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Datasheet for the decision of 8 October 2019

Case Number: T 0109/16 - 3.3.01

Application Number: 05078002.2

Publication Number: 1642578

IPC: A61K31/435, A61P25/04

Language of the proceedings: EN

Title of invention:
Fentanyl salt composition for nasal administration

Patent Proprietor:
Takeda Pharma A/S

Opponent:
Generics [UK] Limited

Headword:
Fentanyl for nasal administration/TAKEDA

Relevant legal provisions:
EPC Art. 56, 83
RPBA Art. 13

Keyword:

Late-filed auxiliary requests - admitted (yes)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

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Beschwerdekammern

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Case Number: T 0109/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 8 October 2019

Appellant: (Opponent)	Generics [UK] Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	Isarpatent Patent- und Rechtsanwälte Behnisch Barth Charles Hassa Peckmann & Partner mbB Friedrichstrasse 31 80801 München (DE)
Respondent: (Patent Proprietor)	Takeda Pharma A/S Dybendal Alle 10 2630 Taastrup (DK)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 29 October 2015 rejecting the opposition filed against European patent No. 1642578 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	M. Pregetter
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 642 578 was filed as patent application No. 05078002.2. It is a divisional application of the parent application 01960190.5, filed as an international application published as WO02/09707.

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(25) Striebel et al., Der Schmerz, 1993, 7, 174-177

(28) Entry for "Fentanyl Citrate" in MedLibrary.org, 2014, 4 pages

(30) Rote Liste 1992, 2 pages

III. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by the person skilled in the art, and extended beyond the content of the application as filed.

The opposition division rejected the opposition.

IV. The opponent (appellant) appealed this decision. In the statement setting out the grounds of appeal, the appellant provided arguments with regard to added subject-matter, sufficiency of disclosure, novelty and inventive step.

V. In its reply to the grounds of appeal, the patent proprietor (respondent) requested that the appeal be

dismissed. It submitted auxiliary requests 1 to 5.

VI. In a communication pursuant to Article 15(1) RPBA, the board indicated certain points to be discussed.

VII. With its letter dated 6 September 2019, the respondent submitted auxiliary requests 4 to 8, with auxiliary requests 4 and 5 replacing auxiliary requests 4 and 5 then on file.

VIII. The oral proceedings before the board on 8 October 2019 took place in the absence of the appellant who had informed the board by letter of 5 September 2019 that it would not attend.

During the oral proceedings, the respondent submitted an amended auxiliary request 6, which subsequently became its main and only request.

Claim 1 of the main request reads as follows:

"1. A medicament comprising a solution of fentanyl citrate in water at a concentration range equivalent to 0.75 to 15 mg/ml of fentanyl for use in the treatment, alleviation or lessening of pain in a mammal, wherein the medicament is to be administered intranasally by means of a nasal spray in a dosage unit amount equivalent to 70 to 500 µg of fentanyl."

IX. The appellant presented arguments for the claims of the patent as granted in the statement setting out the grounds of appeal. No further arguments by the appellant are on file.

The appellant's arguments, as presented in writing for the claims of the patent as granted and insofar as they

are relevant to the present decision, are as follows:

Inventive step

The closest prior art was represented by document (25). The fentanyl solution used in document (25) contained fentanyl citrate in a concentration corresponding to 0.05 mg/ml fentanyl base, as could be derived from the single commercially available product (see document (30)). Furthermore, document (25) disclosed the preparation of a composition having a ten-times higher concentration. The intranasal administration of 90 and 135 µg fentanyl was directly derivable from the closest prior art.

The distinguishing feature was the actual treatment of pain with a highly concentrated fentanyl solution. The technical effect due to the use of fentanyl salt in a concentration range equivalent to 0.5 to 20 mg/ml fentanyl was a faster onset of the therapeutic effect.

Consequently, the technical problem to be solved might be regarded as the provision of a fentanyl-containing composition allowing to avoid titration delivery and possessing shorter time to onset of action.

The solution presented in the claims as granted would have been obvious since document (25) suggested using highly concentrated solutions of fentanyl citrate for intranasal administration thus avoiding the titration method. Furthermore, document (25) noted that a faster onset of action could be expected. Document (25) thus provided a clear motivation to use highly concentrated solutions of fentanyl citrate for intranasal administration.

Sufficiency of disclosure

The invention could not be performed over the whole range claimed. The absolute amount of 70 to 500 µg could not be used in the treatment, alleviation or lessening of pain in each type of mammal. The dose might be life threatening or ineffective. From the LD_{50} values of fentanyl for different mammals, it could be derived that such a dose might be lethal for small non-human primates such as pygmy marmosets (see document (28)). On the other hand, it was not plausible that an amount of 70 to 500 µg would be effective in larger mammals having a body weight of several hundreds kilograms.

X. The respondents argument's, insofar as they are relevant to the present decision, may be summarised as follows:

Admission of the amended main request

The filing of the amended main request was in direct response to issues discussed during oral proceedings. The subject-matter of the amended main request was directly derivable from examples 1 and 2 and thus was restricted to the most preferred embodiments.

Inventive step

Starting from document (25) as the closest prior art, it was not clear whether a free base or a salt was used. There was no disclosure in document (25) identifying the actual form of fentanyl used. The actual amounts in the form of fentanyl equivalents depended on the actual form used.

The amounts and concentrations disclosed in document (25) were much lower than the amounts and concentrations defined in claim 1 of the main request. The technical effect of the administration of the much higher amounts of fentanyl in one administration was a quicker onset of action, due to being able to dispense with administration by titration, and the reduction or absence of severe side effects, which occurred with intravenous administration of comparable doses, as could be seen from example 7 of the patent in suit.

The technical problem was thus to provide a medicament for the treatment or alleviation of pain that had a quicker time to onset after administration, that provided a rapid and sufficiently long lasting pain relief without the need for a titration delivery, which was safe to use by patients without the risk of overdosing, and which had a negligible degree of severe side effects, such as respiratory depression.

The solution as presented in claim 1 of the main request would not have been obvious. The skilled person would have had serious concerns about overdosing in view of the known side effects of fentanyl (see also document (25), page 176, left-hand column, second half of penultimate paragraph and last paragraph). It would have thus been surprising that an even higher concentration than the elevated concentration suggested by document (25) would lead to a safe and effective treatment. Consequently, the subject-matter of the claims of the main request involved an inventive step.

Sufficiency of disclosure

The amount of 70 to 500 µg fentanyl was to be administered to the patient intranasally in a

composition having a certain concentration. The LD_{50} values invoked by the appellant related to intravenous administration. The actual plasma levels in the mammal to be treated resulted from the combination of administration of a solution having an upper limit of 15 mg/ml fentanyl and the level of absorption, which depended on the surface area of the mucosal membrane of the patient in contact with the solution. It was mere speculation that the actually achieved plasma levels would be lethal. In addition, the appellant did not provide any evidence showing that the administration of, for example, 70 µg fentanyl did not lead to any alleviation of pain in large mammals.

XI. The final requests of the parties were as follows:

The appellant (opponent) had requested in writing that the decision under appeal be set aside and the European patent No 1642578 be revoked.

The respondent (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed as 6th auxiliary request at the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. The oral proceedings before the board took place in the absence of the appellant, who had been duly summoned but had chosen not to attend, as announced with the letter of 5 September 2019. According to Rule 115(2) EPC and Article 15(3) RPBA, the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral

proceedings of any party duly summoned who may then be treated as relying only on its written case. Hence, the board was in a position to announce a decision at the conclusion of the oral proceedings, as foreseen by Article 15(6) RPBA.

3. *Admission of the main request (Article 13 RPBA)*

The subject-matter of the claims of the main request, filed during oral proceedings before the board, constitutes a direct response to the arguments raised during oral proceedings. Furthermore, the claims have been restricted to preferred embodiments of the application and the earlier application as filed. No complex subject-matter has been introduced which might raise issues which could not be dealt with without adjournment of the oral proceedings.

Consequently, in the exercise of its discretion according to Article 13 RPBA, the board admitted the main request.

4. *Sufficiency of disclosure*

Claim 1 of the main request is a second medical use claim. For it to be sufficiently disclosed, the claimed effect must be achieved over the whole scope of the claim.

The appellant has alleged that the effect of safely treating or alleviating pain is not achieved for certain small animals, in particular, small non-human primates, or for large mammals having a body weight of several hundred kilograms.

The respondent has pointed to the fact that the

composition of claim 1 is to be administered intranasally and that the LD_{50} data invoked by the appellant related to intravenous administration (see document (28)).

The board notes that the appellant has not provided any comment to the respondent's arguments.

Figures 1 to 4 of the patent in suit show plasma levels after intravenous and after intranasal administration. It is clear from this data that the peak plasma levels differ depending on the mode of administration in humans. The extent to which such levels would differ in non-human primates is not known. In the absence of any further information, the assertion by the appellant that the claimed doses are lethal to some mammals cannot be verified and are thus not proof that these mammals cannot be safely treated.

Concerning very large animals, the board points to the fact that claim 1 does not require a treatment or alleviation of pain all over the body of the mammal. A localised alleviation of pain is also within the scope of claim 1 of the main request. There is no evidence on file that a large mammal would not experience some pain relief at least in the area of the intranasal mucosa.

The lines of arguments and the evidence on file are thus not opposed to a finding of sufficiency of disclosure.

5. *Inventive step (Article 56 EPC)*

5.1 The patent in suit relates to a pharmaceutical composition for use in the treatment of pain, especially acute pain such as breakthrough pain, by

means of a non-invasive administration, in particular, intranasal administration, of fentanyl in the form of a pharmaceutically acceptable salt, this composition being such that at least 70 µg of fentanyl is delivered in a dosage unit (paragraph [0001]). According to claim 1 of the main request, the fentanyl salt is fentanyl citrate, to be used in a concentration range of 0.75 to 15 mg/ml.

5.2 The closest prior art is document (25).

Document (25) teaches to administer six squirts of fentanyl to the nostrils of a patient. Each squirt provides a dose of 0.0045 mg "fentanyl" from a commercially available ("handelsübliche") composition comprising 0.05 mg/ml "fentanyl" (page 175, paragraph bridging the columns). Furthermore, document (25) suggests administering a considerably higher concentration and specifically mentions a composition comprising a ten-times-higher concentration. Here one dose in the form of one squirt comprises 0.045 mg "fentanyl" (page 176, right-hand column, middle of first paragraph).

There is no information in document (25) on which form of fentanyl is used. There is also no disclosure as to whether the amounts of "fentanyl" refer to amounts of a (specific) fentanyl salt or to fentanyl free base (i.e. to equivalents).

However, irrespective of whether the concentrations and amounts of "fentanyl" refer to a specific fentanyl salt or to fentanyl free base, the concentrations and amounts disclosed in document (25) are below the concentration and amount per unit dose defined in

claim 1 of the main request.

5.3 Therefore, the subject-matter of claim 1 of the main request differs from document (25) in the form and in the amount and concentration of fentanyl used.

Concerning the technical effect linked to these differences, the respondent has referred to example 7 of the patent in suit. Example 7 provides comparative data between the intranasal and intravenous administration of fentanyl. The closest prior art in the form of document (25) does, however, not relate to intravenous administration but describes intranasal application. No surprising effect over the teaching of the closest prior art can thus be established by example 7.

5.4 In the absence of any proof of a surprising technical effect linked to the differences over the closest prior art, the problem has to be defined as an alternative medicament for treatment, alleviation or lessening of pain by intranasal administration of fentanyl.

In view of example 6 of the patent in suit and point 4 above, the board considers that the problem has been solved.

5.5 It remains to be determined whether the solution would have been obvious.

Document (25) raises concerns about the side effects of the administration of fentanyl. In this context, it cites a study by Portenoy and Hagen, stating that administration by titration was a key principle in view of the fact that the most effective dose that did not produce intolerable side effects was unknown in any

individual case (page 176, left-hand column, penultimate paragraph). It is then stressed that, as a consequence of this statement, fentanyl was administered in the study of document (25) by adhering to administration by titration strictly adapted to need ("streng bedarfsadaptierte Fentanyltitration", see page 176, left-hand column, last paragraph). Thus, the authors of document (25) pointed to the seriousness of the side effects and the need to consider these side effects when taking decisions on dosing.

In view of the well-known and extremely serious side effects of fentanyl, the skilled person would probably have considered heeding the suggestion of document (25) to prepare a composition having a ten fold higher concentration. However, they would have refrained from using even higher concentrations before the results of the study using the ten-times higher concentration were known. It thus would not have been obvious for the skilled person to go beyond the suggestions made in document (25).

The subject-matter of claim 1 of the main request represents a non-obvious alternative.

6. The appellant has submitted no further objections that could prejudice the maintenance of the patent on the basis of the main request filed during oral proceedings before the board. The board has no further objections either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted thereto:
Claims 1 to 10 of the main request filed as 6th auxiliary request at the oral proceedings.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated