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# Datasheet for the decision of 9 April 2021

**Case Number:** T 2443/18 - 3.3.01

**Application Number:** 11733571.1

**Publication Number:** 2588093

**IPC:** A61K31/135, A61P1/00, A61K31/137

**Language of the proceedings:** EN

**Title of invention:**
TAPENTADOL FOR USE IN THE TREATMENT OF IRRITABLE BOWEL SYNDROME

**Patent Proprietor:**
Grünenthal GmbH

**Opponent:**
Hexal AG / Sandoz International GmbH

**Relevant legal provisions:**
EPC Art. 56

**Keyword:**
Inventive step - (no)

**Decisions cited:**
T 0967/97, T 1742/12

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**Case Number: T 2443/18 - 3.3.01**

# D E C I S I O N
# of Technical Board of Appeal 3.3.01
# of 9 April 2021

| | |
|---|---|
| **Appellant:** (Opponent) | Hexal AG / Sandoz International GmbH<br>Industriestrasse 25<br>83607 Holzkirchen (DE) |
| **Representative:** | Lederer & Keller Patentanwälte<br>Partnerschaft mbB<br>Unsöldstraße 2<br>80538 München (DE) |
| **Respondent:** (Patent Proprietor) | Grünenthal GmbH<br>Zieglerstrasse 6<br>52078 Aachen (DE) |
| **Representative:** | Brosch, Oliver<br>Kutzenberger Wolff & Partner<br>Waidmarkt 11<br>50676 Köln (DE) |
| **Decision under appeal:** | **Decision of the Opposition Division of the European Patent Office posted on 23 July 2018 rejecting the opposition filed against European patent No. 2588093 pursuant to Article 101(2) EPC.** |

**Composition of the Board:**

| | |
|---|---|
| **Chairman** | A. Lindner |
| **Members:** | R. Hauss |
| | R. Romandini |

## Summary of Facts and Submissions

I. European patent No. 2 588 093 (patent in suit) was granted with a set of eight claims. Claim 1 reads as follows:

*"1. Tapentadol for use in the treatment of irritable bowel syndrome."*

The remaining claims 2 to 8 are dependent claims.

II. The patent was opposed under Article 100(a) EPC on the grounds that the claimed subject-matter lacked novelty and did not involve an inventive step.

III. The documents cited in the proceedings included the following:

D1: Drugs of the Future 31(12), 1053-1061 (2006)

D3: J Clin Gastroenterol 35(Suppl), S58-S67 (2002)

D4: Neurology 70(Suppl 1), A164, P03.157 (2008)

IV. The decision under appeal is the opposition division's decision rejecting the opposition, announced on 13 June 2018 and posted on 23 July 2018.

V. According to the decision under appeal, the subject-matter of claim 1 as granted was novel. It also involved an inventive step: Prior-art document D3 taught that loperamide was a compound suitable for the treatment of irritable bowel syndrome (IBS). Loperamide, like tapentadol, belonged to the class of μ-opioid receptor agonists. Starting from D3 as the closest prior art, the technical problem to be solved consisted in providing an alternative μ-opioid receptor agonist useful for the treatment of IBS. This problem was credibly solved by claim 1 of the patent in suit

in view of the experimental data on tapentadol presented in examples 1 and 2. The person skilled in the art would not have found any indication in the cited prior-art documents that tapentadol, instead of loperamide, could be successfully used in the treatment of IBS.

VI. The opponent (appellant) appealed this decision.

VII. Oral proceedings before the board were held on 9 April 2021.

VIII. The appellant's arguments on inventive step may be summarised as follows.

Document D4, which disclosed the efficacy of tapentadol in several animal models of visceral pain, was a promising starting point for the assessment of inventive step. The objective technical problem was to provide a further medical use of tapentadol.

It was known (e.g. from document D3) that visceral pain was a major symptom of IBS. There was no relevant distinction between visceral pain and visceral pain in IBS. The animal models mentioned in D4 included those relied on in the examples of the patent in suit in support of the efficacy of tapentadol in the treatment of IBS. No inventive skill would thus have been required to suggest tapentadol for treating IBS.

IX. The respondent's arguments on inventive step may be summarised as follows.

Document D3 (a review of approved and investigational compounds for the treatment of IBS) had the same object as the patent in suit, namely the treatment of IBS. For this reason, D3 was the closest prior art. It

was also the only suitable starting point for the assessment of inventive step.

In contrast, document D4 was inappropriate as a starting point. The technical problem of finding a further medical use for a specified drug compound was artificial and did not reflect the approach which would have been taken by a research scientist. Drug development was about addressing a given disease by providing a drug compound suitable for its treatment, rather than providing a further therapeutic use for a given drug compound. Hence, it was not possible to formulate a reasonable technical problem starting from the teaching of document D4.

Furthermore, the appellant's conclusion that D4 suggested the suitability of tapentadol for the treatment of IBS was based on hindsight. The pathophysiology of IBS was complex. Neither D4 nor the other prior-art documents cited in the proceedings established a direct link between IBS and the animal models mentioned in D4.

X. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

XI. The respondent (patent proprietor) requested that the appeal be dismissed.

## Reasons for the Decision

1. Admissibility of the appeal

The appeal complies with Articles 106 to 108 EPC and Rule 99 EPC; it is admissible.

2. Inventive step (Articles 100(a), 52(1) and 56 EPC)

*Patent in suit*

2.1 The patent in suit acknowledges that irritable bowel syndrome (IBS) is a highly prevalent disorder characterised by abdominal pain and/or discomfort related to abnormal bowel habits (see paragraphs [0002] and [0051] of the patent). It states as its object to provide a compound and a medicament for use in the treatment of IBS (see paragraph [0006]).

2.2 The compound proposed in the patent (see claim 1) is the analgesic tapentadol.

2.3 Experimental data from two studies are reported in the examples of the patent in suit.

2.3.1 According to example 1, tapentadol was investigated with regard to its ability to modulate gastrointestinal motility. The compound was found to reduce electrically induced twitch contractions of the isolated guinea pig ileum in a concentration-dependent manner.

2.3.2 Example 2 describes a study based on a mouse model of mustard-oil-induced colitis in which tapentadol was administered either five minutes before mustard oil or four hours after mustard oil. Tapentadol showed a dose-dependent inhibition of three visceral pain

parameters (spontaneous visceral pain behaviour, referred allodynia and referred hyperalgesia).

2.3.3 The patent in suit states (see paragraph [0051]) that the studies described in examples 1 and 2

"clearly show the inhibitory effects of tapentadol on ileum contractions and on visceral nociception, referred visceral hyperalgesia and allodynia. Thus, tapentadol addresses major symptoms of IBS, abnormal gastrointestinal (GI) motility and visceral hypersensitivity and referred pain".

*Starting point in the prior art and objective technical problem*

2.4 In the decision under appeal (see point V above), document D3 was used as the starting point in the prior art for the assessment of inventive step.

2.5 The appellant contended, as it had also done in the proceedings before the opposition division, that document D4 was a more suitable starting point. This was contested by the respondent, who argued that D4 was entirely unsuitable.

2.6 If there were several workable routes, starting from different prior-art documents, which might have led the skilled person to the claimed subject-matter, the rationale of the problem-and-solution approach developed in the Boards' case law requires that all these possible routes be assessed before an inventive step can be acknowledged. Conversely, it is sufficient for denying inventive step if the claimed subject-matter lacks an inventive step in respect of one of the possible starting points (see T 967/97, Catchwords; T 1742/12, Reasons 6.6; Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, I.D.3.1).

2.7 A promising starting point is typically a prior-art document that discloses subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and has the most relevant technical features in common. A further criterion is the similarity of the technical problem to be solved.

2.8 It may happen that a piece of prior art is so remote from the claimed invention, in terms of intended purpose or technical features, that it can be argued in a *prima facie* assessment that the skilled person would not realistically have chosen it as a starting point and could not conceivably have modified it so as to arrive at the claimed invention. Such prior art might be referred to as "unsuitable". (Nonetheless, this would in principle not prohibit its consideration as a starting point in the problem-and-solution approach, which may in such a case be expected to result in a finding of non-obviousness.)

2.9 Thus, in view of the respondent's objection, the first question to be answered is whether the disclosure of D4 is a suitable starting point that may give rise to a workable route to the subject-matter claimed in the patent in suit.

2.10 Document D4 relates to tapentadol and its confirmed efficacy in animal models of visceral pain.

Tapentadol is the compound of claim 1 of the patent in suit. While D4 does not specifically refer to IBS, visceral pain is a typical manifestation of IBS, the therapeutic indication named in claim 1 of the patent in suit.

In view of this considerable overlap in technical features and purpose (see point 2.7 above), D4 cannot

be ruled out as a suitable starting point for the assessment of inventive step.

2.11 If inventive step is to be denied, the choice of starting point needs no specific justification (see T 967/97, Catchword II). Since D4 is a suitable starting point and the appellant's objection as to obviousness relied on D4, this approach was considered by the board.

2.12 The subject-matter of claim 1 of the patent in suit differs from the disclosure of document D4 only by giving a more specific medical indication, namely IBS instead of visceral pain.

2.13 Hence, the objective technical problem starting from the disclosure of D4 is to provide a further medical use for tapentadol.

2.14 The respondent took a different view, arguing that a drug developer would typically seek to provide a suitable drug for a given medical indication rather than investigate further medical indications for a given drug. As the objective technical problem formulated in point 2.13 did not reflect reality document D4 could not be considered an eligible starting point for the assessment of inventive step. Moreover, this technical problem did not correspond to the problem stated in the patent in suit (to provide a drug for treating IBS, see point 2.1 above).

2.15 However, this argument cannot succeed.

2.15.1 In fact, either approach may be taken by a person skilled in the art, depending on the stages reached in the development and life of a drug compound and the rationale for its development. After the initial stage

of drug discovery, the suitability of the drug for different therapeutic uses may conceivably be explored.

2.15.2 In the case at hand, tapentadol was modelled, synthesised and developed as an analgesic designed to combine two mechanisms of action, namely μ-opioid receptor agonism and noradrenaline reuptake inhibition (see D1: abstract and page 1055, column 1, second paragraph). Hence, it was clear that the compound's expected activity was pain relief. The logical next step was to investigate its efficacy against different types of pain (as reported in D1: page 1056, paragraph bridging columns 1 and 2, and D4) to determine the medical indications in which this drug might be useful. The objective technical problem as established starting from the teaching of D4 is thus realistic: It reflects the task the skilled person would have faced after the initial development of tapentadol.

2.15.3 According to the problem-and-solution approach developed in the case law of the Boards, the technical problem is determined objectively on the basis of an analysis of the distinctions between the claimed subject-matter and the disclosure of the starting point in the prior art. As a consequence, the objective technical problem does not have to be identical to the problem stated in the patent in suit.

*Solution to the objective technical problem*

2.16 The solution to the problem of providing a further medical use for tapentadol is its use in IBS, as defined in claim 1 of the patent in suit.

*Obviousness of the solution*

2.17 The objective of D4 was to demonstrate the efficacy and potency of tapentadol in animal models of visceral pain.

D4 states that "Because of its lower depressant effect on the activity of the intestine compared to morphine, as shown in the guinea pig ileum twitch model, tapentadol may be an interesting substance for the treatment of visceral pain".

The effects of tapentadol and morphine were investigated in three rodent models of visceral pain: mouse phenylquinone writhing, rat colorectal distension and mouse mustard-oil-induced colitis.

Tapentadol and morphine showed comparable analgetic effects in all models tested. The authors of D4 conclude that tapentadol has a broad efficacy profile in several animal models of visceral pain with efficacy in spontaneous as well as referred parameters of visceral pain.

2.18 The respondent contended that document D4 did not mention IBS, and the cited prior art did not establish a link between the animal models of D4 and IBS.

2.19 This argument is not convincing.

2.19.1 The link between IBS and the animal models of visceral pain mentioned in D4 is the fact that visceral pain was known as a characteristic symptom of IBS, as acknowledged in the patent in suit (see paragraphs [0002] and [0051]) and in document D3 (see page S58, column 2, lines 3 to 5).

The person skilled in the art would have been aware of IBS, its symptoms and its relevance as a highly prevalent gastrointestinal syndrome (paragraph [0002] of the patent in suit and D3: S58, column 1, last paragraph).

Hence, there would have been no hindsight involved in considering IBS as a possible field of application for a drug effective against visceral pain.

2.19.2 If the favourable outcome reported in example 2 of the patent in suit, based on the mouse mustard-oil-induced colitis model, pointed to the efficacy of tapentadol in reducing IBS-related visceral pain, the same must be true for the corresponding results reported in D4 on the basis of the same animal model.

2.19.3 The respondent argued that IBS was a complex disorder with many contributing factors (see paragraph [0002] of the patent in suit) but failed to provide any specific reason why the visceral pain in IBS should be different from the visceral pain addressed in the rodent models of D4, especially in the mustard-oil-induced colitis model also relied on in the patent in suit.

2.19.4 D4 compares tapentadol to morphine. The μ-opioid receptor agonists morphine and loperamide were known to be useful in the treatment of IBS (D3: S63, column 1, first and second paragraphs). Thus, what was known about the efficacy of μ-opioid receptor agonists (a mechanism shared by tapentadol) would not have raised doubts about the potential efficacy of tapentadol in the treatment of IBS.

2.19.5 In conclusion, the board is not aware of any specific reason why the person skilled in the art should have assumed that the visceral pain in IBS would not be susceptible to treatment with an analgesic confirmed to be effective against visceral pain in the animal models of D4.

2.20 The information obtained on the basis of the guinea pig ileum twitch model was the same in D4 as in the patent in suit, namely that tapentadol inhibits ileum contractions. In this context, the patent comments on the potential usefulness of tapentadol in inhibiting abnormal intestinal motility which may be a symptom

of IBS (see paragraph [0051]). D4, on the other hand, mentions that this depressant effect of tapentadol is less pronounced than with morphine, which may be of interest in cases when constipation is an unwanted side-effect. In any case, the results observed on the basis of the guinea pig ileum twitch model do not cast doubt on the expected efficacy of tapentadol in the treatment of IBS.

2.21 For these reasons, and in line with the rationale set out in point 2.6 above, the subject-matter of claim 1 does not involve an inventive step within the meaning of Article 56 EPC.

**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:

M. Schalow A. Lindner

Decision electronically authenticated