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Datasheet for the decision of 24 January 2024

Case Number: T 1327/21 - 3.3.04

Application Number: 12718064.4

Publication Number: 2694049

IPC: A61K31/137, A61P25/04

Language of the proceedings: EN

Title of invention:
Tapentadol for preventing chronification of pain

Patent Proprietor:
Grünenthal GmbH

Opponents:
Hexal AG
Generics [UK] Ltd
Develco Pharma GmbH

Relevant legal provisions:
EPC Art. 100(b), 83

Keyword:
Grounds for opposition - insufficiency of disclosure (yes)

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1327/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 24 January 2024

Appellant: (Patent Proprietor)	Grünenthal GmbH Zieglerstrasse 6 52078 Aachen (DE)
Representative:	Bülle, Jan Kutzenberger Wolff & Partner Waidmarkt 11 50676 Köln (DE)
Respondent: (Opponent 2)	Generics [UK] Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 14 June 2021 revoking European patent No. 2694049 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 2 694 049 (patent in suit) was granted with a set of seven claims. Claim 1 reads as follows:

1. Tapentadol for use in the prevention of chronification of pain.

II. Two oppositions were filed against the patent in suit. After expiry of the opposition period, a third opponent intervened (Article 105 EPC).

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

IV. The patent proprietor requested that the oppositions be rejected. In the course of the proceedings before the opposition division, it furthermore submitted four sets of claims as auxiliary requests 1 to 4.

Claim 1 of ***auxiliary request 1*** reads as follows:

1. Tapentadol for use in the prevention of chronification of pain, wherein the pain is selected from the group consisting of postoperative pain, migraine-related pain, headache-related pain, skeletal pain, muscle pain, post traumatic pain, and tension-type headache.

Claim 1 of ***auxiliary request 2*** reads as follows:

1. Tapentadol for use in the prevention of chronification of pain, wherein the pain is

selected from the group consisting of postoperative pain and post traumatic pain.

Claim 1 of ***auxiliary request 3*** reads as follows:

1. Tapentadol for use in the prevention of chronification of pain, wherein the pain is postoperative pain.

Claim 1 of ***auxiliary request 4*** reads as follows:

1. Tapentadol for use in the prevention of chronification of pain, wherein the pain is postoperative pain and tapentadol is administered

- *during N_1 consecutive days of a postoperative phase P_1,*
- *during N_2 consecutive days of a phase P_2 directly following said postoperative phase P_1,*
- *but not during N_3 consecutive days of a phase P_3 directly following said phase P_2;*

wherein N_1, N_2 and N_3 are independently an integer of from 1 to 100, and

wherein the daily dose of tapentadol that is administered during the N_1 consecutive days of the postoperative phase P_1 is higher than the daily dose of tapentadol that is administered during the N_2 consecutive days of a phase P_2 directly following said postoperative phase P_1.

V. The documents cited in the proceedings before the opposition division included the following:

D12: Pain 64, 483-501 (1996)

D17: Brazilian Journal of Medical and Biological Research 35, 111-119 (2002)

D18: PLoS ONE, 5(5), 1-15 (May 2010)

D19: MMW Fortschritte der Medizin 7, 158 (2016)

D34: Bromley /Brandner (ed), OPML - Acute Pain, pages 38 to 41, Oxford University Press (2010)

VI. The decision under appeal is the opposition division's decision revoking the patent in suit, announced on 23 April 2021 and posted on 14 June 2021. According to the decision under appeal:

(a) The subject-matter defined in claim 1 as granted (main request) was insufficiently disclosed for the following two reasons (Article 100(b) EPC):

- The opposed patent did not provide guidance for selecting the patient group to be treated.
- The experimental data reported in the patent did not show the prevention of pain chronification.

(b) The amendments made in the auxiliary requests did not address, and therefore could not overcome, the objections relating to insufficiency of disclosure.

VII. The patent proprietor (appellant) appealed against this decision. It requested that the patent in suit be maintained as granted and, with its statement setting out the grounds of appeal, submitted four auxiliary claim requests. The auxiliary requests are identical to those considered in the decision under appeal (see point IV. above).

VIII. Opponent 1 and opponent 3 withdrew their oppositions. As a consequence, they are no longer parties to the appeal proceedings. Opponent 2 remains as the sole respondent to the appeal.

IX. The board issued a summons for oral proceedings.

X. The respondent withdrew its request for oral proceedings and advised the board that it would not be represented at the oral proceedings.

XI. In a communication under Article 15(1) RPBA, the board provided its preliminary analysis and opinion in relation to the issue of sufficiency of disclosure. The board was of the preliminary view that the ground under Article 100(b) EPC prejudiced maintenance of the patent as granted, because the suitability of tapentadol for preventing chronification of pain had not been shown. It was noted that the appellant had not explained in its appeal submissions how the amendments in the auxiliary requests might overcome this objection. The amendments proposed according to the auxiliary requests did not appear to overcome the objection of insufficiency of disclosure. It therefore appeared likely that the appeal would be dismissed.

XII. In response to the board's communication, the appellant clarified the ranking of its requests, withdrew its request for oral proceedings and advised the board that it would not be attending the oral proceedings. It requested that a decision be reached based upon the written submissions.

XIII. The board cancelled the oral proceedings.

XIV. The appellant's arguments may be summarised as follows:

At the effective date of the patent in suit, it was within common general knowledge to identify patients who would benefit from prevention of pain chronification, on the basis of known risk factors.

The paw incision rat model used according to example 1 of the patent in suit had previously been described in document D12. It was a model for postoperative incisional pain, which was a common form of persistent acute pain, i.e. pain that was initially acute pain but later converted into persistent pain.

Incision models in rats for postoperative pain, especially the paw incision model according to D12, had also been used by others in their investigations on chronification of pain, as evidenced by D17 and D18.

Hence, it made sense to use the model according to D12 when investigating the prevention of the conversion of acute pain into chronified pain, although it was conceded that the focus of the experiments in D17 and D18 differed from that in example 1.

The results reported in example 1 showed that when tapentadol was no longer administered, it still had a significant outlasting analgesic effect. This would occur in a time window that was critical for preventing the transition of acute pain into chronified pain. At the effective date of the patent, it was within common general knowledge that such an outlasting effect indicated suitability for the prevention of chronification of pain. Document D34 was mentioned in support.

The clinical benefit of tapentadol in preventing chronification of pain had also been confirmed in humans, as shown by D19, which was a case report about the successful preventive medication of a single patient.

Moreover, post-published evidence linked the claimed effect of tapentadol to its dual mode of action, especially norepinephrine reuptake inhibition.

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

The opposition division's finding of insufficiency of disclosure was correct for two reasons. First, because there was no way to identify patients at risk of chronification of pain, and secondly, because the rat

model used for obtaining the data in the patent was not suitable to demonstrate the efficacy of tapentadol in preventing chronification of pain.

Contrary to the appellant's view, suitablilty of the rat model could not be inferred from D17 and D18.

Since the patent included no information that at least made it plausible that tapentadol was suitable for preventing chronification of pain, the appellant could not rely on the post-published article D19 in this regard. In any case, D19 could not provide conclusive evidence of the claimed therapeutic benefit, as it related to a study involving a single patient and without placebo control. Neither could the appellant rely on a speculative mechanistic understanding that was solely based on post-published information and not backed up by evidence.

The appellant had not explained why any of the auxiliary requests would address the issues for any ground of opposition. The objection that the patent did not sufficiently disclose the prevention of chronification of pain applied to every request on file.

XVI. The appellant requested that the decision under appeal be set aside and that the case be remitted to the opposition division for assessment of novelty and inventive step,

or in the alternative, that the patent in suit be maintained as granted,

or in the further alternative, that the patent be maintained in amended form on the basis of the sets of claims of one of auxiliary requests 1 to 4 enclosed with the statement setting out the grounds of appeal.

XVII. The respondent requested that the appeal be dismissed. The respondent also requested that the board not remit the case under any circumstance.

Reasons for the Decision

1. Decision in written proceedings

Since both parties withdrew their requests for oral proceedings, the board was in a position to decide on the basis of their written submissions.

2. Sufficiency of disclosure (Article 100(b) EPC) - main request

2.1 The requirement of sufficiency of disclosure must be satisfied at the effective date of the patent, i.e. on the basis of the information provided in the patent application together with the common general knowledge then available to the skilled person.

2.2 In the case in hand, the most relevant question to be answered in relation to sufficiency of disclosure was whether the data provided in the application as filed demonstrates that the claimed therapeutic benefit of preventing the chronification of pain is achieved by the administration of tapentadol.

2.2.1 According to the established case law of the Boards of Appeal, where a therapeutic application is claimed in the format provided in Article 54(5) EPC, attaining the claimed therapeutic effect is regarded as a functional technical feature of the claim.

2.2.2 In order to meet the requirement of sufficiency of disclosure, the efficacy of tapentadol in the claimed

therapeutic indication must therefore be disclosed in the application as filed.

Example 1 in the application as filed

2.3 The appellant relied, on this account, on example 1 in the patent in suit (identical to example 1 in the application as filed). Figures 1 to 3 relate to this example.

2.4 The rat model that was used according to example 1 had been developed as a model for acute post-operative pain, as described in D12 (see D12: page 500, left-hand column, final paragraph). D12 is referenced in the application as filed (see page 18, second paragraph). According to D12, rats are tested for mechanical hyperalgesia for six days after a surgical treatment by incision in the hindpaw. This rat model may be used for the evaluation of novel analgesics (see D12 and the statement setting out the grounds of appeal, page 10, point 4.2.3).

2.5 The rats used in the experiment according to example 1 in the application as filed were treated with tapentadol from day 1 to day 5 after surgery. After cessation of this treatment, they continued to be tested for mechanical hyperalgesia from days 6 to 13 ("washout period"). Hindpaws with and without surgical lesions were compared in rats treated with tapentadol and with placebo (saline). Increased sensitivity to tactile stimuli, indicative of pain, continued until the end of the study, i.e. for at least 12 days post surgery (see page 19: "Results" and figure 2 in the application as filed, which shows the results for the placebo group). Furthermore, a statistically significant analgesic effect of tapentadol was still present in the washout phase (see figure 3).

2.6 However, it cannot be ruled out that the pain observed in the animals in the washout phase, and treated by the residual effect of tapentadol, may still have been acute post-operative pain (see also the decision under appeal, 20.3.2, final paragraph on page 12).

No evidence was presented about pain chronification in rats, in particular in relation to the experiment described in example 1 and the nature of the washout phase from days 6 to 13 after surgery (figure 2). Thus it is not possible to conclude that the analgesic effect of tapentadol observed during the washout phase must equal prevention of pain chronification. For this reason, example 1 does not show that pain chronification was prevented.

Suitability of the paw incision rat model

2.7 The rat model used in example 1 was and is known as a model for acute post-operative pain, as set out in D12 (see point 2.4 above).

2.8 The appellant did not provide any direct evidence that the washout phase in the rat experiment described in example 1 may indeed serve as a model for chronification of pain, let alone one relevant for non-rodent subjects.

2.9 Instead, the appellant referred to documents D17 and D18 in support of the (indirect) argument that the incision model according to D12 had also been used by others for investigating chronification of pain.

2.10 This argument cannot succeed since D17 and D18 do not contain the information necessary for concluding that the protocol carried out as described in example 1 indeed reflects chronification of pain. The rat model is used in D17 and in D18 as a model for acute surgical

pain. In neither document is it presented as modelling the phase when acute pain changes into chronic pain. The board also notes that both documents are specialised scientific research articles and neither represents common general knowledge.

As correctly pointed out by the opposition division, the experiment reported in D17 relates to preemptive treatment of acute pain before surgery is carried out (see, for instance, the abstract in D17). It involved an observation time of only hours (up to 24 hours post surgery).

According to D18 (see abstract), rats receiving paw incision surgery were used as a model of acute postoperative pain that spontaneously resolves - in other words, for the same purpose as set out in D12. The experiment described was intended to test the hypothesis that endocannabinoid signalling promotes the resolution of acute postoperative pain. This was done by observing the results of blocking this signalling. It cannot be inferred from this teaching of D18 that, without experimental manipulation, rats will go through a phase of pain chronification during days 6 to 13 in the paw incision rat model.

Common general knowledge relating to expected efficacy

2.11 The appellant further argued that, at the effective date of the patent in suit, it was within common general knowledge that an analgesic effect beyond the expected clinical duration of action, such as found for tapentadol in example 1, indicates suitability for the prevention of chronification of pain. In support of this argument, the appellant relied on document D34, specifically on the passage that reads (page 40, penultimate paragraph):

"An analgesic intervention has a 'preventive effect' if it produces an impact on pain score and/or analgesic consumption that extends beyond the expected clinical duration of action of the drug. Positive preventive effects have been demonstrated for NMDA antagonists (ketamine and dextrometorphan), local anesthetic techniques (epidural and peripheral nerve block) and NSAIDs, but not opioids."

2.12 The board does not see any relevance in this passage. The "preventive effect" would seem to relate to high pain scores and to drug consumption. The cited passage neither identifies a precise context nor a timeline. It neither states nor implies that there would be an impact on chronification of pain. The drugs mentioned as examples do not belong to the same substance class as tapentadol. Some confirmation of the efficacy of tapentadol against chronification of pain would be required in any case, which is however lacking in the application as filed (as set out in points 2.3 to 2.6 above).

Supplementary evidence

2.13 The appellant mentioned post-published document D19 as confirmatory evidence of the preclinical results in the patent. D19 relates to one anecdotal instance of tapentadol treatment of a human patient having lumbago who was suffering from persistent, increasing pain.

2.14 For the above-mentioned reasons (points 2.1 to 2.12), the application as filed does not provide any evidence showing that tapentadol is suitable for preventing chronification of pain. The appellant cannot rely exclusively on post-published evidence (such as D19) to establish sufficiency of disclosure, as such

evidence may only be confirmatory in nature. As furthermore conceded by the appellant, D19 does not report statistically significant data.

2.15 The appellant furthermore argued that the claimed therapeutic indication was credible based on mechanistic considerations, which were in particular linked to the dual mode of action of tapentadol (μ-opioid receptor agonism and noradrenaline-reuptake inhibition).

2.16 This argument cannot succeed for the following reasons:

As conceded by the appellant itself (see point 4.2.9 of the grounds of appeal), the mechanistic rationale is not provided in the application as filed but is mainly derived from post-published documents (D7-D9, D15, D16, D22). This goes contrary to the requirement that sufficiency of disclosure must be satisfied at the effective date. The same observations apply as mentioned in point 2.14 above, *mutatis mutandis*. Post-published evidence cannot serve as the sole basis for establishing sufficiency of disclosure.

Subjects to be treated

2.17 As set out in points 2.2 to 2.16 above, the prevention of the chronification of pain by administration of tapentadol is not sufficiently disclosed.

2.18 In these circumstances, it is not necessary to address the further question of whether the person skilled in the art would have been enabled to identify a specific patient group.

Conclusion

2.19 In conclusion, the ground under Article 100(b) EPC prejudices maintenance of the patent as granted.

3. Sufficiency of disclosure - auxiliary requests

3.1 In its appeal submissions, the appellant did not explain how the amendments made in the claims of the auxiliary requests might overcome the objection of insufficient disclosure.

3.2 Claim 1 in auxiliary requests 1, 2 and 3 differs from claim 1 of the main request by listing specific types of pain in relation to chronification. Claim 1 in auxiliary request 4 is limited to postoperative pain and it also outlines a rather general dosage regimen for administering tapentadol after surgery (see point IV. above).

3.3 These amendments do not address, and therefore cannot overcome, the objection set out in section 2 above in relation to insufficiency of disclosure (Articles 100(b) and 83 EPC).

4. Request for remittal (Article 111(1) EPC)

As the board confirmed the opposition division's decision revoking the patent in suit for insufficient disclosure, the question of remittal for examination of the grounds for opposition under Article 100(a) EPC did not arise.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated