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D E C I S I O N
of 23 May 2002

Case Number: T 1031/00 - 3.3.2

Application Number: 92925405.0

Publication Number: 0661970

IPC: A61K 31/44

Language of the proceedings: EN

Title of invention:
Methods and compositions for treating hypertension, angina and other disorders using optically pure (-) amlodipine

Applicant:
SEPRACOR, INC.

Opponent:
-

Headword:
-

Relevant legal provisions:
EPC Art. 52(4), 54(5)

Keyword:
"Main request and first auxiliary request - novelty - no - prior art document and application in suit have the same technical content."
"Second auxiliary request - novelty - no - no new therapeutic application over the prior art"

Decisions cited:
G 0005/83, T 0128/82, T 0019/86, T 0241/95

Catchword:

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Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1031/00 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 23 May 2002

Appellant: SEPRACOR, INC.
33 Locke Drive
Marlborough, MA 01752 (US)

Representative: Jump, Timothy John Simon
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London EC1A 7DH (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 7 April 2000 refusing European patent application No. 92 925 405.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: J. Riolo
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent application No. 0 661 970, published as WO93/10779, was refused, by a decision of the Examining Division pronounced on 2 December 1999, on the ground of lack of novelty.

II. Upon entry into the European national phase the appellant filed a set of 10 claims on 28 June 1994.

Independent claim 1 of this set of claims read:

"1. A composition comprising an amount of (-) amlodipine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, wherein:

(a) the composition is for the treatment of a human in need of antihypertensive therapy and the amount is sufficient to alleviate hypertension but insufficient to cause adverse side-effects associated with the administration of racemic amlodipine;

(b) the composition is for the treatment of a human having angina and the amount is sufficient to alleviate angina but insufficient to cause adverse side-effects associated with the administration of racemic amlodipine; or

(a) the composition is for the treatment of a condition caused by excessive calcium influx in cells in a human and the amount is sufficient to alleviate hypertension but insufficient to cause adverse side-effects associated with the administration of racemic amlodipine."

III. The decision was based on the final and only request the text of which is also that of the second auxiliary request filed during the oral proceedings before the Examining Division and which corresponds to claims 1 to 10 filed on 28 June 1994 limited to the use of (-) amlodipine for the manufacture of a medicament for treating hypertension and wherein the phrase "substantially free from its (+) isomer" has been replaced by the clause "wherein the composition contains at least 90% by weight of (-) amlodipine and 10% by weight or less of (+) amlodipine".

IV. The following documents were inter alia cited during the proceedings before the Examining Division and the Board of Appeal:

(2) EP-A-0 331 215

(3) J. Med. Chem. **29**(9), 1986, 1696-1702

V. According to the Examining Division, document (2) disclosed that amlodipine was a long-acting dihydropyridine calcium channel blocker then in a late stage of clinical development for the treatment of hypertension and that the activity as calcium channel blocker lay predominantly in the (-) isomer. It concluded therefore that the use of (-) amlodipine in the treatment of hypertension was at least implicitly disclosed in document (2) and decided to refuse the application as not meeting the requirements of Article 54 EPC.

VII. The appellant (applicant) lodged an appeal against this decision. During the proceedings, it filed a large volume of citations and experimental data as well as a

number of declarations. It also filed a main and five auxiliary requests on 23 April 2002 which were later withdrawn, except for the second auxiliary request in which independent claim 1 reads:

"1. Use of a composition comprising (-) amlodipine for the manufacture of a medicament for use in a method of treatment comprising administering an amount of (-) amlodipine or a pharmaceutically acceptable salt thereof to a human in need of antihypertensive therapy, the amount being sufficient to alleviate hypertension but insufficient to cause adverse side-effects associated with the administration of racemic amlodipine, wherein the amlodipine present in the medicament comprises at least 90% by weight of (-) amlodipine and 10% by weight or less of (+) amlodipine."

VIII. Oral proceedings were held before the Board on 23 May 2002 during which a new main and a new auxiliary request were filed by the appellant.

Claim 1 of the main request reads:

"1. A composition comprising an amount of (-) amlodipine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, wherein the composition is for the treatment of a human in need of antihypertensive therapy and the amount is sufficient to alleviate hypertension but insufficient to cause adverse side-effects associated with the administration of racemic amlodipine."

Claim 1 of the first auxiliary request differs from claim 1 of the main request in that the phrase

"substantially free from its (+) isomer" has been replaced by the clause "wherein the composition contains at least 90% by weight of (-) amlodipine and 10% by weight or less of (+) amlodipine".

IX. The main argument presented by the appellant during the appeal proceedings was that none of the available prior art documents disclosed the **actual** treatment of a disease practised on a living human or animal body involving the use of the (-) amlodipine isomer. It accordingly concluded that the claimed subject-matter was novel in the sense of Article 54(5) EPC.

X. The appellant requested that the decision under appeal be set aside and that the patent be granted on the basis of the main request filed during the oral proceedings or alternatively on the basis of the first auxiliary request filed during the oral proceedings or the second auxiliary request filed on 23 April 2002.

Reasons for the Decision

1. The appeal is admissible.

2. The sole point addressed by the Examining Division in the decision under appeal was the novelty of the claimed subject-matter in relation to the prior art document (2).

The appellant submitted that document (3) qualified better as closest state of the art than document (2) because the latter contained an error, namely the R isomer of amlodipine was referred to as being the S

isomer.

Since the technical content of both documents is in fact the same, the Board has no objection to considering document (3) as the closest state of the art as submitted by the appellant.

2.1 Main request

2.1.1 Claim 1 is directed to the first therapeutic application of (-) amlodipine, namely the treatment of hypertension.

This claim belongs to the family of claims not precluded under Article 54(5) EPC, which does "not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 52, paragraph 4 [Methods for treatment of the human or animal body by ...therapy...], provided that its use for any method referred to in that paragraph is not comprised in the state of the art".

Thus for novelty purposes it has to be established whether or not a therapeutic application has already been disclosed in the available prior art for (-) amlodipine.

On the one hand, document (3), shows the ability of racemic amlodipine and of (-) and (+) amlodipine to inhibit calcium ion influx into rat aorta tissue in vitro as indicative of their effectiveness in the treatment of hypertension and angina (page 1696, left column, first paragraph; Table I compounds 17, 18 and 19 respectively).

It also discloses that amlodipine was then undergoing phase III clinical trials for hypertension and angina and that *in vitro* evaluation of the enantiomers of amlodipine shows the (-) isomer to be twice as active as the enantiomeric mixture in the rat aorta, the (+) isomer being 1000 times less active (page 1699, left column, lines 30 to 35).

On the other hand, in the patent application in suit it is stated that the (-) isomer of amlodipine is an antihypertensive agent for treating human (claim 1).

However, in spite of the numerous examples in the description, only one deals with hypertension but without going further than *in vitro* experiments. Therefore, the description provides no further evidence or data showing the actual antihypertensive effect of the (-) isomer of amlodipine in humans or animals than did the prior art document (3).

Accordingly, in the absence, in the patent application as originally filed, of any data providing additional technical information in relation to the actual treatment of hypertension in humans or animals compared with the disclosure in the prior art document (3), it must be concluded that the subject-matter of the patent application is anticipated by the disclosure in that document, ie document (3) discloses the same "therapeutic application" as the present application.

2.1.2 According to the appellant, only the disclosure of an actual therapeutic treatment in a prior art document could be novelty destroying for the subject-matter of a claim drafted in the first medical use form.

As support for this argument it pointed out to the decision T 128/82 (JO EPO 1984, page 164, paragraphs 9 and 13) and to the Manual of Patent Practice in the UK Patent Office, Fourth Edition, paragraph 2.53.

The relevant passages in decision T 128/82 read:

"9. Recourse to the travaux préparatoires for Article 54(5) EPC would in fact seem obvious. This article creates substantive patent law that does not go back to the Strasbourg Convention on the Unification of Certain Points of Substantive Law on Patents for Invention of 27 November 1963, and is also not modelled on concepts existing in the national patent laws of most countries represented at the Munich Diplomatic Conference of 1973. In addition to the general concept of novelty (Article 54(1)-(4) EPC) this article also introduces, in respect of substances and compounds used in surgical and therapeutic treatment and in diagnostic processes carried out on humans and animals (hereinafter referred to briefly as "therapy"), a special concept of novelty unknown in other technical fields

13. Attention is also drawn to the following points: Under Article 54(5) EPC a compound which is known but not used therapeutically is to be regarded as novel. Novelty, however, is not only destroyed by the fact that the same specific therapeutic effect is already known in the art, but suffers also from the disclosure of any other specific therapeutic application."

As to the Manual of Patent Practice in the UK Patent Office, it cannot be given more weight than to the Guidelines of the EPO, and neither can be binding on

the Board which, nevertheless has considered the appellant’s submission.

The relevant passage in the Manual reads:

"To provide evidence of a prior use of a substance or composition in therapy, actual disclosure of therapeutic use must be found. It is not sufficient for a research paper to disclose experiments which show an activity which would make the substance or composition suitable for use in therapy, or discloses in vitro testing for such use. The Section requires the use of the substance or composition in a method of therapy to form part of the state of the art."

In fact, the Board agrees with both authorities cited that the disclosure of an actual therapeutic treatment for a known substance in a prior art document would be novelty destroying for a claimed first medical use of the same substance. And the Board could also agree with the guidance given in both texts cited by the appellant for cases where, according to the particular circumstances the technical content of the prior art is limited when compared with that of the application in issue.

In the present case however, as explained under 2.1.1, the situation is different since the subject-matter of the patent in suit does not contain any technical information concerning the claimed therapeutic treatment going beyond that in document (3).

Accordingly, the difference between that document and the application in suit resides merely in the words used but not in their technical content so that no

novel technical feature can be recognised in the present case.

As to decision T 0241/95 (OJ EPO 2001, page 103, paragraph 4.1.2), also cited by the appellant during the oral proceedings, the Board considers that, if anything, it tends to contradict the appellant's submission that document (3) does not disclose an actual treatment. In T 0241/95 it was stated: "It is a well-established and accepted principle that, for the purpose of patent protection of a medical application of a substance, a pharmacological effect or any other effect such as a behavioural effect observed either in vitro or on animal models is accepted as sufficient evidence of a therapeutic application if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application." (paragraph 4.1.2).

In view of the foregoing, the Board considers that the subject-matter of claim 1 does not fulfil the requirements of novelty of Article 54 EPC.

2.2 First auxiliary request

As acknowledged by the appellant during the oral proceedings the clarification of the term "substantially" by the range introduced in claim 1 of this request does not change the claimed subject-matter so that the above conclusions also hold good for this set of claims. Indeed, the range introduced in claim 1 still encompasses the disclosure of document (3) since 100% (-) amlodipine remains covered by the subject-matter of the claim.

2.3 Second auxiliary request

The appellant has worded its claim in the form suggested by the Enlarged Board of Appeal when more particularly considering the so-called **second** medical indication (see G 5/83, OJ EPO 1985, 64, point 9, 65), ie cases in which the medicament resulting from the claimed use is no different from a known medicament.

In its decision, the Enlarged Board of Appeal held that, provided the medicament is for a specified new an inventive application, "the required novelty for the medicament which forms the subject-matter of the [second medical use] claim is derived from the new pharmaceutical use" (G 5/83, points 21 to 23).

In addition, according to the subsequent case law of the boards of appeal, the concept of second medical indication has been extended to cover a number of particular situations including, among others, the treatment of the same disease with the same compound when it is carried out on a new group of subjects distinguishable from the previous subjects (eg T 19/86, OJ EPO 1989, 24): such use also amount to a novel therapeutic application.

In the present case however, no such new pharmaceutical use over document (3) can be seen as explained at 2.1.

During the proceedings, the appellant relied heavily, as novel features, on the absence of side effects of the therapy of claim 1 using the (-) isomer of amlodipine and on the restriction of the method of treatment to human only.

As regards the absence of the side effects the Board considers that, assuming in the appellant's favour that this was not known in the state of the art, this can only be regarded as the discovery of an additional item of knowledge about the known therapeutic application of (-) amlodipine for the treatment of hypertension, but can not in itself confer novelty on this known therapeutic application. To be novel, such a discovery, would have to lead to a new therapeutic application or to the application of the known therapeutic application to a new group of subjects. That clearly not being the case here, as the application in suit contains no such teaching, the Board fails to see how claim 1 could be construed as relating to a second or further medical use.

In the same way, the restriction to humans only can not make claim 1 novel since Article 52(4) EPC refers to humans and animals together in order to cover them both, thus clearly drawing no distinction between them as to therapy. To confine a known therapy for a large group to sub-group thereof cannot be a novel use.

The Board also observes that there is nothing in the patent application to suggest that the claimed treatment is not suitable for animals as well so that the group chosen by the appellant is arbitrary.

Indeed, the appellant provided no evidence that a functional relationship exists between the particular pathological status (hypertension) of its chosen group of subjects (humans) and the therapeutic effect achieved which does not exist between the same pathological status and other groups of subjects.

In view of the foregoing, the Board considers that the subject-matter of claim 1 of this set of claims does not fulfil the requirements of novelty of Article 54 EPC either.

Under these circumstances, there is no need for the Board to consider the evidence provided by the appellant in support of the existence of an unexpected effect (see point VII).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Townend P. Lançon