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Datasheet for the decision of 23 February 2012

Case Number: T 1664/07 - 3.3.02

Application Number: 99968394.9

Publication Number: 1135125

IPC: A61K 31/415

Language of the proceedings: EN

Title of invention:
Controlled-release dosage forms comprising zolpidem or a salt thereof

Patent Proprietor:
SANOFI

Opponent:
Synthon BV

Headword:
Zolpidem controlled-release/SANOFI

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12(4), 13(3)

Keyword:
"Inventive step (no): absence of comparative examples, solution of less ambitious problem obvious in view of the state of the art"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1664/07 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 23 February 2012

Appellant: (Patent Proprietor)	SANOFI 174, Avenue de France F-75013 Paris (FR)
Representative:	Wright, Robert Gordon McRae Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks Kent TN13 1XR (GB)
Respondent: (Opponent)	Synthon BV Microweg 22 NL-6503 GN Nijmegen (NL)
Representative:	Hamm, Volker Maiwald Patentanwalts GmbH Jungfernstieg 38 D-20354 Hamburg (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 13 August 2007 revoking European patent No. 1135125 pursuant to Article 102(1) EPC 1973.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
D. Prietzel-Funk

Summary of Facts and Submissions

I. European patent No. 1 135 125, based on international application No. PCT/EP1999/010454 published as WO 2000/033835 and having application No. 99 968 394.9 in the EPO, was granted with 24 claims.

Independent claim 1 as granted reads as follows:

"A pharmaceutical composition comprising zolpidem or a salt thereof characterized in that it consists of a controlled-release dosage form adapted to release zolpidem or a salt thereof over a predetermined time period, according to a biphasic *in vitro* profile of dissolution when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia in 0.01 M hydrochloric acid buffer at 37ºC stirred at a rate of 75 rpm, where the first phase is an immediate release phase having a maximum duration of 30 minutes and the second phase is a prolonged release phase, and wherein 40 to 70% of the total amount of zolpidem is released during the immediate release phase and the time for release of 90% of the total amount of zolpidem is between 2 and 6 hours."

II. Opposition was filed against the granted patent under Article 100(a) EPC, the sole ground being lack of inventive step.

The documents cited during the proceedings before the opposition division and the board of appeal include the following:

(1) EP-A-0 173 928

(2) Merlotti, L., et al., "The dose effects of zolpidem on the sleep of healthy normals", Journal of clinical psychopharmacology, vol. 9, February 1989, 9-14

(6) Entry "STILNOCT" in the "Monthly index of medical specialities" MIMS, May 1994

(7) Ambien CR® (zolpidem tartrate extended-release tablets), Prescribing data, Sanofi-Synthelabo Inc., New York, NY 10016, September 2005

(8) Sleep, vol. 28 (2005), abstract supplement, A244-A246, abstracts 725, 728-731, 733

(12) Smith, R.B., et al., "Design and pharmacodynamic evaluation of novel dual release formulations of triazolam", International journal of clinical pharmacology, therapy and toxicology, vol. 31(9) (1993), 422-429

(14) Monti, J., "Effect of zolpidem on sleep in insomniac patients", European journal of clinical pharmacology, vol. 36 (1989), 461-466

(15) Besset, A., et al., "Effects of zolpidem on the architecture and cyclical structure of sleep in poor sleepers", Drugs Exptl. Clin. Res. XXI(4) (1995), 161-169

(18) Roth, T., et al., "Efficacy and safety of zolpidem-MR: A double-blind, placebo-controlled study in adults with primary insomnia", Sleep medicine, vol. 7 (2006), 397-406

III. By its decision pronounced at oral proceedings on 10 July 2007 and posted on 13 August 2007, the opposition division revoked the patent under Article 102(1) and (3) EPC 1973.

The opposition division held that the set of claims of the main request did not meet the requirements of Article 56 EPC. The closest prior art was document (2) or, alternatively, document (6), both documents referring to the commercially available immediate release formulation of zolpidem, with the only difference that document (2) additionally gave information on the pharmacokinetic properties of the drug.

In any case, the problem solved by the teaching of the patent in suit was the one formulated in its description, given that the drug was a short acting hypnotic, which was also disclosed in the description. The solution proposed was the provision of zolpidem in a biphasic formulation having the broad characteristics of claim 1 of the patent as granted. Said solution was obvious in view of document (1), which described the use of biphasic formulations *inter alia* for short acting hypnotics.

At the end of the oral proceedings, the "CH (chairman) announced the conclusion of the opposition division (OD) that the subject-matter of claim 1 of the patent as granted (main request) did not involve an inventive step. CH also indicated the provisional view of OD that the auxiliary request did not seem to involve any inventive step" (see minutes of the oral proceedings,

page 2, last paragraph; text terms in brackets inserted by the board). As a consequence, the appellant withdrew the auxiliary request.

IV. The appellant lodged an appeal against the decision of the opposition division and filed grounds of appeal together with a request that the patent be maintained according to its main or its first auxiliary request.

The main request corresponds to the sole request the opposition division decided on and concerns the patent as granted. The first auxiliary request is the same as the request withdrawn before the opposition division.

With its letter of 16 February 2012, the appellant submitted a further set of claims as second auxiliary request.

In claim 1 of the first auxiliary request, with respect to the content of the active substance zolpidem in the claimed composition, a range "4 to 16 mg" was introduced.

In claim 1 of the second auxiliary request, the content of zolpidem was indicated to be 12.5 mg of zolpidem hemihydrate.

V. On 23 February 2012, oral proceedings took place before the board.
The first auxiliary request was admitted into the proceedings, the second auxiliary request was not.

VI. The appellant's submissions may be summarised as follows:

Even beyond the priority date of the patent, it was generally recognised by those skilled in the art that although the commercial immediate release formulation of zolpidem (10 mg) was effective as a sleep onset agent, it fell short in addressing the needs of patients whose sleep was not being maintained. Prepublished documents (2), (6), (14) and (15) related to this immediate release form and each of them could be regarded as the closest prior art.

In this situation, the problem to be solved was to obtain a product containing zolpidem that was

- more effective in the treatment of sleep maintenance, while
- maintaining its beneficial effects on sleep onset and
- without incurring next-day residual effects.

The problem was indeed solved by the subject-matter of claim 1 of the patent in suit, corresponding to the modified release form of zolpidem Ambien MR or Ambien CR® respectively, as could be seen in particular from documents (8) and (18). From the plasma concentration time profile disclosed in document (7), the correlation between the subject-matter of the patent in suit and Ambien CR® could be derived.

However, there was no motivation for the skilled person to combine documents (2) or (6) or (14) or (15) and document (1).

On the contrary, the skilled person was faced with a number of more attractive options for solving the

problem, in particular raising the dose or creating a combination preparation, and would not have thought of a formulation of zolpidem characterised by a biphasic release profile in vitro.

From document (7) it could be derived that the FDA had acknowledged efficacy with respect to sleep maintenance for the commercial, extended-release form Ambien CR®, while being aware of the existence of the immediate release form with its indication for sleep onset only, which could be seen as indicating an improvement, even when comparative scientific and clinical studies were not required by the authorities and, consequently, not conducted by the appellant.

VII. The respondent's arguments may be summarised as follows:

With respect to the admissibility of requests, the appellant could and should have submitted and maintained the sets of claims of its auxiliary requests much earlier; thus, they were not to be admitted into the proceedings before the board.

In particular, auxiliary request 1 had already been submitted before the opposition division but was withdrawn during the oral proceedings. Therefore, the opposition division had been prevented from deciding on this request, and there were no arguments assessing it in the decision. The board, in verifying the decision of the opposition division, therefore had no basis for considering this request.

The second auxiliary request had been filed one week in advance of the oral proceedings before the board and

its subject-matter had never been discussed during the proceedings in any way. In addition, this request would probably give rise to consideration of remittal to the opposition division for further prosecution. With regard to all these reasons, it should not be admitted into the proceedings.

As to the merits of the case, the subject-matter of claim 1 of the patent in suit was characterised solely by a release profile *in vitro*. In the documents cited by the appellant, as far as disclosing advantages of a "modified" or "extended-release" zolpidem formulation was concerned, there was no conjunction with the immediate release form, as for instance set out in documents (2), (14) or (15), and in particular none with the in vitro release profile characterising the subject-matter of the patent in suit.

The opposed patent itself, apart from some plasma level data, did not disclose any results of clinical trials performed with the claimed compositions. In addition, claim 1 comprised embodiments that could not solve the problem of providing an improved composition. In this situation, because of either of these two reasons, the problem had to be formulated less ambitiously, namely as the provision of a further zolpidem-containing composition instead of an improved one. In view of this problem to be solved, it did not matter whether there had been further alternatives for the skilled person when trying to find a solution, or whether there was a direct link in the closest prior art to documents disclosing sustained release modifications in the formulation of hypnotics.

In these circumstances, knowledge of biphasic compositions for short acting hypnotics on the basis of document (1) or document (12) made the subject-matter of the patent in suit obvious, as worded in claim 1 of both the main request and the first auxiliary request.

VIII. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained as granted, or maintained on the basis of the first auxiliary request, filed with its letter dated 24 December 2007, or, alternatively, on the basis of the set of claims filed as second auxiliary request with its letter dated 16 February 2012.

IX. The respondent (opponent) requested that the appeal be dismissed. It additionally requested that both the first and second auxiliary request not be admitted into the proceedings.

Reasons for the decision

1. The appeal is admissible.

2. The amended claims filed by the appellant as first auxiliary request were already contained in its submissions of grounds of appeal and *prima facie* have to be regarded as a response to the arguments of the opposition division as set out in its decision. The opposition division had decided on inventive step and having indicated during the proceedings that the subject-matter of the auxiliary request did not involve an inventive step either, it was only "prevented" from taking and issuing a decision under the same ground of

opposition on slightly restricted subject-matter. Moreover, the subject-matter of the first auxiliary request during the appeal proceedings has already been discussed in writing.

Thus, there is no need for new, complex considerations.

In view of all these particular circumstances of the case, the board uses its discretion and admits the amended claims of the first auxiliary request into the proceedings.

In contrast, the subject-matter of the second auxiliary request, submitted shortly before the oral proceedings before the board, gives rise to new and extended considerations with respect to all relevant articles of the EPC and therefore is not admitted into the proceedings.

3. *Claim 1 of the main request; Article 56 EPC*

3.1 The subject-matter of claim 1 of the patent in suit relates to

- a pharmaceutical composition comprising zolpidem
- consisting of a controlled-release dosage form
- which releases zolpidem
- according to a biphasic *in vitro* profile of dissolution
- when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia in 0.01 M hydrochloric acid buffer at 37ºC stirred at a rate of 75 rpm,
- where the first phase is an immediate release phase

– having a maximum duration of 30 minutes and wherein 40 to 70% of the total amount of zolpidem is released
– and the second phase is a prolonged release phase,
– and the time for release of 90% of the total amount of zolpidem is between 2 and 6 hours.

3.2 Document (15) represents the closest state of the art.

The disclosure of this document relates to

– a pharmaceutical composition comprising zolpidem, a short acting hypnotic (see page 165, "Discussion", lines 1 to 3 (lines 2 to 3 in the right-hand column) and the first line of the summary),

– as an immediate release phase (see page 165, "Discussion", lines 5 to 9 in the right-hand column referring to the short half-life of the compound and thus indicating that no sustained release components are included in the composition).

3.3 There is no evidence on file that zolpidem-containing pharmaceutical compositions according to the patent in suit exhibit an improvement over immediate release compositions according to document (15).

3.4 In the absence of such evidence, the problem to be solved has to be defined as

the provision of another, zolpidem-containing pharmaceutical composition.

3.5 This problem is solved by a pharmaceutical composition according to claim 1 of the patent in suit, namely

a composition where the in vitro release data under control of a standard USP method show a biphasic profile of dissolution characterised by two particular ranges with respect to two points on this release profile.

3.6 The skilled person faced with the problem as defined above knows document (1).

Claim 6 of this document in conjunction with claims 3 and 1, however, relates *inter alia* to a controlled release composition having a biphasic release profile and comprising a short acting hypnotic.

Further, according to example 1 of document (1) the diffusion of the active substance, in this case phenylpropanolamine, was followed by using the "paddle method described in the United States Pharmacopeia, 19th rev., Mack Publishing Co., Easton Pa., 1975, p. 651 (=USP XX)" (see page 7, lines 16 to 19).

The remaining characteristics, concerning two points on the in vitro release profile of the subject-matter of claim 1 of the patent in suit, as part of the solution, are determined by the skilled person using standard methods on the known basis of pharmacokinetic data of zolpidem (e.g. short half-life as already stated under point 3.2 of this decision as being disclosed in document (15)).

3.7 Consequently, the board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step (Article 56 EPC).

4. *First auxiliary request; Article 56 EPC*

Since any evidence relating to the subject-matter of claim 1 of the patent in suit and to an immediate release composition, as known for instance from document (15), is missing, the addition of the feature of zolpidem content in mg in claim 1 does not alter the situation.

There is still no evidence that the subject-matter of the first auxiliary request gives rise to improvements over the immediate release form as known in the state of the art.

The problem to be solved being the same as with respect to the subject-matter of claim 1 of the patent as granted, the solution is obvious in the same way as set out in this decision under point 3.

5. Under these circumstances, the additional arguments of the appellant cannot hold.

Most of the arguments of the appellant related to the formulation of the problem to be solved as providing for an improvement. In view of the absence of evidence in support of such improvement, none of these arguments can succeed.

Even the acknowledgement of the indication "for the treatment of difficulties with sleep maintenance" by

the FDA does not indicate that compositions according to claim 1 of the patent in suit represent an improvement over the closest state of the art, because this acknowledgement was based on experiments relating to placebos only, not to prior-art compositions.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald