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Datasheet for the decision of 25 February 2016

Case Number: T 1716/14 - 3.3.07

Application Number: 06743167.6

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Title of invention:
DICLOFENAC FORMULATIONS AND METHODS OF USE

Applicant:
APR APPLIED PHARMA RESEARCH S.A.

Headword:
DICLOFENAC FORMULATIONS AND METHODS OF USE/APR Applied Pharma Research S.A.

Relevant legal provisions:
RPBA Art. 13(3)
EPC Art. 54, 56

Keyword:
Late-filed request - justification for late filing (yes)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

Catchword:

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Case Number: T 1716/14 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 25 February 2016

Appellant: (Applicant)	APR APPLIED PHARMA RESEARCH S.A. Via Corti 5 6828 Balerna (CH)
Representative:	Leissler-Gerstl, Gabriele Hoefer & Partner Patentanwälte Pilgersheimer Strasse 20 81543 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 26 March 2014 refusing European patent application No. 06743167.6 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	I. Beckedorf

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application n° 06 743 167.6. The decision was based on 4 sets of claims filed with letter of 23 May 2013 as main request and auxiliary requests 1-3 filed during oral proceedings.

II. Claim 1 of the requests on which the decision of the examining division is based read as follows, the difference with respect to the main request being indicated by **bold** (addition):

a) Main request

"1. Liquid formulation for oral administration comprising 50 mg of diclofenac or a pharmaceutically acceptable salt thereof for use as a medicament for humans for treating migraine associated with photophobia or phonophobia, wherein said formulation achieves a mean t_{max} in from about 10 to about 30 minutes."

b) Auxiliary request 1

"1. Liquid formulation for oral administration comprising 50 mg of diclofenac **potassium and a buffering agent**, wherein said formulation achieves a mean t_{max} in from about 10 to about 30 minutes, for use as a medicament for humans for treating migraine associated with photophobia **and** phonophobia for relief from photophobia and phonophobia within two hours of administration. "

c) Auxiliary request 2

"1. Liquid formulation for oral administration comprising 50 mg of diclofenac **potassium and a buffering agent**, wherein said formulation achieves a mean t_{max} in from about 10 to about 30 minutes, for use as a medicament for humans for treating migraine associated with photophobia **and** phonophobia for relief from photophobia and phonophobia within two hours of administration **and relief of recurrent migraine associated with photophobia or phonophobia in a human patient, for a period of twenty four hours from administration without rebound.**"

d) Auxiliary request 3

"1. Liquid formulation for oral administration comprising 50 mg of diclofenac **potassium and a buffering agent**, wherein said formulation achieves a mean t_{max} in from about 10 to about **20** minutes, for use as a medicament **for treating migraine patients for relief of recurrent headache within twenty-four hours from initial administration.**"

III. The following documents were cited in the examination procedure:
(1): WO97/44023
(2): Arzneim. Forschung/Drug Res. 51 (II), 885-890, (2001), V. Reiner et al, „Increased Absorption Rate of Diclofenac from Fast Acting Formulations Containing Ist Potassium Salt".
(4): Drugs, 1999 June, 57(6), 991-1003, W. McNeely and al, "Diclofenac-Potassium in Migraine".

IV. According to the decision under appeal, document (4) was the closest prior art and disclosed the use of diclofenac potassium in the treatment of migraine and its accompanying symptoms like photophobia or

phonophobia. Figure 3 on page 998 showed a reduced level for both phonophobia and photophobia two hours after oral administration of a 50 mg diclofenac potassium tablet. Document (4) emphasized the more rapid onset of activity for the immediate release tablet which had a mean t_{max} of 45 minutes. The difference between the claimed subject-matter of the main request was the t_{max} of 10 to 30 minutes instead of 45 minutes. Hence, the problem to be solved was the provision of an alternative diclofenac formulation. For the skilled person, it was obvious that a liquid formulation was faster absorbed than a tablet formulation. Moreover, document (1) disclosed a formulation of diclofenac potassium showing a t_{max} of 10 minutes (see example 1 and Figure 3). The solution was obvious and the subject-matter of claim 1 of the main request was not inventive.

As regards auxiliary request 1, the problem was seen as the provision of a diclofenac formulation to be used in treating migraine associated with photophobia and phonophobia wherein the effect of the treatment was achieved rapidly. Figure 3 of document (4) showed a reduction of photophobia and phonophobia 2 hours after administration of diclofenac 50 mg. Hence the subject-matter of claim 1 of auxiliary request 1 did not involve an inventive step.

The subject-matter of claim 1 of auxiliary request 2 did not meet the requirements of Article 123(2) EPC, in view of the features “for relief from phonophobia, photophobia and pain” and “relief of recurrent migraine associated with photophobia or phonophobia in a human patient for a period of twenty-four hours from administration without rebound”.

As regards auxiliary request 3, the problem to be solved was seen as the provision of migraine patients for relief of recurrent headache within 24 hours from initial administration. The solution provided was the use of a liquid formulation comprising 50 mg of diclofenac potassium and a buffering agent wherein said formulation reached a t_{max} in 10 to 20 minutes. Since the application did not show that the problem of 24 hours relief of recurrent headache was solved by the claimed formulation, the Examining Division could not acknowledge inventive step.

V. The applicant (appellant) filed an appeal against that decision.

VI. With the letter dated 5 August 2014, the appellant filed 3 sets of claim as main request and auxiliary requests 1 and 2, and submitted a new document:
(9): Declaration of William Maichle

VII. A communication expressing the board's preliminary opinion of the board was sent to the applicant.

VIII. With the letter of 8 February 2016 the appellant submitted a new main request and auxiliary requests 1-2 to replace all previous requests on file and four new documents:
(10): Center for Drug Evaluation and Research, Application Number 22-165, "Clinical Pharmacology and biopharmaceuticals review(s)"
(11): Center for Drug Evaluation and Research, Application Number 22-165, "Statistical review(s)"
(12): "A short introduction to pharmacokinetics", Eur. Review for Medical and Pharmacological Sciences, 2002;6:33-44

(13):Cambia (Diclofenac Potassium for Oral Solution), Highlights of prescribing information

IX. Oral proceedings before the board of appeal took place on 25 February 2016 during which a new set of claims were submitted as auxiliary requests 3-6. During oral proceedings, the appellant stated that they defended the application only on the basis of auxiliary request 5, said request being the only request with all other requests withdrawn.

X. Claim 1 of auxiliary request 5 read as follows:

"1. Liquid formulation for oral administration comprising 50 mg of diclofenac potassium and a buffering agent selected from alkali metal carbonates and bicarbonates wherein the weight ratio of buffering agent to diclofenac is in a range of 1:5 to 5:1, for use as a medicament for humans for treating migraine associated with photophobia and phonophobia."

XI. The appellant's arguments can be summarised as follows:

The subject-matter the auxiliary request 5 addressed all the objections of the Board raised under Article 84 and 123(2) EC. It should therefore be admitted into the proceedings.

By rapidly treating the migraine with a fast-acting liquid formulation of diclofenac potassium, the treatment was very effective. This was specifically proven by document (9). Document (9) showed that with the formulations of the present invention having a fast onset of pain relief, at 24 hours post-dose a greater percentage of patients were pain-free, compared to patients which had been treated with the tablet of the

prior art. None of the documents cited suggested that a rapidly bioavailable formulation of diclofenac could be therapeutically valuable for the treatment of migraine. The same evidence was brought by documents (10) and (11).

XII. Requests

The appellant finally requested that the decision under appeal be set aside and that a patent be granted on the basis of the sets of claims filed as auxiliary request 5 during the oral proceedings.

Reasons for the Decision

1. Admission of auxiliary request 5 into the proceedings

The appellant's request was filed during the oral proceedings before the Board, thus at a very late stage of the proceedings.

The subject-matter of claims 1-3 of auxiliary request 5 relates to the same subject-matter as the other requests on file. It constitutes a simplification with regard to the subject-matter of the claims as refused by the Examining Division or previously discussed during the oral proceedings before the Board. It also does not raise new issues and *prima facie* address all the issues raised by the board without giving rise to new ones and without adding complexity to the case under consideration. They constitute a direct, clear and fair attempt to respond to the board's objections. Therefore, the Board exerts its discretionary power and auxiliary

request 5 is admitted into the proceedings (Article 13(3) RPBA).

2. Auxiliary request 5 - Amendments

The subject-matter of claims 1 to 3 finds a basis in the original description of WO2006/133954 on page 4 third paragraph to page 5 first paragraph, pages 7 first and second paragraphs or page 8, first paragraph, on page 12, third paragraph and page 13 first and second paragraphs.

As to the omission of the pharmacokinetic parameter t_{max} cited in said passages and which is essential to the characterization of the invention, but is nevertheless a parameter unable to define clearly the claimed composition in view of its inter-subject variability, the introduction of the features relating to the specific potassium salt of diclofenac and to the presence of a carbonate or bicarbonate buffer in the claimed weight ratio compensates this omission. It is indeed clear from the description of the application, in particular from its examples, that a liquid formulation comprising 50 mg of diclofenac potassium and a buffering agent selected from alkali metal carbonates and bicarbonates has inevitably and always a mean t_{max} of less than 20 minutes (see in particular Tables 12, 13, 15 and description pages 21-22). This technical teaching is further confirmed by the teaching of prior art document (2) in its Table 4) and by document (10) in its Tables 3, 4 and 11.4.2.

Auxiliary request 5 meets thus the requirements of Article 123(2) EPC.

3. Auxiliary request 5 - Novelty

Among the cited prior art, only documents (4) and (5) relate to the treatment of migraine associated with photophobia and phonophobia, and both documents disclose the use of an immediate release tablet comprising diclofenac potassium, and not of a liquid formulation (see document (4) par. 2.2.1 and Table II, and see document (5), page 118, "Study design" and "Efficacy Assessment").

Documents (1) and (2) disclose liquid formulations of 50 mg diclofenac potassium, but do not disclose its use for treating migraine (see document (1), examples 1 or 2, see document (2) Tables 1 and 2).

The subject-matter of claim 1 of auxiliary request is thus novel and this request meets the requirements of Article 54 EPC.

4. Auxiliary request 5 - Inventive step

4.1 The claimed invention relates to methods and formulations for treating migraine associated with photophobia and phonophobia, and formulations of diclofenac that provide both rapid and sustained relief (see page 1, first paragraph).

4.2 The closest prior art is document (4) which relates also to the treatment of migraine associated with photophobia and phonophobia. This document discloses immediate release tablets comprising 50 mg of diclofenac potassium used for the treatment of migraine, and accompanying symptoms such as phonophobia or photophobia. The immediate release tablet disclosed in document (4) has a mean t_{max} of about 45 minutes (see Figure 2).

4.3 The problem to be solved according to the application as filed is to provide an improved treatment of migraine associated with photophobia and phonophobia.

4.4 The solution is a liquid formulation for oral administration comprising 50 mg of diclofenac potassium and a buffering agent selected from alkali metal carbonates and bicarbonates wherein the weight ratio of buffering agent to diclofenac is in a range of 1:5 to 5:1.

4.5 Documents (9) and (11) have been provided by the appellant to demonstrate the existence of an effect linked with the administration of liquid formulation comprising diclofenac.

Document (9) shows that a liquid formulation according to the invention has a faster onset of action, namely 45 minutes sooner (see par. 11 and 13), but also a longer duration of action in the treatment of migraine, since at 24 hours a significant greater percentage of patients were pain free, namely 22.3% versus 15.1%, when compared to the immediate release tablets of the prior art (See Table 1 and par. 11). It also shows an improvement in the ability to treat phonophobia and photophobia, since a greater percentage of patient treated with he claimed liquid formulation were relieved from these symptoms, when compared to a treatment with the same immediate release tablets (see par. 19, 20, 21, and Table 4).

Document (11) confirms that sachets comprising 50 mg diclofenac potassium provide a better treatment of migraine at two hours post-dose, since the number of patients pain free is always and significantly higher in comparison to a treatment with 50 mg diclofenac

potassium tablets (see Table 9 and Table 19). This document confirms also that the treatment of photophobia with the same potassium sachets is significantly improved in comparison to the immediate release tablet (see Tables 10, 12 and 19). The treatment of phonophobia by by the same sachets appears does however not appear to be significantly better in comparison to the treatment by the tablets (see Tables 10, 12 and 19)).

The existence of a beneficial effect over the closest state of the art is thus plausibly demonstrated by the teaching of documents (9) and (11). The Board is thus convinced that the claimed composition presents an improvement in the treatment of migraine associated with photophobia and phonophobia, so that the problem is credibly solved.

4.6 It remains to determine whether the solution was obvious to the person skilled in the art.

The closest prior art (4) does not suggest any alternative fast release form the disclosed immediate release tablets of diclofenac potassium.

The use of liquid formulations for the treatment of migraine is also not disclosed or suggested in any cited prior art. Liquid formulations were known as such from documents (1) and (2), and only the latter mentions that that the liquid fast-acting formulations of diclofenac potassium were expected to produce a faster onset of analgesic action. None of these documents relates however to the specific treatment of migraine and its associated symptoms.

An improvement in the treatment of migraine and of the associated symptoms of photophobia and phonophobia over the known treatment with an immediate release tablet of diclofenac potassium is also not disclosed or suggested in any cited prior art, and is unexpected. It is unforeseeable from any cited prior art that a liquid formulation of diclofenac potassium would provide an improved rapid and above all sustained relief of migraine, and simultaneously an improved ability to treat phonophobia and photophobia, in comparison to the existing immediate release tablets disclosed in document (4).

The solution according to the subject-matter of claim 1 is therefore not obvious. The same applies to the dependent claims.

4.7 The conditions of Article 56 EPC are met by the main request.

5. Other point

The set of claims of the only remaining auxiliary request 5 include 3 claims, namely independent claim 1 and dependent claims 2 and 3. The subject-matter of dependent claim 2 refers to a particular feature, namely the treatment of "recurrent migraine", which was dependent from a claim which was present in a subsequently withdrawn higher-ranking auxiliary request and which was deleted during the oral proceedings in the only remaining auxiliary request 5. Given its specific subject-matter which differs from the subject-matter of independent claim 1 relating to the treatment of "migraine associated with photophobia and phonophobia", claim 2 obviously can neither be dependent from claim 1 nor be seen as an independent

claim. Moreover, the suppression of this specific feature relating to a a specific medical indication was necessary to acknowledge the presence of an inventive step. The omission of its deletion during the oral proceedings in appeal constitutes obviously an error.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division with the order to grant a patent on the basis of the set of claims filed as auxiliary request 5 during the oral proceedings and a description to be adapted.

The Registrar: The Chairman:

K. Boelicke J. Riolo

Decision electronically authenticated