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**Datasheet for the decision
of 6 March 2007**

Case Number: T 0055/04 - 3.3.02

Application Number: 94303920.6

Publication Number: 0635266

IPC: A61K 31/20

Language of the proceedings: EN

Title of invention:

Composition comprising an omega 9 series unsaturated fatty acid in the treatment of medical symptoms caused by leucotriene B4

Applicant:

SUNTORY LIMITED

Opponent:

-

Headword:

Omega 9 series fatty acids/SUNTORY

Relevant legal provisions:

EPC Art. 56, 52(4)

Keyword:

"Inventive step no - obvious to use further compounds as claimed to treat known disease"

Decisions cited:

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Catchword:

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Case Number: T 0055/04 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 6 March 2007

Appellant:

SUNTORY LIMITED
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Representative:

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Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 25 July 2003
refusing European application No. 94303920.6
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
P. Mühlens

Summary of Facts and Submissions

- I. European patent application No. 94 303 920.6 was refused by a decision of the examining division on the basis of Article 97(1) EPC.

Claim 1 of the main request before the examining division read as follows:

"Use of 6,9-octadecadienoic acid, 8,11-eicosadienoic acid or 5,8,11-eicosatrienoic acid in the manufacture of a medicament for the prevention or alleviation of rheumatoid arthritis, mediated by leucotriene B₄ (LTB₄)."

The wording of claim 1 of the second auxiliary request was:

"Use of 6,9-octadecadienoic acid or 8,11-eicosadienoic acid in the manufacture of a medicament for the prevention or alleviation of rheumatoid arthritis, mediated by leucotriene B₄ (LTB₄)."

- II. The following documents were cited inter alia during the proceedings before the examining division and before the board of appeal:

- (1) W. Stenson et al, "Leukotriene B Formation by Neutrophils from Essential Fatty Acid-Deficient Rats", The Journal of Biological Chemistry, vol. 259, no. 19, 1984, 11784 - 89
- (9) EP-A-0 260 655

III. The examining division held the subject-matter of the main request and that of the first auxiliary request to be obvious with respect to a combination of document (1) and document (9).

These documents disclosed that 5,8,11-eicosatrienoic acid was useful for blocking the synthesis of leucotriene B₄ and hence for the treatment of inflammation and rheumatoid arthritis.

The application finally had to be refused, because the appellant had expressed its disapproval of the text of the second auxiliary request.

IV. The appellant lodged an appeal against the decision of the examining division.

V. A communication was sent out on 1 December 2006, drawing the appellant's attention to possible problems concerning Article 123(2) EPC and to the fact that in the proceedings before the board all the current requests, even the one which was the same as the second auxiliary request before the examining division, would have to be scrutinised in respect of all the provisions of all relevant articles of the EPC.

VI. Oral proceedings took place on 6 March 2007.

After discussion at the oral proceedings, the appellant filed three sets of claims replacing all previously filed requests.

The wording of claim 1 of the main request is:

"Use of 5,8,11-cis-eicosatrienoic acid, in the form of free fatty acid, salt, mono-, di- or tri-glyceride, ester of monohydric alcohol having up to 6 carbon atoms, phospholipid, glycolipid or amide, in the manufacture of a medicament for the prevention or improvement of the chronic inflammation rheumatoid arthritis, caused by leucotriene B₄ (LTB₄)."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request only in a restricted definition of the form the acid may appear in. It reads in essence:

"Use of 5,8,11-cis-eicosatrienoic acid, in the form of triglyceride or ester of monohydric alcohol having up to 6 carbon atoms, in the manufacture"

Claim 1 of auxiliary request 2 reads (differences with respect to auxiliary request 1 are in bold):

"Use of 5,8,11-cis-eicosatrienoic acid, in the form of triglyceride or ester of monohydric alcohol having up to 6 carbon atoms, in the manufacture of a medicament for the prevention or improvement of the chronic inflammation rheumatoid arthritis, caused by leucotriene B₄ (LTB₄), **by means of a daily dose of 1 to 500 mg for adult human oral administration.**"

VII. The arguments of the appellant both in the written procedure and in the oral proceedings may be summarised as follows:

In document (9), only compounds were disclosed that were structurally different from the omega 9 series unsaturated fatty acid of the application in suit,

together with the mere speculation that they were useful as drugs for the treatment of inflammatory states such as rheumatoid arthritis because of potent anti-leucotriene B₄ activity. There were no experimental data to support this allegation.

The teaching of document (1) could not fill the gap to make the invention in the application in suit obvious in the light of document (9). The experimental data in document (1) were contradictory and at best inconclusive. The skilled reader would not have acted on its speculative suggestion to use 5,8,11-eicosatrienoate as a dietary supplement to selectively block the synthesis of leucotriene B₄.

Thus, having regard to these documents, the subject-matter of the application in suit was not obvious to the skilled person.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of one of the main, first or second auxiliary requests filed in the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.
2. The amended claims filed by the appellant as main request and auxiliary requests 1 and 2 represent an attempt to overcome the objections raised during the proceedings. Consequently, they are admitted into the proceedings.

3. The claims of the main request and of the auxiliary requests may be seen as being based on the claims and the description as originally filed (Article 123(2) EPC).

The board is also satisfied that the formal requirements of Articles 84 and 83 EPC are fulfilled.

4. The subject-matter of the main request and of auxiliary requests 1 and 2 is new with respect to documents (9) and (1).

Neither these documents nor the others introduced into the proceedings refer to the use of 5,8,11-cis-eicosatrienoic acid in the manufacture of a medicament for the prevention or improvement of the chronic inflammation rheumatoid arthritis caused by leucotriene B₄ (LTB₄), as disclosed in the application in suit. The provisions of Article 54(1) EPC are fulfilled.

5. *Inventive step*

- 5.1 The subject-matter of the main request concerns the "use of 5,8,11-cis-eicosatrienoic acid, for instance in the form of an amide or in general in the form of special ...trienoates, in the manufacture of a medicament for the prevention or improvement of the chronic inflammation rheumatoid arthritis, caused by leucotriene B₄."

Following the definition of "improvement" on page 9, lines 8 to 9, of the application in suit, "treatment of a patient" is included in this wording.

5.2 Document (9) represents the closest state of the art.

According to its text, this document relates, for example, to the use of (6E,8Z,10E)-N,N-dimethyl-5,12-dihydroxy-eicosa-6,8,10-trienamide, a trienoic acid amide or trienoate, in the manufacture of a medicament for the treatment of inflammatory states such as rheumatoid arthritis because of its potent anti-leucotriene B₄ activity (see in particular claims 1, 13 and 23 together with page 3, lines 35 and lines 31 to 33).

In most cases of rheumatoid arthritis, the inflammatory state is chronic. Therefore the wording "inflammatory states" with respect to rheumatoid arthritis in document (9) also includes chronic inflammation.

5.3 In the absence of any comparative study with respect to document (9) as closest state of the art, the technical problem underlying the application in suit can only be seen in the provision of a further compound, in particular a further trienoate for use in the manufacture of a medicament for the treatment of inflammation such as rheumatoid arthritis.

5.4 The solution to this problem is the use of a medical agent exhibiting the features of claim 1 of the main request.

5.5 Having regard to examples 1, 2, 3 and 6 set out in the application in suit (see pages 11 to 15 of the application as filed), the board is convinced that the problem has been solved.

- 5.6 Faced with the problem defined above, the skilled person would also be aware of document (1).

This document refers to the formation of leucotriene B₄ playing a major role as a soluble mediator of inflammation and concludes by indicating a practical use of the leucotriene B₄ blocking feature of 5,8,11-eicosatrienoate, namely its use as a dietary supplement (see document (1), page 11784, title and lines 8 to 9 in the right-hand column together with the paragraph bridging the left- and right-hand columns on page 11789).

Since naturally produced 5,8,11-eicosatrienoate is always 5,8,11-cis-eicosatrienoate, this isomer is obvious in the light of the disclosure of document (1) in the form of the shortened expression 5,8,11-eicosatrienoate (see also page 6 of the application in suit, lines 27 to 29).

In trying to find a further compound for use in the manufacture of a medicament for the treatment of inflammation such as rheumatoid arthritis, the person skilled in the art takes into account the teaching of (1) and accordingly is led to the use of 5,8,11-cis-eicosatrienoate for the treatment of the chronic inflammation rheumatoid arthritis, caused by leucotriene B₄.

- 5.7 Consequently, the board can only conclude that the subject-matter of claim 1 of the main request does not involve an inventive step (Article 56 EPC).

5.8 The same holds for the subject-matter of auxiliary request 1, since it is only restricted, with respect to the trienoic acid, to the "form of triglyceride or ester of monohydric alcohol having up to 6 carbon atoms". The reasoning according to the subject-matter of the main request applies *mutatis mutandis* since 5,8,11-eicosatrienoate is isolated in document (1) as a lipid (see page 11785, right-hand column, paragraph 3 with the heading "Lipid extraction and fatty acid analysis") and it is clear to the skilled person that he can provide the fatty acid part of these lipids to the animal particularly in the form of triglycerides.

5.9 The subject-matter of claim 1 of auxiliary request 2 differs from that of auxiliary request 1 in the added advice that the rheumatoid arthritis is to be treated by means of a daily dose of 1 to 500 mg for adult human oral administration.

In this special case, there is no need to discuss the question whether such a feature complies with Article 54(2) EPC or whether it could contribute to the inventive step the subject-matter of the application had to involve, because in any case there is no inventive step and the appellant did not even submit that this feature contributed to non-obviousness.

Determining the dose for the application of an active compound is routine work for the skilled person as soon as there are in vivo experiments with animals, in particular when the quantity to be administered is not a critical parameter with respect to damage for the patient.

5,8,11-cis-eicosatrienoic acid is biosynthesised in vivo in an essentially fatty acid-deficient condition and therefore it could be expected that there were no critical conditions with respect to its dosage (see also page 9, line 33 to page 10, line 4 of the application in suit). Therefore, in the current case the dosage for human adults to be administered to treat inflammation such as rheumatoid arthritis was an obvious conclusion from the results of the animal experiments.

Thus, for the same reasons set out with respect to the main request and auxiliary request 1, the subject-matter of auxiliary request 2 does not comply with the provisions of Article 56 EPC.

6. The appellant argued that it was mere speculation in document (9) that drugs were useful for the treatment of inflammatory states such as rheumatoid arthritis because of potent anti-leucotriene B₄ activity, in particular since in document (9) there were no experimental data to support this allegation.

The board cannot share this opinion:

As may be seen from the introductory lines on page 3 of document (9) (starting at line 6) the sequence of conclusions with respect to the treatment of inflammation such as rheumatoid arthritis by virtue of potent anti-leucotriene B₄ activity as set out in this document represented the general knowledge of the person skilled in the art at that time as the result of "a tremendous amount of research" having been performed.

Therefore, the description of exact experiments concerning the special compounds in document (9) was not necessary to make it the starting point for examining inventive step in respect of the subject-matter of the application in suit.

7. With reference to the experimental data in document (1) the appellant argued that the skilled person would never think that it would be possible to develop the suggestion to use 5,8,11-eicosatrienoate as a dietary supplement on the basis of these data and therefore would not take document (1) into account.

- 7.1 This suggestion was derived from 5,8,11-eicosatrienoate being produced in animals on essential fatty acid-deficient diet concomitantly with a lower production of leucotriene B₄, and not from experiments where 5,8,11-eicosatrienoate was administered to the animal from outside.

In the view of the appellant, the lower production of leucotriene B₄ could easily be explained by a deficiency of arachidonic acid in the diet, since this acid was the necessary precursor of leucotriene B₄.

So it was even unclear whether the reduced leucotriene B₄ production had any causal relation to the appearance of 5,8,11-eicosatrienoate and it was all the more unjustified to suggest that such a reduction could be caused by administering this substance.

In so far as experimental data were presented in document (1) in favour of a leucotriene B₄ reducing effect by means of 5,8,11-eicosatrienoate, these data

showed such effects only as a result of administration in hugely excessive amounts, which does not allow the conclusion that the same effects could be achieved by reasonable amounts administered to animals which lead to much lower concentrations of this substance in vivo (see the quantity of 30 μM used in the experiment leading to the results in table I on page 11787 of document (1) in comparison with the concentration of 5,8,11-eicosatrienoate set out in table II on the same page, namely 0.6 nmol/ 1×10^7 cells).

7.2 The board, however, cannot follow this argumentation either:

The first statement in document (1) is that the reduced level of arachidonic acid in animals on a fatty acid-deficient diet could not be the only reason for the reduced production of leucotriene B₄, since the decrease of 34% of arachidonic acid could not match the 87% decrease in leucotriene B₄ production (see page 11788, right-hand column, second paragraph under the heading "Discussion", lines 15 to 21, with the 34% decrease of arachidonic acid being derived from the data at the top of the left-hand column on page 11786 and the 87% decrease of leucotriene B₄ being derived from table I with its underlying experiments).

On the other hand, in table I, the use of 30 μM of 5,8,11-eicosatrienoate together with the neutrophils of normally fed rats causes the same reduction of leucotriene B₄ production as the fatty acid-deficient diet in the neutrophils of rats which have been on diet. This undoubtedly occurs even when the neutrophils of

the normally fed rats are able to produce leucotriene B₄ from a full normal level of arachidonic acid.

Even if, under the circumstances of the experiment summarised in table II of document (1), a much lower level of 5,8,11-eicosatrienoate production is shown, there is no doubt that administration of this substance has a lowering effect on the production of leucotriene B₄ (see table I) and that neutrophils of rats on a fatty acid-deficient diet produce 5,8,11-eicosatrienoate whereas neutrophils of normally fed rats do not (see table II). The levels set out for the quantity of 5,8,11-eicosatrienoate in table II cannot be compared with the quantity of 5,8,11-eicosatrienoate used in the experiments according to table I since both experiments are not designed to permit such a comparison.

Thus the board is convinced that the suggestion to use 5,8,11-eicosatrienoate as a dietary supplement to selectively block the synthesis of leucotriene B₄ and hence to treat inflammation is plausibly formulated in document (1) and that it is supported by the experimental data.

8. Consequently, in these circumstances the appellant's arguments cannot succeed. The board concludes that the subject-matter of the application in suit, with reference to the main request and to auxiliary requests 1 and 2, is obvious with regard to the state of the art (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Townend

U. Oswald