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Datasheet for the decision of 1 April 2009

Case Number: T 1409/06 - 3.3.02

Application Number: 94911178.5

Publication Number: 0689437

IPC: A61K 31/435

Language of the proceedings: EN

Title of invention:
Use of granisetron for the treatment of post-operative nausea and vomiting

Patentee:
F.HOFFMANN-LA ROCHE AG

Opponent:
Teva Pharmaceutical Industries Ltd.

Headword:
Use of granisetron for the treatment of PONV/F.HOFFMANN-LA ROCHE AG

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request and auxiliary request 1 - inventive step (no): a dosage regimen which merely optimizes an already known or obvious pharmacological effect does not establish an inventive step"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1409/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 1 April 2009

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 10 July 2006 rejecting the opposition filed against European patent No. 0689437 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: J. Riolo
Members: A. Lindner
C.-P. Brandt

Summary of Facts and Submissions

I. European patent No. 0 689 437 based on application No. 94 911 178.5 was granted on the basis of a set of 5 claims.

The sole independent claim reads as follows:

"1. The use of granisetron in the manufacture of a medicament for the treatment of post-operative nausea and vomiting (PONV)."

II. An opposition was filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of inventive step, under Article 100(b) EPC for insufficiency of disclosure and under Article 100(c) EPC.

III. The documents cited during the opposition and appeal proceedings included the following:

(1) Andrews, P. L. R., Br. J. Anaesth., 1992, 69 (Suppl. 1), 2S-19S – Supplement on Postoperative Nausea and Vomiting – "Physiology of Nausea and Vomiting"

(7) Seynaeve, C., et al., Anti-Cancer Drugs, 1991, 2, 343-355 – "5-NT3 receptor antagonists, a new approach in emesis: a review of ondansetron, granisetron and tropisetron"

(8) Wynn, R.L., et al., Eur. J. Pharmacol., 1993, 241, 47-54 – "The effects of different antiemetic agents on morphine-induced emesis in ferrets"

IV. In the decision pronounced on 13 June 2006, the opposition division rejected the opposition. Its

principal findings were as follows: the ground of opposition raised under Article 100(c) EPC had not been substantiated. Moreover, the requirements of Article 83 EPC were found to be met, because the contested patent described at least one way of carrying out the invention.

In connection with inventive step, the opposition division defined document (1) as closest prior art, in which ondansetron was used for the treatment of PONV. The opposition division defined the provision of an alternative agent for the treatment of PONV as the problem to be solved. The replacement of ondansetron by granisetron was found to involve an inventive step, as there was no indication for a reasonable expectation of success in the prior art. As regards the objections that the claims comprised embodiments which did not solve the problem as defined above, the opposition division concluded that the opponent had not proven that any type of PONV was not treatable with granisetron.

V. The appellant (opponent) lodged an appeal against that decision.

VI. With his letter dated 26 February 2009, the respondent (patentee) filed auxiliary request 1.

Claim 1 of auxiliary request 1 reads as follows:

"1. The use of granisetron in the manufacture of a medicament for the treatment of post-operative nausea and vomiting (PONV) wherein granisetron is administered in a 1 mg to 3 mg unit dose."

VII. Oral proceedings took place on 1 April 2009.

VIII. The respondent's arguments can be summarised as follows:

In connection with inventive step, the skilled person, starting from document (1) as closest prior art, could have selected granisetron for the treatment of PONV, but he would not have done so as there was no reasonable expectation of success for a variety of reasons. Firstly, documents (7) and (8) showed that granisetron was ineffective against nausea caused by morphine. More importantly, it could be derived from document (8) that there was no "class effect" for 5-HT_3 receptor antagonists: ondansetron was effective against nausea caused by morphine while granisetron was not. Therefore, the person skilled in the art would not associate effects obtained with ondansetron to other 5-HT_3 receptor antagonists.

In connection with auxiliary request 1, it was argued that optimum results were obtained by applying the unit dose as defined in claim 1. Moreover, it was surprising that these results were obtainable with such low doses.

IX. The appellant contested the arguments submitted by the respondent and held that, starting from the teaching of document (1), the person skilled in the art would select granisetron for the treatment of PONV with a reasonable expectation of success.

X. The appellant requested that the decision under appeal be set aside and that the European patent No. 689 737 be revoked.

The respondent requested that the appeal be dismissed or that the patent be maintained on the basis of auxiliary request 1, filed with letter dated 26 February 2009.

Reasons for the Decision

1. The appeal is admissible.

2. Main request:

2.1 Article 100(b) EPC:

The appellant did not maintain the objection raised during the opposition procedure with respect to Article 100(b) EPC, and the Board sees no reason to disagree with the favourable conclusions of the opposition division in that respect (see paragraph IV above, and the opposition division's decision, point 3).

2.2 Inventive step:

2.2.1 The subject-matter of the main request concerns the use of granisetron for the manufacture of a medicament for the treatment and prophylaxis of PONV (see paragraph [0009] of the patent in suit).

2.2.2 Document (1), which constitutes the closest prior art, is a scientific article in which the physiology of nausea and vomiting and in particular of PONV is discussed. It contains the teaching that 5-HT_3 receptor

antagonists such as ondansetron and granisetron are successful in treating emesis caused by anticancer chemotherapy (page 2S, second complete paragraph of the right-hand column). As a consequence, the problem underlying the invention as defined in the main request can be seen in the provision of an alternative therapeutic indication for granisetron. This problem was solved by the use of granisetron in the manufacture of a medicament for the treatment of PONV.

2.2.3 The board is convinced that the above-mentioned problem was solved in the light of the clinical studies described on pages 3-7 of the patent in suit.

2.2.4 As was mentioned above in paragraph 2.2.2, document (1) concerns the physiology of nausea and vomiting and in particular of PONV. The fact that there are no suitable animal models is one of the reasons that the mechanism of PONV is largely unknown. Even cats, dogs, ferrets and laboratory primates, which respond to virtually the same range of emetic stimuli as man, are not entirely suitable (see the paragraph bridging pages 2S and 3S of document (1)). As a consequence, the tendency in PONV research has been to undertake clinical trials of agents whose antiemetic activity has already been demonstrated against other stimuli and this approach continues with the trials of 5-HT_3 receptor antagonists which are known to be effective against emesis caused by chemotherapy and radiotherapy (see page 3S, first full paragraph of the left-hand column). In fact, the further research with 5-HT_3 receptor antagonists in connection with PONV is of particular interest, as the problem of PONV has some parallels with emesis induced by cytotoxic chemotherapeutic agents, and as it is

hoped that the mechanism of PONV can be better understood if the 5-HT_3 receptor antagonists turn out to be effective in the treatment of PONV (see page 16S, first and last sentences of the last paragraph of the right-hand column). Furthermore, ondansetron, a 5-HT_3 receptor antagonist known to be useful against emesis caused by anticancer chemotherapy, has also shown some effect against PONV (see last paragraph of the right-hand column of page 16S).

2.2.5 In the light of this teaching, the person skilled in the art, trying to find an alternative therapeutic indication for granisetron, would apply it in the treatment of PONV. He would apply it with a reasonable expectation of success, as

(a) the 5-HT_3 receptor antagonists, and in particular those whose antiemetic effect in connection with anticancer chemotherapy is known, are a preferred group of compounds for the further research in PONV, in view of the fact that they "may have the key to the mechanism of PONV";

(b) ondansetron, a 5-HT_3 receptor antagonist which has been successfully used as an antiemetic agent in anticancer chemotherapy, has been shown to be effective in PONV;

(c) granisetron, which has also been successfully used as an antiemetic agent in anticancer chemotherapy, is the only 5-HT_3 receptor antagonist specifically mentioned in document (1) in addition to ondansetron.

As a consequence, the subject-matter of claim 1 of the main request is obvious in the light of document (1), so that the requirements of Article 56 EPC are not met.

2.2.6 Additional arguments of the respondent:

Documents (7) and (8) showed that the ferret is a suitable animal model for PONV. Table 2 of document (7) proved that granisetron was not effective in the treatment of PONV, as there was no antiemetic effect against morphine in the ferret model. Moreover, there was no "class effect" of 5-HT_3 receptor antagonists in connection with PONV: table 2 of document (8) demonstrated on the basis of a ferret model that ondansetron was effective in the treatment of PONV while granisetron was not. Granisetron was even lethal to one of the ferrets used in the series.

These arguments cannot succeed for the following reasons: firstly, it is noted that document (8) was published between the priority date and the filing date of the patent in suit. As the respondent did not provide convincing evidence for an invalid priority, the teaching contained therein cannot be taken into consideration for the assessment of inventive step.

The ferret model used in document (7) does show that granisetron is not effective against nausea caused by morphine (see table 2). However, this fact is already acknowledged in document (1), where it is stated that 5-HT_3 receptor antagonists in general, which include ondansetron, do not block morphine, morphine 6-glucuronide or loperamide (see the first complete paragraph of the right-hand column on page 8S). And yet, despite

this finding, ondansetron is mentioned as having some effect in the treatment of PONV. This is not contradictory, as there are many causes for PONV (see the paragraph bridging the two columns on page 2S of document (1)). The fact that 5-HT_3 receptor antagonists are reported to be ineffective against nausea caused by morphine does not imply that they are equally unsuitable for all the other possible causes of PONV. As a consequence, the person skilled in the art would not be kept from following the teaching of document (1), which calls for further clinical tests of 5-HT_3 receptor antagonists and in particular of granisetron in the treatment of PONV.

3. *Auxiliary request 1:*

3.1 Formal aspects:

The subject-matter of claim 1 comprises the additional feature that granisetron is administered in a 1 mg to 3 mg unit dose. This feature is based on claim 5 as originally filed and therefore allowable under Article 123(2) EPC. Moreover, this feature has a limiting character, so that the requirements of Article 123(3) EPC are also met.

3.2 Inventive step:

3.2.1 As was mentioned above in paragraph 3.1, the subject-matter of claim 1 of auxiliary request 1 comprises the additional feature that "granisetron is administered in a 1 mg to 3 mg unit dose". The data obtained from the clinical study of the patent in suit reveal that the best antiemetic effects were obtained by i.v.

administration of 1 mg and 3 mg granisetron as compared to 0.1 mg where the effect was less accentuated. The problem underlying claim 1 of auxiliary request 1 can therefore be defined as optimising the effect of granisetron in the treatment of PONV.

The board is of the opinion that the mere determination of the dosage which yields the best effect does not involve an inventive step when, as in the present case, the effect as such is already known or obvious. The person skilled in the art is aware that the intensity of a pharmacological effect depends inter alia on the concentration of the active agent. Finding the optimum dosage is a matter of routine experimentation, which does not require inventive skill. There is no evidence for any additional non-obvious effects that might be attributed to the unit dose of 1 mg to 3 mg. As a consequence, the requirements of Article 56 EPC are not met.

3.2.2 Additional arguments by the respondent:

The respondent held that it was surprising that the optimum effect could be obtained with such a low dosage unit. With ondansetron, much higher concentrations were needed.

This argument cannot succeed, as it is well known that there are big variations in the optimum concentrations of therapeutic agents. It is again emphasised that the optimum dosage can easily be determined, e.g. by a test series, which does not require inventive skill. It is additionally noted that a low dosage unit does not mean that the agent is safer or otherwise more advantageous,

as unwanted side-effects may also set in at lower concentrations. Therefore, this argument cannot succeed.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The European patent no. 689 437 is revoked.

The Registrar: The Chairman:

N. Maslin J. Riolo