareil" method as an obvious alternative, disclosed, and even recommended for low dosage drugs, in document (6), in order to prepare stable pellets containing the "low dose drug" Omeprazole and since the use of rotary type fluidised bed machine and the other distinguishing features of the claimed process amounted merely to a juxtaposition of obvious and well-known features, it considered that the patent did not fulfil the requirements of Article 56 EPC.

IV. The appellant (patentee) lodged an appeal against the said decision.

V. Oral proceedings were held before the Board on 10 February 2004.

During the appeal proceedings, the appellant filed a main request and an auxiliary request.

Independent claim 1 of the set of claims of the main request reads:

"1. A production method for pellets containing Omeprazole, wherein the pellets are finally filled into a gelatine capsule characterized in that the process consists of the following steps:

- preparation of an inert core including 65-85% of saccharose, 15-25% of starch and 2-6% of glucose, being sieved through a mesh to be 90% within 0.71 and 0.85 mm,
- micronizing and sieving the active substance containing Omeprazole through a 150 mesh sieve and dispersing it in a buffered aqueous dispersion at pH = 7.1 +/- 0.1% with the addition of an anionic surface active agent,
- spraying said dispersion comprising the active substance onto the inert core pellets in the cabin of a rotary type fluidized bed machine,
- protective coating with HPMC in the cabin of a rotary type fluidized bed machine,
- enteric coating with HPMC phthalate, diethyl phthalate, acetone and ethyl alcohol using a rotary type fluidized bed machine,
- drying to obtain a water content of less than 1 %."

Independent claim 1 of the set of claims of the auxiliary request reads:

"1. A production method for pellets containing Omeprazole, wherein the pellets are finally filled into a gelatine capsule characterized in that the process consists of the following steps:

- preparation of an inert core consisting of 65-85% of saccharose, 15-25% of starch and 2-6% of glucose, being sieved through a mesh to be 90% within 0.71 and 0.85 mm,

- micronizing and sieving the active substance containing Omeprazole through a 150 mesh sieve and dispersing it in a buffered aqueous dispersion at pH = 7.1 +/- 0.1% with the addition of an anionic surface active agent,

- spraying said dispersion the content of active dispersion phase for one dose (capsule with a capsule content of 233 mg +/- 10%) is as follows: 20 mg Omeprazole, 5.3 mg hydroxypropylmethylcellulose, 8 mg lactose anhydrous, 6 mg L-hydroxypropyl-cellulose, 0.5 mg sodium lauryl sulphate, 0.8 mg disodium hydrogen phosphate dihydrate and 0.21 ml water onto the inert core pellets in the cabin of a rotary type fluidized machine,

- protective coating with HPMC with an amount of coating material per capsule of 3.4 mg HMPC and 0.06 ml water in the cabin of a rotary type fluidized bed machine,

- enteric coating by spraying the following coating solution 24 mg HPMC phthalate, 0.13 mg diethyl phthalate, 225 mg acetone and 96 mg ethyl alcohol using a rotary type fluidized bed machine,

- drying to obtain a water content of less than 1 %."

VI. The appellant submitted that the skilled person would not combine documents (1) and (6) because, as apparent from document (14), Omeprazole in the amount as used in the contested patent would not be considered as "a low dose" drug.

Moreover, it argued that, having regard to the high acid lability of Omeprazole, there was a technical prejudice which would prevent the skilled person trying to prepare pellets with the active substance on the outside of the inert core and without mixing it with an alkaline reactive compound.

Finally, it also stressed that the product obtained by the claimed process was, in fact, more homogeneous than the prior art product according to (1) and that the yield of the active ingredient was higher.

VII. In summary, respondents 1 and 2 (opponents O1 and O2) argued mainly that the combination of document (1) and (6) was, in fact, a straightforward combination and that the beneficial merits of the process added nothing to the assessment of inventive step as they were merely the foreseeable and known result linked to the use of the "nonpareil" methodology.

VIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main or auxiliary request filed in the oral proceedings.

Respondents 1 and 2 requested that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.
2. No objections with respect to Articles 123, 84 and 54 EPC were raised against the main and auxiliary requests and the Board sees no reason to differ.
3. *Main request*

Inventive step

The appellant's submissions relating to inventive step over the combination of documents (1) and (6) made during the oral proceedings do not contain any new matter not properly dealt with in the Opposition Division's decision.

The Board therefore agrees with the Opposition Division's reasoning and conclusions as to inventive step of the subject-matter of the patent in suit over the available prior art documents (see Opposition Division's decision, pages 7 to 11, point 3.3).

In particular, contrary to the appellant's submissions, the Board agrees with the Opposition Division that there is no technical prejudice preventing the skilled person from combining document (6) with (1).

In that respect, it is not correct that, whereas document (1) teaches the use of Omeprazole in admixture with an alkaline reacting constituent in order to prevent acid degradation, the present process solves this problem differently, namely by the use of a buffered aqueous dispersion at pH around 7.

In fact, document (1) not only teaches precisely the same means as the patent in suit, but even gives an example wherein a buffered system similar to the one in the example in the patent in suit is used (see (1), page 2, lines 26 to 40, in particular line 36; example 2, lines 50 to 52: 2000 g Omeprazole, 50 g sodium lauryl sulphate, 80 g disodium hydrogen phosphate; contested patent, page 3, lines 4 to 7: 20 mg Omeprazole, 0.5 mg sodium lauryl sulphate, 0.8 mg disodium hydrogen phosphate).

Moreover, the Board also does not agree that the skilled person would not apply the "nonpareil" method, wherein the drug is dispersed on an inert core instead of being mixed together with the ingredients of the core, because of the instability in an acidic environment of Omeprazole.

In that respect, document (5) discloses the possibility of making "nonpareil" pellets containing Omeprazole (page 3, lines 39 to 44).

It is moreover pointed out that the pellets according to the patent in suit are in fact acid-protected by the same means as the ones disclosed in document (1), ie a protecting coating with HMPC ((1), example 2, lines 60 to 63, page 2, lines 45 to 65).

Accordingly, the Board is convinced that there is no technical prejudice preventing the skilled person from combining document (6) with document (1).

As to the argument relating to the definition of a "low dose drug", it is indeed correct that document (14) recites that "the mixing technique is most important but is difficult to perform for micro dose preparations where the active ingredient represents less than 5% of the total mixture" (page 159, left column, lines 3 to 7).

This does not however mean that a reference to a "low dose drug" implies in any case that the active ingredient must represent less than 5% of the total mixture.

In that respect, it is noted that the amount of 8,6% used in the patent in suit is close to that value and that moreover document (6) clearly teaches that "nonpareil" are also advantageous in case of "high dose drug", the limit being obviously merely that the amount must remain such that the pellets are not too big to be swallowed, as explained by respondent 1 during the oral proceedings (page 75, middle column, lines 21 to 28, and illustration 1).

Again, the Board sees no hindrance to combining the teaching of document (1) with document (6), which shows the advantages of the "nonpareil" method over the method used in document (1).

Finally, as regards the various advantages achieved by the process of the contested patent, it appears that

the skilled person would have expected them in the light of the disclosure in document (6).

It is indeed clear from document (6) that the skilled person can choose any type of inert core as starting material such as for instance pellets having "Ideale Kugelform" (in that respect, the contested patent itself mentions that the inert cores used in the process can be purchased (page 2, line 51). It is therefore not surprising that a homogenous product is obtained when the starting product is a homogenous pellet (page 76, middle column, last two sentences of the first paragraph, table on page 77). In that respect, respondent 2 mentioned during the oral proceedings that it was a well-known fact in the art that "nonpareil" gives a homogeneous product. This was not contested by the appellant.

Concerning the higher yield of the active ingredient Omeprazole in the claimed process, this advantage is also clearly derivable from the disclosure in document (6), which recites that "The weak point [in a process like the one in document (1)] is that the pharmacologically active ingredients are involved in the process from the beginning on. There may be a loss of material by friction and a thermal stress during drying." and "The cylindrical extrudate is transformed to spherical particles by plastic deformation and friction. A disadvantage is a loss of material as dust, but sometimes it is possible to compensate this by recycling." (page 75, middle column, lines 25 to 33, and page 70, middle column, lines 24 to 30. respectively).

Finally, the Board does not contest that the release pattern of the active drug might not be the same in the pellets according to (1) compared to the pellets according to the contested patent.

However, in the absence of any element showing that the skilled person would *a priori* expect some kind of problems with the release pattern of the pellets according to the patent in suit, the Board can see no reason for not trying the promising "nonpareil" formulation disclosed in document (6).

Accordingly, the Board concludes that the subject-matter of the main request does not fulfil the requirements of inventive step as required by Article 56 EPC.

Under these circumstances, there is no need to consider the remaining claims.

4. *Auxiliary request*

As the subject-matter of the auxiliary request corresponds in fact to the subject-matter of the main request, and is merely restricted by the addition of further technical features from the concrete example of the description of the contested patent - additional features which are moreover all disclosed in example 2 of document (1) as far as the nature of the chemical ingredients of the pellets are concerned - the Opposition Division's conclusions hold good for this request as well.

As a matter of fact, since the appellant did not provide any additional arguments as to inventive step with respect to these features, this mere juxtaposition of a *priori* usual technical features, which does not lead to any particular technical effect, cannot provide for an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

M. Townend

U. Oswald