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Datasheet for the decision of 11 January 2010

Case Number: T 0715/07 - 3.3.01

Application Number: 01906880.8

Publication Number: 1252170

IPC: C07F 9/58

Language of the proceedings: EN

Title of invention:
Selective crystallization of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium as the hemipentahydrate or monohydrate

Patentee:
THE PROCTER & GAMBLE COMPANY

Opponents:
HEXAL A/S
Egis Gyogyszergyar RT.

Headword:
Hydrates of sodium risedronate/PROCTER & GAMBLE

Relevant legal provisions:
EPC Art. 123(2)(3)

Keyword:
"Main Request - Inventive step (no) - obvious solution"
"First auxiliary request - Remittal (yes) - not discussed before the first instance"

Decisions cited:
T 0181/82

Catchword:
-

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Case Number: T 0715/07 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 11 January 2010

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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 19 February 2007 concerning maintenance of European patent No. 1252170 in amended form.

Composition of the Board:

Chairman: C. M. Radke
Members: J.-B. Ousset
D. S. Rogers

Summary of Facts and Submissions

I. The appellant (opponent I) lodged an appeal against the interlocutory decision of the opposition division to maintain the European patent No. 1 252 170 on the basis of the second auxiliary request.

II. The following documents were *inter alia* cited:

E1 Center for Drug Evaluation and Research - Application number: 020835, Chemistry Review(s), 5 pages

E5 Journal of Organic Chemistry, G.R. Kieczykowski et al. vol. 60, (1995), 8310-9312

E12 US-A-4 687 767

H5 EP-B-0 186 405

H8 Internet information on "Annual Report 1998" retrieved under the address: http://www.archive.hoechst.com/txt_e/publikationen/gb98/lsl.html on 12 May 2005, 3 pages.

H10 Package Insert Text ACTONEL®, Procter and Gamble Pharmaceuticals, revised April 2000, 21 pages.

H11 Report of Kenny Ståhl: "Assessment of X-ray powder diffraction patterns from sodium residronate on behalf of Gea Pharmaceuticals A/S", dated 15 June 2007, 14 pages .

H15 Letter of the US Department of Health and Human Services dated of 21 May 1998 (2 pages) and annexed thereto the Approval Package for ACTONEL® from the "Center for Drug Evaluation and Research" (7 pages) in response to the request of FOI Services, Inc (1 page) dated of 14 April 1998.

H16 Email correspondence between J.S. Bennekou and C. Lagerquist, 21-23 May 2007, 2 pages.

III. Claims 1 and 9 of the second auxiliary request considered as patentable by the opposition division read as follows:

"1. A process for selectively producing 3-pyridyl-1-hydroxyethlidene-1,1-bisphosphonic acid sodium hemipentahydrate and monohydrate comprising the steps of :
a) providing an aqueous solution of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium;
b) heating the aqueous solution to a temperature from about 45°C to about 75°C;
c) adding a solvent to the aqueous solution characterized in that the solvent is selected from the group consisting of alcohols, esters, ethers, ketones, amides, and nitriles; and
d) optionally cooling the aqueous solution."

"9. A pharmaceutical composition comprising 3-pyridyl-1-hydroxyethlidene-1,1-bisphosphonic acid sodium characterized in that the composition contains both 3-pyridyl-1-hydroxyethlidene-1,1-bisphosphonic acid sodium hemipentahydrate and 3-pyridyl-1-hydroxyethlidene-1,1-bisphosphonic acid sodium monohydrate, and in that the 3-pyridyl-l-hydroxyethlidene-1,1-bisphosphonic acid sodium is about 50% or more hemipentahydrate and about 50% or less monohydrate."

IV. The opposition division decided that:

- Claim 9 of the second auxiliary request met the requirements of Article 123 (2) and (3) EPC.

- The subject-matter of the claims of the second auxiliary request was novel. The alleged prior use based on the marketed compound Actonel® was not convincingly shown by the opponent. The opposition division considered document H8 as the closest prior art and decided that the claimed subject-matter involved an inventive step.

V. During the written part of the appeal proceedings, the respondent-proprietor maintained the second auxiliary request held patentable in the decision under appeal as its main request (see point III above). Claims 1 to 8 of the first auxiliary request were submitted during oral proceedings before the board. These claims were identical to claims 1 to 8 of the main request, that is to claims 1 to 8 of the claims 1 to 10 of the second auxiliary request maintained by the opposition division.

VI. The appellant's (opponent I's) arguments which are relevant for the main request may be summarized as follows:

- Claim 9 contravened the requirements of Article 123(2) and (3) EPC, since the word "both" was not present in the originally filed application document as well as the expressions "or more" and "or less". It contended that "both" cannot extend beyond the meaning of the word "and" found on page 1, line 13 of the application as originally filed. Moreover, the expressions "or more" and "or less" were open-ended definitions and still embraced the values 100% and 0%, thus extending the claimed protection of the claims as granted.

- Novelty of the subject-matter of claim 9 was disputed on the basis of document H15 (corresponding to E1 submitted during opposition procedure), which disclosed the hemipentahydrate of the 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium (HPH) and was made available to the public in 1998. In order to show that the monohydrate of 3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium (MH) was also present, it was referred to document H10, in which was mentioned that Actonel® contained not only the HPH but also small amounts of MH (see paragraph "Description" on page 1). Document H16 was also cited to show that the composition of the drug made available to the public in 1999 remained unchanged until 2004. Furthermore, in document H11 were displayed different X-rays spectra corresponding either to placebo tablets containing the non active ingredients of the tablet core as well as tablets comprising in addition 35 mg of HPH of which 1, 3 and 5% have respectively been replaced by the MH. It concluded on the basis of the different spectra that the lower limit of detection of MH was 5% and thus the person skilled in the art would have been able to detect this small amount present in Actonel® according to document H10. As to the production of the MH, the person skilled in the art would have considered document H21 and would have applied the procedure for producing the olpadronate in this document to the formation of the MH.

- Inventive step of claim 9 was questioned on the basis of H15 as the closest prior art. No advantage was shown for the claimed composition and the MH, being less stable than the HPH, would bring instability into the final tablet, thereby reducing the shelf life. In the absence of a beneficial effect, the problem might only be seen in the provision of an alternative composition of sodium residronate hydrates. The person skilled in the art would have arrived at this composition without any inventive skill in view of its knowledge as mentioned in [0005] of the patent in suit.

VII. The arguments of the respondent (patent proprietor) can be summarized as follows:

- It was argued that "both" and "and" had the same meaning, namely requiring the presence of both HPH and MH. The basis for the term "or more" and "or less" was to be found in original claim 9 and on page 1, lines 10 to 15, page 2, lines 2 to 3, page 3, lines 28 to 29 of the description as originally filed.

- It was argued that novelty of claims 9 and 10 had to be acknowledged in view of document H15, this document being not enabling, because no process for making the HPH was mentioned and furthermore Actonel® was not analysable. It was further added that, although the file of the FDA was made available to the public on the date of approval, some parts of the file might have been kept secret and there was no proof that the cited part

(document H15) was available to the public on the date of approval. Furthermore, no X-ray spectrum of the MH was disclosed at the priority date of the patent in suit and the one depicted on page 11 of H11 did not show any peak at 6° (2 theta). It was also added that even if the small hump at 6° (2 theta) was to be considered as a peak, one single peak was not sufficient to characterize the presence of the MH.

- In case document H15 would be considered as the closest prior art, then there was no mention of the presence of the MH and thus the person skilled in the art would not have had any reason to add any MH to the HPH. H5 was rather to be seen as the closest prior art, as acknowledged by the opposition division, although it did not identify the MH and did not provide any hint as to the solvates of its salts.

VIII. Opponent II did not submit any written arguments during the appeal proceedings and informed the board that it would not participate at the oral proceedings on 11 January 2010.

IX. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

X. The respondent (patent proprietor) requested that:

- The appeal be dismissed; or
- that if documents E1/H15 were found to be part of the state of the art, the case be remitted to the department of the first instance; or

- that the patent in suit be maintained in an amended form upon the basis of claims 1-8 of the first auxiliary request submitted at the oral proceedings on 11 January 2010.

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. *Added matter*

2.1 The word "both" is not mentioned in the description as originally filed; it means that at least two constituents must be present in the claimed compositions (here the MH and the HPH). The basis for this amendment is found in the expression "compositions containing said hemipentahydrate **and**/or monohydrate" (emphasis added) disclosed in the description as originally filed (see page 1, lines 11 to 14 or page 2, lines 13 to 15). Due to the compulsory presence of these two hydrates, the limits of 0% of MH and 100% of HPH disclosed in original claim 9 are inevitably excluded, so that the terms "50% or more" and "50% or less" have a proper basis in the application as filed.

2.2 This amendment does not extend the scope of the claims as granted because it merely excludes compositions containing the MH or the HPH alone which were included in the scope of the granted claim 9.

2.3 Hence, the claimed subject matter fulfils the requirements of Article 123(2) and (3) EPC.

3. *Document H15*

3.1 The respondent argued that document H15 disclosed the HPH but not its process of preparation. Document E5 could not render the disclosure of document H15 enabling, because document E5 was a scientific article and thus did not form part of the general technical knowledge of the person skilled in the art. Moreover, the respondent (patent proprietor) doubted that all the pages of document E1 "forming part of document H15" were available to the public before the priority date of the patent in suit.

3.2 It is, however, apparent from the correspondence in document H15 that the "Approval Package for Actonel® " was available to the public except for "information...not required to be publicly disclosed" (see page 1 of the letter dated 21 May 1998). Document E1 consists of pages of said Approval Package concerning the active ingredient Actonel®, its dosage form and strength and its pharmaceutical use. This information is of such a general nature that the public health service had no reason or obligation to keep it secret. Hence, it is evident that document E1 indeed formed part of the package enclosed with the letter dated 21 May 1998 and thus became public before the priority date of the patent in suit.

3.3 Document E5 discloses a process for making (2-(3-pyridyl)-1-hydroxyethylidene) bisphosphonic acid hydrate (residronic acid hydrate) (see page 8312,

paragraph bridging the two columns). It also discloses how the pH-value is to be adjusted in order to yield the monosodium salt instead of the acid (see page 8311, right-hand column, the two first paragraphs under the heading "General Procedure for..."). Therefore, it enables the person skilled in the art to produce monosodium residronate and its thermodynamically most stable hydrate, namely HPH (see [0009] of the patent in suit).

Scientific articles such as document E5 are normally not considered to be part of the person skilled in the art's general knowledge. However, document E1/H15 discloses the Chemical Abstracts Registry Number of the HPH (see the second page of document E1, right to the structural formula: "CAS #: 115436-72-1"). Under this number, literature allowing the preparation of the corresponding compound may be retrieved, if available, and thus in the present case document E5. Hence, by means of reference, document H15(E1) discloses a process for preparing HPH.

3.4 The board therefore concludes that document H15(E1) is an enabling disclosure for the compound HPH and thus can be used as a prior art document.

Main request

4. Novelty

4.1 The appellant only considered the subject-matter of claim 9 of the main request not to be novel. The disclosure of document H15 differs from the claimed

subject-matter of claims 9 and 10 in that H15 does not disclose that Actonel® contained MH.

4.2 Document H10 is dated 14 April 2000 and thus cannot give reliable information about the presence of the MH in Actonel® before the priority date of the patent in suit, that is to say before 01 February 2000. The appellant argued that the composition of Actonel® has not been changed until the publication date of document H10 and provided document H16. This document, however, refers to the product "Optinate" rather than to Actonel®. Document H16 thus cannot serve as a basis for this argument. Nor did the appellant provide a chemical analysis of sample of Actonel® bought before the priority date of the patent in suit. (see point 6.2 of the reasons of the decision of the opposition division)

4.3 In view thereof and since the board is unaware of any other cited document mentioning the presence of the MH in combination with the HPH, the novelty of the subject matter of claims 9 and 10 is acknowledged (Article 54 EPC).

4.4 In view of the outcome of this decision on inventive step and remittal, it is not necessary to assess whether or not the subject-matter of claims 1 to 8 is novel.

5. *Inventive step - claims 9 to 10 of the main request*

5.1 Determination of the closest prior art

5.1.1 The appellant considered that document H15(E1) was to be regarded as the closest prior art whereas the

respondent argued that, in accordance with the findings of the opposition division, document H5 was the closest prior art.

5.1.2 Document H5 mentions on page 6, line 26, the specific compound "2-(3-pyridyl)-1-hydroxy-ethane-1,1-diphosphonic acid" and line 54 the corresponding pharmaceutically-acceptable salts of the said compound. On page 7, line 40, sodium salts are cited as pharmaceutically-acceptable salts. However, this document does not relate to hydrates of such salts.

Document H15 relates specifically to HPH (see the paragraph "Chemical names, structural formula, molecular formula, mol. wt." on page 2 of the Approval Package) in a composition (tablets; see "dosage form").

Both documents refer to the use of these salts in pharmaceutical compositions for the treatment of diseases of bone and calcium metabolism (see H15, page 1 of the Approval Package, "Pharmacol. Category/Indication" and H5, page 1, lines 3 to 5).

One of the two hydrated salts mentioned in claim 9 of the patent in suit is disclosed in document H15 whereas H5 does not relate at all to hydrated salts. Therefore, H15 represents the closest approximation to the claimed subject-matter which the person skilled in the art would start from.

5.2 The problem to be solved

5.2.1 Thus, for defining the objective technical problem to be solved in view of document H15, the technical

results or effects successfully achieved by the claimed subject-matter need to be determined.

The respondent (patent proprietor) contended that the pharmaceutical compositions claimed in the patent in suit had good stability and good handling properties. Moreover, good flowing properties of the claimed compositions conferred by the stability of both hydrates could not be deduced from the teaching of the prior art, since none of the cited documents referred to the MH.

Any alleged advantageous effect has to be substantiated by comparison with the closest prior art (T 181/82, OJ EPO 1984, 401). The content of the description as originally filed as well as the respondent's written submissions do not contain any evidence relating to the favourable properties mentioned above allowing a fair comparison with the composition described in document H15. Hence, it is not evident that the problem defined by the respondent (patent proprietor) is solved in view of document H15.

5.2.2 Consequently, a less ambitious problem has to be formulated.

Therefore, the problem underlying the patent in suit can only be seen as the provision of an alternative composition suitable as an active ingredient for the treatment of Paget's disease.

Starting from the disclosure of H15, describing the HPH and seeking to make a further composition retaining the same pharmaceutical properties, the person skilled in

the art knows that bisphosphonates such as residronate are used for treating these diseases. Thus, when adding to the composition of document H15 another hydrate of the same salt (e.g. the MH), it would have expected that the composition would retain the same pharmaceutical properties, since the pharmaceutically active part of the hydrates is identical in both hydrates (residronate) and was known to be useful in the treatment of diseases of bone and calcium metabolism such as Paget's disease (see document H5, page 2, lines 17 to 18). All the more, due to the fact that the hydrate (here the MH) can be added in very small amounts, tending to zero, and thus approaching the disclosure of H15. The addition of very low amounts of the MH to a composition containing the HPH (see H15) to make available alternative compositions useful in the treatment of diseases related to bone and calcium metabolism loss cannot be seen as the result of an inventive approach. The person skilled in the art would have thus expected that such a composition containing a very small amount of the MH would retain the same properties as the ones containing only the HPH (see document H15).

5.3 For these reasons, the subject-matter of claim 9 and dependent claim 10 of the main request is not based on an inventive step (Article 56 EPC).

5.4 The board may only treat a request as a whole. Hence, the main request is refused.

6. *Remittal*

6.1 According to Article 111(1), the board of appeal may exercise any power within the competence of the department of the first instance or remit the case to it for further prosecution.

6.2 The claims of the first auxiliary request are identical to claims 1 to 8 of the second auxiliary request on which the decision under appeal is based. The opposition division held compositions containing both hydrates, HPH and MH, to be novel and inventive and concluded that the subject-matter of process claims 1 to 8 was new and involved an inventive step (see points 8.2 and 8.3 of the reasons of the opposition division decision).

6.3 The board found that document H15 discloses HPH (see point 3.2 above). Hence, the reasons for which the opposition division decided that the subject-matter of claims 1 to 8 was novel and inventive no longer apply. Therefore, novelty and inventive step will have to be reassessed. As far as inventive step is concerned new aspects may be taken into account (see, e.g. document H5, page 7, lines 25 to 36, where an analogue of residronic acid is precipitated from its hot aqueous solution by adding methanol; see also document E12, which discloses a process for making an analogue of residronic acid monohydrate and a standard method for making the respective monosodium salts in column 8, example 1). In this context, it could be necessary to discuss whether or not the temperature range indicated in claim 1 ("from **about** 45°C to **about** 75°C" (emphasis added)) could delimit the claims from the prior art.

6.4 In order to give the respondent (patent proprietor) the possibility to have these points discussed before two instances, the board exercises its discretion under Article 111(1) EPC by remitting the case to the department of the first instance.

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 for further prosecution upon the basis of claims 1-8 of the first auxiliary request submitted at the oral proceedings.

The Registrar The Chairman

B. Atienza Vivancos C. M. Radke