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Datasheet for the decision of 17 April 2009

Case Number: T 0912/06 - 3.3.01

Application Number: 99948994.1

Publication Number: 1121375

IPC: C07J 1/00

Language of the proceedings: EN

Title of invention:
High purity compound
(7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one

Patentee:
N.V. Organon

Opponent:
NORTON HEALTHCARE LTD
Helm AG
Industriale Chimica S.R.L.
Zentiva a.s.
TECNIMEDE

Headword:
High purity tibolone/N.V. ORGANON

Relevant legal provisions:
EPC Art. 100(a), 56, 54(2)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request - novelty (no)"
"Auxiliary requests 1 and 2 - inventive step (no)"
"No improvement - obvious alternative solution"

Decisions cited:
T 0150/82, T 0181/82, T 0197/86, T 0487/89, T 0728/98, T 0990/96

Catchword:
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Case Number: T 0912/06 **-** 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 17 April 2009

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 7 April 2006 revoking European patent No. 1121375 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. Ranguis
Members: J.-B. Ousset
D. S. Rogers

Summary of Facts and Submissions

I. The appellant (patent proprietor) lodged an appeal against the decision of the opposition division revoking the European patent No. 1 121 375.

II. Claim 1 of the main and first auxiliary requests before the Opposition Division read as follows:

"1. A high purity compound (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, characterized in that said compound comprises (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5%."

Claim 1 of the second auxiliary request before the Opposition Division read as follows:

"1. A high purity compound (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (tibolone) comprising (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (OM38) in an amount less than 0.5% obtainable by a process wherein crystals of tibolone are allowed to age in the presence of water for at least 24 hours."

Claim 1 of the third and fourth auxiliary requests before the Opposition Division read as follows:

"1. A process for preparing a high purity compound (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (tibolone) comprising (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (OM38) in an amount less than 0.5%, characterized in that crystals

of tibolone are allowed to age in the presence of water for at least 24 hours."

III. Oppositions were filed against the patent in suit for lack of novelty and inventive step (Article 100(a) EPC), insufficiency of disclosure (Article 100(b) EPC) and on the ground that the subject-matter of the patent in suit extended beyond the content of the application as originally filed (Article 100(c) EPC).

IV. The oppositions were supported inter alia by documents:

(1) EP 0 389 035
(5) N.P. van Vliet et al. Rechl. Trav. Pays-Bas, 1986, 105, 111-115.
(16) W. Alexeev, "Analise Quatitativa" Lopes da Silva Editora, 1983,

V. The opposition division considered that:

- neither the subject-matter of claim 1 of the granted set of claims (main request) nor that of claim 1 of the first auxiliary request was novel in view of the disclosure of document (1) and on the basis of the conclusions of the decisions T 990/96 (OJ EPO 1998, 489) and T 728/98 (OJ EPO 2001, 319) that the purity of a low molecular compound may normally not be considered to represent a new feature over prior art describing such compound.

- claim 1 of the second auxiliary request did not contain any further distinguishing technical

feature with respect to claim 1 of the main request. It was therefore not novel.

- Claim 6 of the third auxiliary request was lacking novelty in view of the disclosure of document (1).

- claim 1 of the fourth auxiliary request was considered as not inventive starting from document (1) or document(5) and in combination with document (16), the latter representing the person skilled in the art's common general knowledge.

VI. Oral proceedings took place before the board on 17 April 2009. At the beginning of these oral proceedings, the appellant was invited by the board to resubmit its auxiliary requests. The respondent declared that its previous main and first auxiliary requests were abandoned and requested that the procedure should be continued on the following main, first and second auxiliary requests:

Claim 1 of the main request reads as follows:

"1. A high purity compound (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (tibolone) comprising (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (OM38) in an amount less than 0.5% obtainable by a process wherein crystals of tibolone are allowed to age in the presence of water for at least 24 hours."

Claim 1 of the first auxiliary request read as follows:

"1. A process for preparing a high purity compound (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (tibolone) comprising (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (OM38) in an amount less than 0.5%, characterized in that crystals of tibolone are allowed to age in the presence of water for at least 24 hours."

Claim 1 of the second auxiliary request is identical to claim 1 of the first auxiliary request.

VII. The appellant argued for the novelty and inventive step of the main request as follows:

- the conclusions of the decisions T 990/96 (op. cit.) and T 728/98 (op. cit.) on inventive step and the degree of purity of low molecular compounds were not applicable to the present case, because the tibolone as well as the pharmaceutical dosages containing it had both a high chemical purity and an excellent stability. This new feature of improved stability should be read into claim 1 in view of the content of the description.

- columns 2 of table 2 and table 3 of the patent in suit and more particularly the amounts of OM38 after 6, 12 and 18 months showed an improved storage stability for compounds in accordance with the patent in suit (table 3) but also a lack of correlation between purity and stability, since at "month 0", the amount of OM38 was identical in both samples.

- the data displayed in the different tables of the patent in suit did show a high purity for the claimed compounds. The process of the invention rendered the tibolone obtained more stable to chemical degradation.

- the claimed tibolone as well as the compositions containing them distinguished themselves from the tibolone of the prior art in that they have a high purity (amount of initial OM38) and an excellent stability (low rate of formation of OM38 by storage). The feature stability was not disclosed in the prior art.

- the process of the invention made tibolone more resistant to degradation and allowed the preparation of tibolone more stable than the one obtained by a method of synthesis.

- the pharmaceutical dosages were different from the ones of the prior art due to the presence of tibolone with high purity in term of OM38 and an excellent stability in terms of improved storage by a low rate of formation of OM38.

- the problem of providing tibolone of high purity and stability in terms of presence of OM38 was not addressed in the prior art. Therefore, an inventive step was to be acknowledged.

- document (1) neither mentioned the presence of OM38 as an impurity nor were stability data provided in document (1). The problem of providing

a high purity tibolone and pharmaceutical dosages containing it having a decreased rate of formation of OM38 was solved in view of examples 1 and 2 of the patent in suit. The data of the patent in suit showed an improvement in stability, which was not to be expected in view of the disclosure of document (1). Further data were provided with the statement of the grounds of appeal to show the presence of this improved stability (examples 7 and 8).

- the presence of the term "obtainable by" is to be allowed, since there is no other means to define the compound and since the compound fulfilled the requirements of patentability (see T 150/82 OJ EPO 1984, 309 and T 487/89). This term constituted a causal relationship with the properties of the tibolone in terms of high purity and improved stability. These properties were technical features of the tibolone. The data provided with the statement of grounds of appeal, along with examples 1 and 2 and Tables 1 to 3 of the patent in suit showed that the compound of claim 1 was to be distinguished from the prior art by a physical property, namely improved stability. The absence of any suggestion in the prior art of such stability rendered the claimed invention non-obvious. For all these reasons, novelty and inventive step of the main request should be acknowledged.

As to the presence of an inventive step for the process claims, the appellant argued that:

- the problem to be solved by the patent in suit was considered as the provision of an alternative process for making tibolone, which provided advantages. The process described in document (1) only mentioned that the suspension obtained by pouring the tibolone in water was stirred for 15 minutes before filtration but did not mention the aging of the tibolone for at least 24 hours in the presence of water. After 15 minutes, all the tibolone was crystallized and there was no need to wait longer. The aging process of the patent in suit required that tibolone remained in the presence of water, the latter being an anti-solvent, to obtain the compound in high purity and with an improved stability. This was not to be deduced from document (1). An unexpected effect was shown by the examples 7 and 8. The claimed process was different from the process of document (1), since a further step (aging in the presence of water) was added in the patent in suit and improved properties resulted from this step. An inventive step was thus to be acknowledged.

VIII. The respondents (opponents) argued as follows:

- document (1) described tibolone as a pure crystal and more particularly example 3 of document (1), which mentioned a purity of 100% for the crystalline form I of tibolone. Pharmaceutical carriers were also mentioned in document (1) and also anticipated the composition claims of the patent in suit. Novelty of the process-claims was not questioned.

- starting from document (1), which disclosed a process differing from the claimed process only by the time of aging, the problem was considered as an alternative method to provide tibolone crystals with the same purity as the ones of document (1). The absence of any surprising technical effect obtained by the aging process rendered the claimed process not inventive.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted upon the basis of the main request or upon the basis of the first or second auxiliary request, all submitted during oral proceedings.

X. The respondents requested that the appeal be dismissed.

XI. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Novelty*

2.1 Document (1) describes pure forms of crystalline tibolone (see page 2, lines 45 to 48). Moreover, example 3, relating to example 2 disclosing a process to prepare crystalline tibolone, describes that a crystalline form I of tibolone is obtained with a

purity of 100%, the latter determined by means of diffuse reflectance infrared Fourier transform (DRIFT)). Similarly, example 5 on page 4 also describes a process, which leads to a crystalline form II of the tibolone having a purity of 100%.

2.2 The appellant mainly submitted that OM38 was the impurity in the tibolone and that the analysis techniques mentioned in document (1), namely X-ray diffraction, ^{13}C-NMR and infra-red were not appropriate for determining the purity of a compound. He also maintained that the "improved stability" is an inherent characteristic of the claimed subject-matter and referred to paragraphs [0006], [0011] and [0013] of the patent in suit.

2.3 Example 3 as well as example 5 of document (1) discloses a process to obtain tibolone in a pure form (100% purity). Hence, the content in OM38 of these forms described in document (1) is lower than 0.5% as required for the claimed compound. Therefore, the feature of purity set out in claim 1 of the patent in suit is met by these compounds of document(1). In relation to the "improved stability", the board observes that this feature is not mentioned in the wording of claim 1 of the main request and cannot thus be relevant for distinguishing the claimed subject-matter from the prior art represented by document (1). Indeed, whereas the description can be used to clarify ambiguous terms present in the claims, it cannot be used to read additional features into the claims. The additional feature of Claim 1, namely, "obtainable by a process …", could be considered as a technical feature of the substance claimed provided that it was shown

that the resulting product differs from the compound disclosed in document (1). However none of the examples of the patent in suit may be considered as a reproduction of either example 3 or example 5 of document (1). Likewise examples 7 and 8 submitted with the statement of grounds of appeal are meant to show the improvement due to the aging step but do not reproduce the steps involved in examples 3 and 5 of documents (1). Therefore, no conclusion can be drawn from the evidence submitted by the appellant regarding the novelty of the claimed substance due to its process of preparation. Finally, it is noted that the decisions T 990/96 (op. cit.) and T 728/98 (op. cit.) are irrelevant in the present case, since these decisions relate to an impure compound, whereas 100% pure tibolone is described in the prior art.

2.4 In the absence of any distinguishing technical feature between form I of example 3 and/or form II of example 5 of document (1) and the claimed subject-matter, the board concludes that the latter lacks novelty under Article 54 EPC.

2.5 Since the board can only decide on a request as a whole, the main request is rejected.

First and second auxiliary requests

3. Claims 1 of the first and second auxiliary requests are identical (see point VI above). The board concurs with the respondents that the claimed process fulfils the requirements of Article 123(2) and (3) EPC.

4. *Novelty*

4.1 Claim 1 is distinguished from the disclosure of document (1) in that crystals of tibolone are allowed to age in the presence of water **for at least 24 hours** (emphasis added by the board). It should be noted in that respect that contrary to the appellant's contention, the expression "… in the presence of water …" does not exclude the presence of other solvents. This is actually confirmed by the description of the patent in suit in which the aging step may be carried out in water containing pyridine (see examples 2 and 3).

5. *Inventive step*

5.1 Document (1) recites that form I can be obtained by crystallizing the polymorphous tibolone in a polar solvent (see page 2, last line). This document also discloses that a suitable method of recrystallisation can be performed by dissolving the polymorphous tibolone in acetone or ethanol and then adding this solution to water or adding water to the solution (see bridging part of pages 2, last line to page 3, line 3). Furthermore, a process to make available 100% pure tibolone as crystalline form I is also exemplified in this document (see example 3). Form I so obtained is chemically appreciably more stable than the already known polymorphic compounds. This improvement in stability yields great advantages in respect of the shelf-life of the pharmaceutical product in which form I is incorporated (see page 2, lines 42 to 44). Hence, the difference between the subject-matter of document (1) and the one of the patent in suit lies in the fact

that tibolone is allowed to age in the presence of water for at least 24 hours. The board concurs with the parties that document (1) is the closest prior art.

5.2 Thus, for defining the objective technical problem to be solved in view of document (1), the technical results or effects successfully achieved by the claimed subject-matter need to be determined.

5.2.1 The appellant argued that the data provided with the statement of grounds of appeal (see examples 7 and 8) show an improved stability for the compound obtained after aging in the presence of water for 24 hours at room temperature. In example 7, in which no aging was performed, a stress test at 40°C for one week indicated an increase in the amount of OM38 from 0.3% to 0.6% whereas the same stress test with the compound of example 8, in which an aging of 24 hours at room temperature was performed, indicated that the amount of OM38 was unchanged (0.1%).

5.2.2 However, according to the well-established jurisprudence of the boards of appeal, if comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect, the nature of the comparison with the closest state of the art must be such that the effect is convincingly shown to have its origin in the distinguishing feature of the invention (see T 197/86, OJ EPO 1989, 371, point 6.1.3, referring to T 181/82, OJ EPO 1984, 401, point 5). In the present case, to be relevant, the comparison should have been made with pure form I disclosed in document (1) to show that the product obtained according to the claimed process exhibited an improved stability. It is

undisputed that example 7 does not meet this requirement.

5.3 In the absence of any proven advantages provided by the claimed process vis-à-vis the process disclosed in document (1), the problem underlying the patent in suit can be seen as the provision of an alternative process to make available pure and stable tibolone.

5.4 In view of the examples set out in the patent in suit, the board finds it plausible that the problem has been solved.

5.5 It is thus necessary to investigate whether the person skilled in the art would consider the claimed solution obvious in the light of the cited prior art.

5.5.1 Document (1) teaches that tibolone with a purity of 100% can be obtained after **one hour** by crystallisation of tibolone from a mixture of acetone and water at a temperature of around 5°C (see example 3 in conjunction with example 2).

5.5.2 The board observes that after the one hour crystallisation process in the presence of water described in example 3 of document (1), a 100% pure tibolone is obtained, which according to the teaching of document (1) shows an improved stability. As a consequence, the choice of an aging process of 24 hours in water according to the claimed process is regarded by the board as arbitrary, because the person skilled in the art would in any case arrive at the same result after one hour.

5.6 The board thus concludes that the subject-matter of claim 1 represents an obvious solution to the given problem.

5.7 Since the board can only decide on a request as a whole, the first and the second auxiliary requests are rejected because they do not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chairman

D. Meyfarth P. Ranguis