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Datasheet for the decision of 31 May 2018

Case Number: T 0614/14 - 3.3.01

Application Number: 08749016.5

Publication Number: 2148670

IPC: A61K31/137, A61P25/04

Language of the proceedings: EN

Title of invention:
TITRATION OF TAPENTADOL

Patent Proprietor:
Grünenthal GmbH

Opponent:
Generics [UK] Limited

Headword:
Titration of tapentadol/GRÜNENTHAL

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

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:

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Case Number: T 0614/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 31 May 2018

Appellant: (Opponent)	Generics [UK] Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Respondent: (Patent Proprietor)	Grünenthal GmbH Zieglerstrasse 6 52078 Aachen (DE)
Representative:	Bülle, Jan Kutzenberger Wolff & Partner Theodor-Heuss-Ring 23 50668 Köln (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 24 January 2014 concerning maintenance of the European Patent No. 2148670 in amended form.**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	M. Blasi

Summary of Facts and Submissions

I. The present appeal by the opponent (appellant) lies from the interlocutory decision of the opposition division that European patent No. 2 148 670 could be maintained in amended form, based on the set of claims filed as a main request on 26 March 2013, with the following claim 1:

"*1. Tapentadol for use in the treatment of pain, wherein*

- dose **a** of tapentadol is administered during a first administration interval and

- dose **b** of tapentadol is administered during a second administration interval following said first administration interval,

*where dose **a** < dose **b**.*"

II. The following documents are referred to in the present decision:

(1) US-B-6,605,644

(2) EP-A-0 693 475

(4) G.E. Ruoff, Pharmacotherapy 19(1), 1999, 88-93

(10) H.J. McQuay, Br. J. Anaesth. 63, 1989, 213-226

III. In the decision under appeal, the opposition division considered that the claims of the main request did not add subject-matter and that their underlying invention

was sufficiently disclosed. In addition, the claimed subject-matter was considered to be novel and inventive.

In its analysis of inventive step, the division viewed document (2), in particular its example 25, as the closest prior art. This example disclosed the preparation of tapentadol in the context of the provision of analgesic substances that do not exhibit the side effects of tramadol (see point 6.1 of the decision). The problem to be solved was then seen in the reduction of the somnolence frequency caused by tapentadol without a diminution of its therapeutic efficacy. Starting from the closest prior art, the division considered that neither of documents (1) and (4) rendered the claimed subject-matter obvious. This opinion was essentially based on the facts that the documents did not deal with tapentadol but with tramadol, that they focused on side effects other than somnolence, and that the outcome of titration was unpredictable, especially when applied to a different active agent.

IV. With its statement of grounds of appeal, the appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety. At the same time, it filed, among others, document (10).

V. In its reply to the grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed or, alternatively, that the patent be maintained on the basis of any of the claim sets filed with the reply as auxiliary requests 1 to 7. In addition, the respondent requested that, among others, document (10) not be admitted into the appeal proceedings.

VI. With a letter dated 4 April 2017, a third party filed observations and four further documents.

VII. In its preliminary opinion, annexed to the summons to oral proceedings, the board noted *inter alia* that it was minded to admit document (10) and to agree with the appellant that, starting from document (2) and in view of documents (1), (4) and (10), the subject-matter of claim 1 of the main request was not inventive.

VIII. Oral proceedings were held before the board on 31 May 2018. In the course of the proceedings, the respondent withdrew its seven auxiliary requests and maintained only its main request.

IX. The appellant's arguments, where relevant to the present decision, may be summarised as follows:

On the admission of document (10), the appellant argued that the document had been filed in response to the decision under appeal.

In its assessment of inventive step, the appellant considered document (2) to be the closest prior art (see letter dated 4 January 2018, E.2 and E.3). The subject-matter of claim 1 differed from the closest prior art in that the dose of tapentadol was titrated. On the formulation of the technical problem the appellant disagreed with the opposition division and considered that the problem could not be artificially restricted to a reduction of the somnolence events caused by tapentadol. At most, it had to be seen in a general reduction in tapentadol's side effects. This was clear from paragraphs [0007], [0010], [0024], [0117], and [0154], in the patent, where the reduction

in side effects was not confined to somnolence. Somnolence was merely taken as an indicator of typical opioid-related adverse events, as stated in paragraph [0168].

The solution proposed in claim 1 (i.e. titration) was obvious in the light of documents (1), (4) and (10), which demonstrated that, at the filing date, titration was the usual way to start opioid treatment in order to provide the lowest possible effective dose to the patient and the lowest level of side effects. In particular, the appellant noted that, even though documents (1) and (4) dealt specifically with the weak opioid tramadol, they also contained some teaching directed to opioids in general (see document (1), column 2, lines 52-56, and document (4), page 89, left column, lines 20-23), namely that slow titration of a therapeutic agent is often used by practising clinicians to minimise adverse events associated with centrally-acting agents such as analgesics. This was confirmed by document (10), a review article on the treatment of chronic pain with opioids, which recommended on page 224, left column, the titration of both weak and strong opioids. In particular, document (10) suggested the titration of strong opioids (to which tapendadol belongs) to find the dose at which the patient is pain-free for at least four hours without unacceptable side effects. As a result, it was obvious to the skilled person that tapentadol's adverse side effects could be minimised by titration. In this connection, any reduction in somnolence that resulted from titration was merely a bonus effect and could not confer inventive step on the claimed subject-matter.

X. The respondent's arguments, where relevant to the present decision, may be summarised as follows:

With respect to the admission of document (10), the respondent stated that the document was not *prima facie* relevant and that the appellant had not explained why it could not have been filed during the proceedings before the opposition division (see letter dated 15 October 2014, page 3, paragraph 2).

Turning to the issue of inventive step, the respondent likewise considered that document (2) represented the closest prior art (see letter dated 15 October 2014, page 19, line 3) and that the subject-matter of claim 1 differed from it in that the dose of tapentadol was titrated. The problem however had to be formulated in terms of a reduction in the psychiatric side effects associated with the administration of tapentadol, such as somnolence and dry mouth. This problem had been solved satisfactorily by titration, as shown by the examples in the patent and the additional evidence filed with the letter of 15 October 2014 (see pages 11 to 13).

On the issue of obviousness, the respondent considered that the teaching of documents (1) and (4) related to tramadol, a weak opioid which had a mode of action different to that of tapentadol, which was a strong opioid. For that reason, the teaching of documents (1) and (4) could not be extrapolated to tapentadol. In addition, those documents showed a reduction of nausea, vomiting, dizziness and vertigo but they did not demonstrate any reduction in psychiatric side effects. In this respect, the results in table 3 of document (4) proved that the effect of titration on psychiatric side effects, such as somnolence, was unpredictable. This

was reinforced by the results depicted in figures 5, 6 and 8 of the patent, which demonstrated that titration could reduce the somnolence caused by tapentadol but not that of oxycodone, a closely-related strong opioid.

On document (10), the respondent contended that it was particularly focused on morphine, that it was silent on psychiatric effects, and that it proposed solutions other than titration to reduce adverse side effects, e.g. another route of administration or the addition of compounds that suppress side effects. Furthermore, document (10) did not contemplate the replacement of morphine with another strong opioid (see page 218, paragraph 2), let alone tapentadol.

In conclusion, the effect of titration on the psychiatric side effects of an opioid was unpredictable and could not be expected to be maintained from one opioid to another. Moreover, titration was merely one of several possible ways of reducing side effects; the skilled person could equally have considered the use of drug combinations, different routes of administration, drug targeting or release adjustment. Hence, the claimed subject-matter was inventive.

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

- The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

- The respondent requested that the appeal be dismissed.

XII. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of document (10) - Article 12(4) RPBA

In the appealed decision (see points 6.3 and 6.4), the opposition division rejected the appellant's argument, based on the teaching of documents (1) and (4), that the claimed subject-matter lacked inventive step because, at the filing date, titration was the usual method of dosing opioids for the treatment of pain and that this was known to reduce side effects in general. It rejected it because the teachings of documents (1) and (4) were directed to tramadol only and were not applicable to other opioids such as tapentadol. In addition, documents (1) and (4) did not deal with a reduction in adverse psychiatric side effects (e.g. somnolence) but focused, rather, on nausea, vomiting, dizziness and vertigo.

Document (10) *prima facie* supports the rejected argument in that it broadly relates to the titration of weak and strong opioids and to its link with the reduction in side effects in general (see abstract; page 223, right column, lines 1-4; and page 224) and somnolence or drowsiness in particular (see page 220, left column, last paragraph; and page 224, right column, lines 5-8). It is therefore considered as an adequate response to the appealed decision. Moreover, the appellant filed document (10) at the earliest possible stage after the decision had been issued, i.e.

with its statement of grounds of appeal. Therefore, the board decided to take document (10) into account pursuant to Article 12(4) RPBA.

3. Inventive step of the subject-matter of claim 1 of the main and sole request - Article 56 EPC

3.1 The patent in suit is directed to the titration of the strong opioid tapentadol in the treatment of pain (see claim 1). This mode of administration achieves the desired analgesic effect and, at the same time, reduces the onset of adverse side effects, in particular somnolence, thereby improving tapentadol tolerability and patient compliance (see paragraphs [0001], [0007], and [0010]).

3.2 The parties concurred with the opposition division that document (2) represents the closest prior art. This document deals with the provision of new analgesic compounds for the treatment of strong pain which do not cause the typical side effects of opioids. In particular, the new compounds should not have the side effects that occasionally arise in treatment with tramadol, such as nausea and vomiting (see page 2, lines 26-29). Example 25 of document (2) discloses tapentadol as one of those new analgesic compounds.

The parties also concurred that the subject-matter of claim 1 differs from the closest prior art in that the dose of tapentadol is titrated.

3.3 Problem to be solved

On the issue of the formulation of the technical problem to be solved, the parties had different views.

The respondent agreed with the opposition division's proposed formulation of the problem as a reduction in the frequency of somnolence associated with the administration of tapentadol without diminishing its efficacy. It nevertheless stated that somnolence was an indicator of psychiatric side effects and that it was more accurate to define the problem in terms of a reduction in the psychiatric side effects caused by tapentadol.

By contrast, the appellant saw the problem in a broader context as the reduction in the side effects of tapentadol that may lead to an early discontinuation of therapy. This formulation of the problem was based on the consideration that a separation of the different side effects which may lead to an early discontinuation of the tapentadol therapy would be artificial and unrealistic.

In the following, the board has analysed the outcome of the problem-solution approach starting from the technical problem as defined by the respondent, i.e. reducing the psychiatric side effects associated with the administration of tapentadol without diminishing its efficacy.

3.4 Solution

The solution proposed in claim 1 is the titration of the tapentadol dose. In view of the results depicted in section 6.3.6. of the respondent's reply to the grounds of appeal, titration effectively reduces the incidence of early discontinuation of tapentadol therapy due to somnolence as an indicator of psychiatric side effects. The board is therefore satisfied that the problem is solved.

3.5 Obviousness

The authors of documents (1), (4) and (10) concur in generally stating that titration was a practice commonly followed by clinicians to reduce the adverse side effects arising from analgesics in the treatment of chronic pain (see document (1), column 2, lines 52-56; document (4), page 89, left column, lines 20-23; and document (10), page 224, left column). At a more specific level, the analgesics referred to in those documents are opioids in general (document (10)) or the weak opioid tramadol (documents (1) and (4)). Hence, it is apparent from the general teaching of these documents that the use of titration for generally reducing opioid side effects in the treatment of chronic pain belonged to the skilled person's general knowledge and was therefore obvious.

Somnolence or its synonyms drowsiness, "feeling drugged" or "having a clouding of thought" were also known in the art as being one of the frequent opioid side effects that lead to an early discontinuation of therapy. This was acknowledged in the patent for tapentadol (see paragraph [0007]), in documents (1) and (4) for tramadol (see document (1), column 2, lines 7-13; and document (4), page 89, left column, lines 16-19, and table 3) and in document (10) for strong opioids in general (see page 220, left column, last paragraph, and page 224, right column, lines 5-8). Moreover, those documents contained indicators that somnolence, either specifically or as part of the combined side effects of opioids, could be effectively reduced by titration. Thus, although document (1) focused particularly on dizziness and nausea, it taught that tramadol titration generally reduced adverse side

effects that lead to therapy discontinuation (see column 2, lines 59-64, and column 4, lines 44-47 and 55-58). Similar conclusions were reported in document (4), also in connection with tramadol titration (see page 91, left column, paragraph 3). Lastly, document (10) specifically taught a reduction in clouding of thoughts by titration of morphine (see page 220, left column, last paragraph) and suggested the titration of both weak and strong opioids as a way of achieving good pain relief without unacceptable side effects (see page 224, left column).

Taking these disclosures into consideration, the board holds that, starting from document (2) and in the light of documents (1), (4) and (10), the skilled person would have regarded titration as a suitable measure for generally reducing tapentadol's adverse side effects, including psychiatric side effects, since there was no indication in the prior art which would have led the skilled person to believe that psychiatric side-effects were an exception or that they needed to be treated differently. Hence, the solution proposed in claim 1 is not inventive (Article 56 EPC).

3.6 The respondent and the opposition division maintained that the effects observed in documents (1) and (4) associated with the weak opioid tramadol could not be extrapolated to the strong opioid tapentadol due to their different modes of action. Furthermore, the examples in documents (1) and (4) showed a reduction in gastrointestinal side-effects but did not address the issue of psychiatric side effects. Thus, a reduction in psychiatric effects could not be expected, especially taking into consideration that document (4) showed in table 3 that the result of titration on somnolence was unpredictable. Lastly, the respondent and the

opposition division concurred that the patent showed in figures 5, 6 and 8 that somnolence was not generally reduced by titration because this way of dosing reduced the somnolence caused by tapentadol but not that of oxycodone, a closely-related strong opioid. In conclusion, the effect of titration was unpredictable and a reduction in the somnolence caused by tapentadol could not be expected.

As an additional argument, the respondent and the division considered that titration was not the only method known to reduce side effects; it represented merely one option among others, such as drug combinations, choosing different routes of administration, drug targeting or release adjustment. Consequently, for this reason too, the selection of titration was not obvious.

3.7 The board does not find these arguments convincing for the following reasons.

As explained above, reducing opioid side effects by titration was part of the general knowledge at the filing date, as expressed in documents (1), (4) and (10). This principle was clearly taught to be general and no considerations were made in relation to the mode of action, the chemical structure or the strength of the opioid. This is particularly apparent from document (10), which suggests the titration of both weak and strong opioids. Accordingly, the skilled person could have reasonably expected that titration of tapentadol would reduce its adverse side effects.

Having regard to the reduction in the psychiatric side effects in particular, the prior art does not contain any teaching which raises doubts about the

applicability of the general principle that titration reduces side effects to the specific case of psychiatric side effects. The board concedes that the result of the application of a general principle is subject to a certain degree of variability depending on circumstances, e.g. the specific opioid and its side-effect profile. However, that variability was not seen in the prior art as invalidating the general principle that titration consistently reduced side effects. In this respect, the results in table 3 of document (4) are considered to merely reflect such variations in a very specific case and are not sufficient to invalidate the general knowledge recognised in documents (1), (4) and (10).

With respect to the evidence in figures 5, 6 and 8 of the patent, allegedly proving that the somnolence caused by tapentadol would be reduced by titration while that caused by oxycodone would not, the board notes that those results cannot be considered as being conclusive because, according to paragraphs [0167] and [0177], the patients that did not complete the treatment until the fourth week were discarded. Hence, the results represented in figures 5, 6 and 8 excluded the essential information of how many patients had discontinued the treatment before the fourth week and, in particular, how many did so due to somnolence. The exclusion of that information raises serious doubts about the conclusiveness of the results.

As to the argument that the skilled person could have chosen among several strategies to reduce the psychiatric side effects of tapentadol (e.g. titration, drug combinations, a different route of administration, etc.), the existence of several options to achieve the same effect does not necessarily render any of them

inventive. Given that titration was one of the solutions that the skilled person would have expected to successfully solve the problem posed, it was obvious irrespective of the existence of other (possibly obvious) solutions.

3.8 In view of the outcome of the problem-solution approach starting from the problem as formulated by the respondent, there is no need for the board to follow the approach starting from the less ambitious problem proposed by the appellant.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

K. Boelicke A. Lindner

Decision electronically authenticated