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Datasheet for the decision of 16 September 2015

Case Number: T 1378/11 - 3.3.01

Application Number: 04719852.8

Publication Number: 1601350

IPC: A61K31/135, A61K9/20, A61K9/48, A61P29/02

Language of the proceedings: EN

Title of invention:
TITRATION DOSING REGIMEN FOR CONTROLLED RELEASE TRAMADOL

Patent Proprietor:
EURO-CELTIQUE S.A.

Opponent:
Biovail Corporation

Headword:
Tramadol dosage/EURO-CELTIQUE

Relevant legal provisions:
EPC Art. 113(1), 100(a), 100(c)
RPBA Art. 12(4)

Keyword:

Decisions cited:
R 0001/08, R 0011/12, R 0002/13, R 0003/13, R 0005/13, R 0016/13, T 1634/06

Catchword:

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Case Number: T 1378/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 16 September 2015

Appellant: (Patent Proprietor)	EURO-CELTIQUE S.A. 2, avenue Charles de Gaulle 1653 Luxembourg (LU)
Representative:	Bühler, Dirk Maiwald Patentanwalts GmbH Elisenhof Elisenstrasse 3 80335 München (DE)
Respondent: (Opponent)	Biovail Corporation 7150 Mississauga Road Mississauga ON L5N 8M5 (CA)
Representative:	Lane, Cathal Michael Tomkins & Co. 5 Dartmouth Road Dublin 6 (IE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 12 April 2011 revoking European patent No. 1601350 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	C. M. Radke
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 601 350 relates to a dosing regimen for administering tramadol to a patient in a controlled release dosage form.

II. An opposition was filed against the grant of this patent. It was directed against the patent as a whole and was based on grounds under Article 100(a)(alleged lack of novelty and inventive step and exception to patentability under Article 53(c) EPC) and 100(c) EPC.

III. The documents filed during the opposition procedure include the following:

(D1) Business Wire, Article "Biovail Reports Second Positive Phase III Clinical Result for Tramadol Extended Release Formulation", dated 14 January 2002, two pages

(D3) Business Wire, Article "Biovail Presents Tramadol Results at American College of Rheumatology", dated 28 October 2002, two pages

(D4) Medscape Conference Coverage, E. Hitt "Extended-Release Tramadol Reduces Symptoms of Chronic Knee Pain", dated 27 October 2002, two pages

(D5) Medscape article, L. S. Simon, "Clinical Advances in Osteoarthritis", updated 27 November 2002, five pages

(D6) Copy of the poster of S. Sista et al., "STEADY STATE DOSE PROPORTIONALITY OF A NOVEL FORMULATION OF TRAMADOL HCL EXTENDED RELEASE TABLETS", alleged to have been presented at the AAPS Annual Meeting of 26-30 October 2003, three pages

(D6a) S. Sista et al., AAPS Pharm. Science 2003, vol. 5(S1), abstract 1803, one page

(D7) Copy of the poster of J. C. Lai et al., "THE

PHARMACOKINETICS OF NOVEL ONCE DAILY TRAMADOL HYDROCHLORIDE EXTENDED RELEASE TABLETS IN HEALTHY SUBJECTS", alleged to have been presented at the AAPS Annual Meeting of 26-30 October 2003, three pages

(D7a) J. C. Lai et al., AAPS Pharm. Science 2003, vol. 5(S1), abstract 1814, one page

(D13) WO-A-03/072 025

(D14) Cancer pain relief with a guide to opioid availability, second edition, WHO, Geneva 1996, 70 pages

(D15) Rote Liste 2001, ECV Editio Cantor Verlag, Aulendorf/DE, 05 051-05 073

(D18) R. D. Colucci, "EXPERT STATEMENT" dated 21 February 2011, three pages + 30 pages annexes

(D19) Excerpts from clinical study TRJ1001, report dated 1 June 2001, enclosed with Appellant's letter dated 22 February 2011

(D21) WO-A-00/25 769

IV. The opposition division revoked the patent.

In particular, the opposition division decided that

- the claims of the **main request** and of **auxiliary request I** contained added subject-matter under Article 100(c) or 123(2) EPC as far as they referred to "moderate to severe pain",
- the subject-matter of the claims of **auxiliary requests IIA and IIIA** was not inventive, and
- that the claims of **auxiliary requests IIB and IIIB** were not clear.

V. The patent proprietor appealed this decision.

VI. The additional documents cited during the appeal proceedings include the following:

(D20) Information on "ULTRAM® ER (tramadol HCl) Extended-Release Tablets", revised in December 2011, file:///C:/Users/Ed/AppData/Local/Microsoft/Windows/Temporary%20Internet%20Fil...", retrieved on 12 August 2015, 20 pages, enclosed with appellant's letter dated 14 August 2015

(D23) "CLINICAL REVIEW" on Tramadol Extended Release, Submission Number 21-692, completion date 29 October 2004, applicant: Biovail, 77 pages

(D24) Purdue Pharma Products L.P et al. vs. Par Pharmaceuticals, Inc. et al., U.S. District Court for the District of Delaware, 14 August 2009, 103 pages

(D25) "Memo of the Proprietor concerning the oral proceedings before the Opposition Division on March 22, 2011", letter of the appellant to the EPO dated 14 April 2011, ten pages

VII. The present decision is based on the following sets of claims:

- claims 1-21 of the main request,
- claims 1-21 of the first auxiliary request, and
- claims 1-8 of the second auxiliary request,

all filed under cover of the letter dated 22 August 2011 setting out the grounds for appeal.

a) The claims of the **main** request are identical to the claims as granted. Claim 1 reads as follows:

"1. Use of tramadol in the manufacture of a medicament in a controlled-release dosage form for the treatment of moderate to severe pain or mild to moderate pain, wherein

75 mg to 125 mg of tramadol once-a-day for 4 to 10 days;
then 175 mg to 225 mg of tramadol once-a-day for 4 to 10 days;
then 275 mg to 325 mg of tramadol once-a-day for at least one day and optionally thereafter, is to be administered."

b) Claim 1 of the **first auxiliary request** differs from that of the main request in that the expression "moderate to severe pain" has been deleted.

c) Claim 1 of the **second auxiliary request** reads as follows:

"1. Use of tramadol in the manufacture of a medicament in a controlled-release dosage form for the treatment of mild to moderate pain, wherein 100 mg of tramadol once-a-day on days 1 through 7, then 200 mg of tramadol once-a-day on days 8 through 14,
then 300 mg of tramadol once-a-day on day 15 and optionally thereafter, is to be administered."

VIII. The appellant's arguments as far as relevant to this decision may be summarised as follows:

Alleged procedural violation of the proprietor's right to be heard during the oral proceedings before the opposition division

In view of the board's communication of 18 May 2015 pursuant to Article 15(1) RPBA setting out the board's preliminary opinion on procedural issues raised by the appellant in its letter dated 14 April 2011 (D25) and in its statement of grounds of appeal, the appellant

clarified at the oral proceedings that it considered that its right to be heard had been violated by the opposition division's assessment of the clinical data in the patent. The appellant only learned from the contested decision that the opposition division doubted that the clinical data in the opposed patent showed a reduction in side effects by the dosage regimen according to the opposed patent. The opposition division did not bring its doubts to the appellant's attention during the opposition proceedings. It was thus not possible to explain the clinical data and to clarify the relevance of these data and the contribution of the patent to the state of the art. The opposition division's evaluation of the clinical data in the assessment of inventive step was significant and causal for its conclusions. The situation was thus similar to the case considered in decision R 16/13. Moreover, the opposition division assigned the legal burden of proof incorrectly.

The appellant confirmed during the oral proceedings that it requested neither the remittal of the case to the department of first instance nor the refund of the appeal fee.

Documents (D23) and (D24)

These documents were filed with the statement of the grounds of appeal to support the argument that document (D1) did not represent the closest prior art. Moreover, the filing of document (D23) was a reaction to the surprising conclusion by the opposition division that the data contained in the patent in suit were not sufficient to show a surprising effect.

Articles 100(c) and 123(2) EPC

Original claim 1 was not limited to any severity of pain. Tramadol was known to be suitable for the treatment of mild to moderate pain (see page 18, line 6, of the application as filed). It was evident to the person skilled in the art that the dose disclosed there was also suitable for the treatment of moderate to severe pain (see document (D15), which discloses a daily dose up to 400 mg for tramadoc; see also page 1, lines 17-19 of the application as filed). There was a certain degree of variability among patients to the responsiveness to a given dose of active agent. There was no scientific reason why tramadol could not also be used to treat mild to moderate pain.

Inventive step

Document (D1) was not the closest prior art, as it did not focus on improving the titration phase to reduce the drop-out rate. (D1) related to an "enrichment design" to pre-select test subjects with have a greater likelihood of responding to the drug (see (D23), page 11, 6th paragraph). This was also confirmed in document (D13). As could be taken from document (D18), the interest in optimising the dosage regimen arose from the high drop-out rates. The high drop-out rate observed in document (D1) would not have motivated the person skilled in the art trying to reduce said rate to consider said document. Moreover, the person skilled in the art would be more likely to trust in a patent document, such as (D21), than in the press release (D1), which is directed to investors, so document (D21) should be considered as the closest prior art. This document related to a dosing regimen of immediate-release tramadol which was to minimise side effects and to prevent patients from discontinuing treatment. The subject-matter of the

present claims differed from the disclosure in document (D21) in that the drug was provided in a controlled release form.

The data in the patent showed that a much higher dose could be applied without causing severe side effects if a controlled release form of tramadol was used.

The problem to be solved was to provide a dosing regimen for extended release formulations of tramadol that reduced adverse side effects and thus reduced the number of patients who discontinued treatment. Table 1 of the patent in suit showed that this problem had been solved. The onus was on the opponent to prove that the dosage regimen according to (D1) provided the same benefits as the claimed one; the opposition division was wrong to shift the burden of proof to the patent proprietor. The present dosage regimen provided the advantage that no patient dropped out in example 1 of the patent in suit, whereas in the study disclosed in document (D1), 37 % of the patients dropped out, mostly due to adverse effects. Neither document (D1) nor (D21) rendered it obvious to dose tramadol at 100 mg and at 200 mg per day for at least four days, respectively.
Although there were no data comparing the process of document (D1) with the claimed subject-matter, it was evident from the declaration (D18) - which suggested a minimum period of four days - and the document of approval of the FDA (D20), which disclosed the maintenance of the dose for five days at each step, that a minimum of four days was advantageous in order to link the clinical effects with a certain dose.

Contrary to the argument of the opposition division, Table 1 of the patent in suit showed that the occurrence

of side-effects was not linked to the overall dose of the drug.

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

Late-filed documents

Documents (D23)-(D25) were filed late, were not relevant and should not be admitted into the proceedings.

Articles 100(c) and 123(2) EPC

There was no basis in the application as filed for the expression "moderate to severe pain" in the claims as granted (main request), as this expression was disclosed there only in relation to the prior art. It was irrelevant that moderate to severe pain could also be treated with tramadol. This was all the more so the case as in titration dosage, the dosage regimen was matched to the pain being treated.

The expression "mild to moderate pain" had only been used in relation to the specific formulation of example 1. Its generalisation in the claims of the auxiliary requests contravened Article 123(2) EPC.

Novelty

The subject-matter of the claims lacked novelty in view of document (D1) or (D13). Document (D1) and document (D13)(see example 11) disclosed that the patients started on 100mg QD and maintained that dose for at least three days, and that on day 4 and for the remainder of the first week, patients were permitted to have their dose increased to 200 mg QD, meaning that some patients moved to 200 mg on any one of days

4 to 7.

Inventive step

Document (D1) represented the closest prior art. Any difference in the subject-matter claimed, if present, could reside only in the dosage regimen. To adjust the dosage, e.g. by increasing the dose, was common in order to alleviate the symptoms faster, and thus was not inventive, especially in view of documents (D3)-(D6), (D6a), (D7), (D7a) and (D13). It was well known to start with lower doses and to uptitrate when this lower dose was tolerated. The very essence of dose titration was to maximise benefit while minimising side effects. Hence, the subject-matter of the claims did not involve an inventive step.

X. The board summarised its preliminary opinion in a communication attached to the summons to oral proceedings. In this communication the board gave reasons why it considered that

- Document (D25) was not late-filed,
- the appellant's right to be heard had not been violated by the opposition division,
- the insertion of the term "moderate to severe pain" into the claims violated Article 123(2) EPC whereas the term "mild to moderate pain" did not, and
- the subject-matter of the claims was novel.

XI. The respondent/opponent had been duly summoned, but did not attend oral proceedings, as announced in its letter dated 3 September 2015.

The oral proceedings were thus continued in the absence of the duly summoned respondent in accordance with Rule 115(2) EPC.

XII. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or, alternatively, on the basis of the first or second auxiliary requests, all filed with the statement of grounds of appeal dated 22 August 2011. Furthermore, it requested that documents (D23) and (D24) were admitted into the proceedings.

The respondent requested in writing that the appeal be dismissed. Furthermore, it requested that documents (D23) to (D25) not be admitted into the proceedings.

XIII. In the course of the oral proceedings the Chairman announced the decision of the board.

Reasons for the Decision

1. The appeal is admissible.

2. The alleged violation of the appellant's right to be heard by the opposition division.

2.1 Article 113(1) EPC states that the decisions of the EPO may only be based on grounds or evidence on which the parties concerned have had an opportunity to present their comments. This implies that a party may not be taken by surprise by the reasons of a decision, referring to unknown grounds or evidence (R 3/13 of 30 January 2014, point 2.2 of the Reasons). If a party was aware, or could have been aware, of the ground or evidence on which the assessment or reasoning of a decision was based, and had an opportunity to comment

thereon, it cannot be taken by surprise. It must also be added that the right to comment does not extend to every possible assessment or reasoning in a decision (R 2/13, point 2.1.3 of the Reasons). No provision of the EPC requires the deciding body to provide a party in advance with all foreseeable reasons in favour or against a request (R 1/08 of 15 July 2008, point 3.1 of the Reasons).

The alleged new ground is to be found in the first paragraph of point 4.4.5.3 on page 15 of the contested decision. It concerns the opposition division's analysis of the data of the clinical study (pages 20 to 23 of the application as filed; paragraphs [0099] to [0107] of the patent) with respect to the issue, whether these data demonstrate a technical effect linked to the differences of the claimed subject-matter with the dosage regimen of the closest prior art document (D1). The opposition division had raised this issue in its communication of 20 September 2010 (see point 6.4.1) and the appellant commented thereon in its letter of 22 February 2011 (see pages 14-20) and filed additional documents (D18) to (D20) in support. The issue was also discussed at the oral proceedings (see page 8 of the minutes). In its decision, the opposition division dealt with the appellant's submissions regarding this issue and found the clinical data of the patent to be inconclusive. This evaluation of the appellant's evidence did not introduce any change to the factual or legal framework of the debate. It does not constitute a new ground within the meaning of Article 113(1) EPC either, since it is part of the opposition division's detailed assessment and reasoning relating to the grounds and evidence which have been put forward by the parties (as to the distinction between new grounds and reasons see R 2/13, point 2.1.3 of the Reasons). The opposition division has

to evaluate the evidence before it, even in the absence of any objections from the adverse party. Such lack of objections raised cannot render the evidence conclusive.

The appellant relied on decision R 16/13 of 8 December 2014. It appears from points 5.2 to 5.4 of the reasons of said decision that the Enlarged Board of Appeal considered that the technical board had ignored the petitioner's argument that the reference to the micronisate of the invention in the comparative data provided by the petitioner implied that the respective samples had the parameters as claimed by the product claim of the main request, and that, as a consequence, the petitioner could not have been expected to have anticipated the board's view that the comparative data were deficient to show the alleged advantage. In view of the specific circumstances and the further jurisprudence of the Enlarged Board of Appeal in review cases, decision R 16/13 cannot, in the board's judgment, be understood to have given the parties the right to find out from the deciding body how it assesses the facts and arguments on which its decision will likely be based. The decision has rather to be seen in connection with the reference in decision R 3/13 of 30 January 2014 (point 2.6 of the Reasons) to the jurisprudence of the Federal Court of Justice, according to which the obligation to inform the parties only exists under German law if the parties, despite conducting the proceedings with all due care, could not foresee the legal considerations on which the court's decision might ultimately be based. This is, however, not the situation in the present case. It is established jurisprudence that, if comparative tests are chosen to demonstrate an inventive step on the basis of an advantageous effect, the nature of the comparison with the closest state of the art must be such that the alleged advantageous

effect is **convincingly shown** to have its origin in the distinguishing feature of the invention compared with the closest state of the art, and that alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underlying the invention (see Case Law of the Boards of Appeal, 7th edition 2013, I.D.10.9). Since the appellant could have been expected to know this jurisprudence and since it relied on its own data, the opposition division had no obligation to warn it of deficiencies within its own responsibility. In so far as the appellant alleges that the opposition division evaluated the clinical data of the patent incorrectly, this amounts to an error in judgment only, which is open to review in appeal, and cannot be characterised as a procedural violation, let alone a substantial one.

For the above reasons, the appellant could not, on an objective basis, have been surprised by the decision in the sense that it discovered a ground for the first time in the written decision.

2.2 With respect to the alleged error in the determination of the burden of proof, the Board notes that, as a matter of principle, the legal burden of proof lies with the party who makes the assertion. The legal burden of proof that the patent is lacking inventive step thus lies on the opponent. The opponent has to show that, in the light of the state of the art it has put forward, the skilled person would arrive at the claimed invention without inventive skills. However, if the patentee relies on an improvement, the burden is on the patentee to prove that, compared with the closest prior art, there is an improvement. The mere assertion that an improvement exists is not sufficient to discharge the burden of proof. There must be at least a single

experimental result showing the alleged improvement. The experimental evidence should show that the improvement is attributable to the claimed difference vis-à-vis the closest state of the art. The opponent can challenge such experimental evidence either by saying the experimental result reported is not correct, or by showing that equally valid experimental comparisons do not confirm the improvement. However, the opponent does not, as alleged by the appellant, bear the burden of proof that there is no improvement.

Since the opposition division allocated the burden of proof in accordance with the principles set out above, it did not contravene Article 113(1) EPC.

2.3 The appellant did not raise any further objections under Article 113(1) EPC. Consequently, there is no reason to conclude that the opposition division did not respect the patent proprietor's right to be heard.

3. Admission of documents (D23) to (D25)

3.1 Article 12(4) of the Rules of Procedure of the Boards of Appeal (RPBA) states that the board has the power to hold inadmissible those facts and evidence "which could have been presented ... in the first instance proceedings" (see Supplementary Publication of OJ EPO 1/2015, 41-50).

3.2 Documents (D23) to (D25) were enclosed with the statement setting out the grounds of appeal dated 22 August 2011.

3.2.1 Document (D23)

This document was used by the appellant as evidence in support of its argument that document (D1) could not be the closest prior art. It merely supplements the information of the press release (D1) and thus does not introduce facts which change the factual framework of the first instance proceedings. Hence, the board decided to admit document (D23) into the proceedings.

3.2.2 Document (D24)

During the oral proceedings before the board, the appellant declared that he would not rely on this document. Hence, there was no reason to decide on the admission of this document into the appeal proceedings.

3.2.3 Document (D25)

Document (D25) is a "Memo of the Proprietor concerning the oral proceedings before the Opposition Division on March 22, 2011". As it relates to the final step in the opposition procedure, it could not have been presented before the opposition division. Moreover, it related to the procedural issues raised in the statement of grounds of appeal. Hence, the conditions under Article 12(4) RPBA for not admitting this document were not met. Therefore, document (D25) was admitted into the proceedings.

Main Request

4. Article 100(c) EPC

The feature "moderate to severe pain"

4.1 This feature is disclosed in the application as filed in the section "BACKGROUND OF THE INVENTION" on page 1,

line 19. Furthermore, the appellant pointed out that the use of tramadol for the treatment of moderate to severe pain was generally known from document (D15).

In contrast to this, the formulations in example 1 of the application as filed "were developed for the relief of mild to moderate pain" (see page 18, lines 5-6). This leads to the conclusion that the dose of tramadol in this example was lowered to such a degree that only mild to moderate pain, and not severe pain, could be alleviated to an acceptable level. Such a lowering of the dose whenever possible is clearly linked to the object of the invention to reduce "the occurrence of and concomitant severity of adverse tramadol elicited side effects" (see page 2, lines 1-6, of the application as filed).

The dosage forms disclosed in example 1 of the application as filed comprise those containing 100 mg, 200 mg and 300 mg of tramadol HCl (see page 19, line 19; page 18, line 10; page 20, line 4). This corresponds to the dosing regimen defined in claim 1 as originally filed, in which the three steps of 75 to 125 mg, 175 to 225 mg and 275 mg to 325 mg are to be used.

4.2 Hence, the person skilled in the art would have derived directly and unambiguously from the application as filed that the aim of the dosage regimen claimed therein was to alleviate "mild to moderate pain" as disclosed in its example 1, but not "moderate to severe pain" as stated in the background section.

4.3 The fact that document (D15) recommends a maximum dose of 400 mg per day of tramadol HCl for the treatment of moderate to severe pain does not mean that a dose of 275 to 325 mg is generally sufficient to treat severe pain.

This is all the more so the case as (D15) allows for higher daily doses for the treatment of pain caused by tumours.

4.4 Consequently, grounds under Article 100(c) EPC prejudice the maintenance of the patent on the basis of the claims as granted (main request). Hence, the main request was refused.

First Auxiliary Request

5. Article 123(2) EPC

In the claims of the first auxiliary request, the expression "moderate to severe pain", which gave rise to the rejection of the main request, was deleted.

For the reasons given under point 4 above, the insertion of the expression "mild to moderate pain" does not contravene the requirements of Article 123(2) EPC.

6. Novelty

6.1 The respondent considered the subject-matter claimed to lack novelty in view of document (D1) or (D13).

6.2 Document (D1) reports on a 12-week placebo controlled double blind study with 300 mg or 200 mg tramadol extended release formulations with patients suffering from low back pain. Said extended release formulations are "once-daily" formulations (see page 2, line 2).

During a three-week run-in period patients were

- initiated on 100 mg per day for at least three days,

- permitted to increase to 200 mg QD based upon the tolerability of the side effects on days 4-7,
- maintained at 200 mg per day and titrated upward to 300 mg QD depending on the tolerability of the side effects during week 2,
- escalated to 300 mg at the beginning of the third week and maintained at this dose for one week, and, if the patient was responsive and the side effects were acceptable, for the remainder of the twelve weeks (see the third paragraph on page 2).

6.3 There is no direct and unambiguous disclosure in (D1) that some patients moved to 200 mg on any of days 5, 6 or 7. Even if one were to concur with the respondent in this respect, document (D1) does not disclose in a clear and unambiguous manner that those patients who moved to 200 mg on any of days 5, 6, or 7 maintained a dose of 200 mg for at least four consecutive days.

6.4 The same applies to the corresponding information in document (D13) (see example 11 on page 67, lines 6-13).

6.5 Therefore, neither document (D1) nor document (D13) disclose all the features of present claim 1.

Hence, the board considers the subject-matter claimed to be novel.

7. Inventive step

7.1 Closest prior art

7.1.1 Whereas the respondent considered document (D1) to represent the closest prior art, the appellant argued that document (D1) was not the closest prior art as it did not focus on improving the titration phase to reduce

the drop-out rate. Therefore, it held that document (D21) was closer (see points VIII and IX above).

7.1.2 The closest state of the art is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objectives as the claimed invention and having the most relevant technical features in common. A further criterion for the selection of the most promising starting point is the similarity of the technical problem (see T 1634/06 of 4 March 2011, point 2.2.1 of the reasons).

7.1.3 It is clear from the foregoing that the "objectives" and the "technical problem" are not considered to be identical. The objective of the patent in suit is defined in paragraph [0002]:

" 2. FIELD OF THE INVENTION
[0002] This invention relates to a titration dosing regimen for the administration of controlled release dosage forms of tramadol to patients."

7.1.4 Document (D1) reports on the results of a phase III study for the treatment of low back pain with **extended release** (once-daily) tramadol (see the title and the first sentence of the second page). During a three week run-in period, the patients were **titrated from 100 mg QD to 200 mg and finally to 300 mg QD**. "Patients with pain unresponsive to appropriate dosage adjustments or with unacceptable side effects were dropped from the study" (see the third paragraph on the second page).

7.1.5 Document (D21) "relates to a dosing regimen for the administration of the analgesic tramadol. The dosing regimen achieves the desired analgesic effect while reducing or delaying the on-set of the side effects

generally associated with the administration of tramadol." (see page 1, lines 8-12). The aim is to minimise side effects commonly associated with discontinuation of the treatment (see page 3, lines 26-32). Document (D21) does **not** relate to **extended release** tramadol.

7.1.6 Hence, a dosing regimen for extended-release tramadol is disclosed in document (D1); it is not disclosed in (D21), as the latter does not concern a controlled release dosage form. Consequently, this is an indication that the person skilled in the art would have used the teaching of document (D1) rather than that of (D21) as a starting point for the invention claimed in the patent in suit. Indeed, the person skilled in the art who is wishing to provide a titration dosing regimen for the administration of **controlled release** dosage forms of tramadol to patients would use a **controlled release** dosage form of this drug as the starting point, and not an immediate release form.

7.1.7 As mentioned above, a further criterion for the selection of the most promising starting point is the similarity of the technical problem. The technical problem of the closest prior art should be **similar** to the one of the claimed invention. That does not mean that the technical problems must be identical, as the appellant seemed to imply.

7.1.8 The problem addressed in the patent in suit is the provision of "an advantageous dosing regimen for a controlled release dosage form of tramadol. More specifically, ... a dosage regimen for a controlled release tramadol which significantly reduces the occurrence of and concomitant severity of adverse tramadol elicited side effects, and thus, reduces

potential discontinuation by patients due to these effects and increases the number of patients who may successfully be treated" (see paragraph [0010] on page 3; see page 2, lines 1-6, of the application as filed).

7.1.9 The technical problem to be solved in document (D1) was "to evaluate the efficacy and safety of Biovail's extended release tramadol (once-daily) formulation in the treatment of chronic low back pain" (see the first sentence of the second page).

7.1.10 It is evident that the safety of the formulation addressed in document (D1) is linked to the severity of its adverse side effects as referred to in the patent in suit. Furthermore, the final titration step up to 300 mg QD (see document (D1), third paragraph on page 2) is based on the tolerability of the side effects, which is a further indication that the avoidance or reduction of side effects is an issue in document (1).

Therefore, the problem addressed in document (D1) and the one defined in the patent in suit are similar.

7.1.11 In view of this similarity, the fact that patients were taken out of the study would not have dissuaded the skilled person, trying to solve the problem defined in point 7.1.8 above, from taking the teaching of document (D1) into consideration, as was alleged by the appellant. In this context, it is noted that 100% success rates are hardly ever achieved with medicaments.

The appellant gave no reasons for its allegation that the person skilled in the art would be more likely to use a patent application as the starting point than a press release such as document (D1); due to the detailed disclosure of the test in document (D1), the board has

no doubt that the person skilled in the art would consider its disclosure to be credible and useful.

7.1.12 For these reasons, document (D1) (rather than (D21)) is considered to represent the closest prior art.

7.2 The problem to be solved

The appellant and patent proprietor defined the problem to be solved as providing a dosing regimen for extended release formulations of tramadol that reduced adverse side effects and thus reduced the number of patients who discontinued treatment. This definition is in accordance with page 2, lines 2 to 6, of the application as filed. The appellant did, however, concede that he could not present data showing that this problem was solved in view of document (D1). As is evident from point 2.4 above, the burden of proof that the problem set out in the patent in suit is solved in view of the closest prior art lies with the patent proprietor. Hence, there is no evidence that the problem mentioned above was solved. Consequently, the problem to be solved can only be considered as the provision of an **alternative** dosing regimen for extended release formulations of tramadol with **low** adverse side effects.

7.3 Example 1 of the patent in suit shows that this problem was indeed solved.

7.4 The appellant argued with reference to the declaration (D18) that it was essential that each of the two lower doses according to claim 1 (75 to 125 mg and 175 to 225 mg) had to be taken for a minimum period of four days.

7.4.1 Points 10 and 11 of the declaration (D18) state that the tramadol hydrochloride controlled release formulation (THCR)

"has a half-life of approximately 10 hours. One typically assumes that it would take 5 to 6 half-lives until steady state is reached during continuous oral administration. In the case of tramadol, one can thus assume that steady state is reached after approximately 2 - 3 days. Occurrence of adverse events, however, does not only depend exclusively on blood plasma concentration values but is also influenced by other factors. Clinically relevant effects such as an adverse event may therefore appear not only some time after the steady state has been reached but also during the time period leading to steady state.
11. It is my experience that for tramadol a minimum period of four days will be sufficient to reliably link clinically relevant effects (i.e. efficacy and safety) with an administered dose."

7.4.2 Hence, this declaration extrapolates from the half-life of THCR, using several assumptions, that a minimum of four days is sufficient for the given purpose. Such an extrapolation does not rule out a minimum period of less than four days also being sufficient. Therefore, in the absence of more reliable data, the minimum period of four days indicated in claim 1 of the first auxiliary request is considered to be arbitrary.

7.4.3 During the three-week run-in period reported in document (D1) patients were

- initiated on **100 mg QD for at least three days**,
- permitted to increase to 200 mg QD based upon the tolerability of the side effects on days 4-7,

- **maintained at 200 mg QD** and titrated upward to 300 mg QD depending on the tolerability of the side effects during week 2, and
- escalated to 300 mg at the beginning of the third week (see the third paragraph on page 2).

7.4.4 Therefore, document (D1) requires the patients to maintain

- a daily dose of 100 mg for at least three days and up to a maximum of seven days, and
- a daily dose of 200 mg for up to a maximum of eleven days (week 2 and days 4 to 7 of week 1).

Consequently, the teaching of document (D1) encompasses completely the subject-matter of claim 1 of the first auxiliary request. As mentioned under point 7.4.2 above, the selection of the minimum number of four days is considered to be arbitrary and thus cannot contribute to the presence of an inventive step.

In this context, it is irrelevant that the FDA approved the dosing regimen of document (D20), which recommends increasing the dose every five days by an increment of 100 mg, up to a maximum dose of 300 mg per day (see the first paragraph on page 17).

7.4.5 For these reasons, the subject-matter of claim 1 of the first auxiliary request 1 does not involve an inventive step. Hence, the first auxiliary request was also refused.

Second Auxiliary Request

8. Claim 1 of this request differs from claim 1 of the first auxiliary request in that the former specifies that each of the daily doses of 100 mg and 200 mg are to

be maintained for a week and that the final dose is 300 mg per day (see above under point VII c)).

The conclusions drawn above under point 7, that the requirement to maintain the lower doses for a minimum of four days cannot contribute to the presence of an inventive step, apply *mutatis mutandis* to the requirement to maintain them for a week.

Therefore, the subject-matter of claim 1 of the second auxiliary request does not involve an inventive step either. Hence, the second auxiliary request was refused.

9. The main request was refused because grounds under Article 100(c) EPC prejudice the maintenance of the patent as granted. The first and second auxiliary requests were refused as the subject-matter of their claims 1 does not involve an inventive step. The appellant did not file any further auxiliary requests. Hence, the appeal had to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated