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Datasheet for the decision of 27 February 2013

Case Number: T 0396/09 - 3.3.02

Application Number: 99946470.4

Publication Number: 1115389

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Language of the proceedings: EN

Title of invention:
Fructosamine oxidase: antagonists and inhibitors

Applicant:
PhilERA New Zealand Limited

Headword:
Triethylenetetramine dihydrochloride/PHILERA

Relevant legal provisions:
EPC Art. 123(2), 84, 56
RPBA Art. 13

Keyword:
"Admissibility of the main request and auxiliary request 1 (no)"
"Clarity and support, auxiliary request 2 (no): term 'acetylated metabolic derivative' not clear"
"Auxiliary request 3, inventive step (yes), remittal to the first instance"

Decisions cited:
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Catchword:-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0396/09 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 27 February 2013

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 16 September 2008 refusing European patent application No. 99946470.4 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: D. Boulois
R. Cramer

Summary of Facts and Submissions

I. European patent application No. 99 946 470.4 was refused by a decision on the state of the file taken by the examining division on the basis of the communication dated 18 April 2008, on the grounds of non-compliance with Articles 123(2), 84 and 56 EPC.

II. The decision on the state of the file was based on the claims filed with the letter dated 24 August 2006.

Independent claim 1 read:
"1. Use of a triene for the preparation of a medicament for the treatment of a human patient predisposed to or suffering from diabetes".

III. The documents cited during the examination proceedings included the following:

(2) Cameron Norman et al., J. Clin. Invest., 96, August 1995, pages 1159-1163, "Neurovascular Dysfunction in Rats; Potential Contribution of Autoxidation and Free Radicals Examined Using Transition Metal Chelating Agents"

(4) Keegan A. et al., Free Radical Biology & Medicine, Vol. 27, nos. 5/6, (1999), pages 536-543, "Effects of Chelator Treatment on Aorta and Corpus Cavernosum from Diabetic Rats"

(7) Seaquist E.R., Microvascular Complications, 103, No. 1, January 1998, pages 61-68, "Microvascular Complications of Diabetes"

(8) Squadrito G. et al., Annali Italiani di Medicina Interna, 6, 1991, pages 126-136, "The late Complications of Diabetes Mellitus".

IV. The examining division held in the communication dated 18 April 2008 that the subject-matter of claims 1-21 filed with the letter dated 24 August 2006 did not meet the requirements of Articles 123(2), 84 and 56 EPC.

As regards Article 123(2) EPC, the examining division considered that the text passage cited by the applicant as a basis for claim 1 appeared insufficient, because the passage did not mention the term "*triene*", let alone "*a triene*".
The examining division noted that most of the text passages cited as a basis for claims 1-21 did not provide a sufficient basis for combining the additional technical features specified in said claims with the features newly introduced into claim 1, namely the features "*triene*" and a "*human patient*".

As regards Article 84 EPC, the examining division considered the term "*triene*" as unclear and misleading, because the expression was commonly understood to designate polyenes with three double bonds. The definition set out in the description for the expression "*triene*" appeared also unclear itself.
The examining division noted that the terms "*reducing the likelihood*" in claims 3, 4, "*amelioration of*" in claim 5, "*accelerated*" in claim 6 had no well-recognised meaning and left the reader in doubt as to the meaning of the technical features to which they referred, thereby rendering the definition of said claims unclear.
Moreover, the terms "*analogue and metabolite of triene*" and "*long acting release form*" also appeared vague and unclear.

In its communication, the examining division noted that no definitive assessment of novelty and inventive step could be given at this stage. In order to expedite the procedure, it was considered that a "*triene*" in claim 1 was to be interpreted as "*triethylenetetramine dihydrochloride*".

As regards inventive step, document (2) was considered to represent the most relevant state of the art. It disclosed a method for correcting nerve conduction and blood flow changes by oral administration of triethylenetetramine dihydrochloride to streptozotocin-diabetic rats, an animal model for diabetes. The treatment was performed on an animal model instead of a human patient in document (2).
The problem could be formulated as the provision of a medicine for the treatment of human patients suffering from diabetes.
The solution was not considered inventive, because document (2) explicitly taught that the results were applicable to human patients.

V. The applicant (appellant) filed an appeal against the first-instance decision. He filed with the statement of grounds of appeal a main request and 2 auxiliary requests.

VI. Proceedings before the EPO were interrupted under Rule 142 EPC as from 13 July 2010.

VII. With a letter dated 25 May 2011, the EPO was provided with an assignment agreement between the formerly

registered applicant Protemix Corporation Limited and PhilERA New Zealand Limited dated 1 December 2010.

VIII. The Legal Division of the EPO informed the applicant that the proceedings would be resumed in accordance with the filed evidence on 04 October 2011.

IX. A communication expressing the board's preliminary opinion of the board was sent to the applicant on 19 November 2012.

The preliminary opinion of the board was that the main request did not meet the requirements of Articles 123(2), and 84 EPC. Moreover, the subject-matter of claim 1 of the main request was not novel over document (2). For a possible discussion on inventive step of the main request, document (2) was seen as the closest prior art.

The same opinion was given for auxiliary request 1.

As regard auxiliary request 2, the board was of the opinion that it did not meet the requirements of Articles 123(2) and 84 EPC, but was novel over document (2), which did not disclose the specifically claimed medical indications. For a possible discussion on inventive step, document (2) was seen as the closest prior art.

X. The appellant sent a letter on 26 January 2013 as a reply to the board's communication dated 19 November 2012. It filed therewith a new main request and three auxiliary requests, replacing the main and auxiliary

requests previously on file. It filed therewith also two additional documents.

The independent claims of the requests read as follows:

a) Main request:

"1. Use of triethylenetetramine dihydrochloride, or acetylated metabolic derivative thereof, for the preparation of a medicament for the treatment of a human patient, wherein the medicament is for treating or reducing the likelihood of diabetic cardiomyopathy or for treating or reducing the likelihoood of diabetic nephropathy."

"8. Triethylenetetramine dihydrochloride, or acetylated metabolic derivative thereof, for use in a method of treating or reducing the likelihood of diabetic cardiomyopathy or treating or reducing the likelihoood of diabetic nephropathy in a human patient."

b) Auxiliary request 1:

"1. Use of triethylenetetramine dihydrochloride for the preparation of a medicament for the treatment of a human patient, wherein the medicament is for treating or reducing the likelihood of diabetic cardiomyopathy or for treating or reducing the likelihoood of diabetic nephropathy."

"8. Triethylenetetramine dihydrochloride for use in a method of treating or reducing the likelihood of diabetic cardiomyopathy or treating or reducing the

likelihoood of diabetic nephropathy in a human patient."

c) Auxiliary request 2:

"1. Use of triethylenetetramine dihydrochloride, or acetylated metabolic derivative thereof, for the preparation of a medicament for the treatment of a human patient, wherein the medicament is for treating or reducing the likelihood of diabetic cardiomyopathy."

"7. Triethylenetetramine dihydrochloride, or acetylated metabolic derivative thereof, for use in a method of treating or reducing the likelihood of diabetic cardiomyopathy in a human patient."

d) Auxiliary request 3:

"1. Use of triethylenetetramine dihydrochloride for the preparation of a medicament for the treatment of a human patient, wherein the medicament is for treating or reducing the likelihood of diabetic cardiomyopathy."

"6. Triethylenetetramine dihydrochloride for use in a method of treating or reducing the likelihood of diabetic cardiomyopathy in a human patient."

XI. Oral proceedings before the board of appeal took place on 27 February 2013.

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

As regards the admissibility of the requests, the appellant considered that they represented a genuine

attempt to overcome the grounds of objection. The amendments restricted the scope of the claims, removed the deficiencies, and served to reduce the number of issues to be discussed at a stage of the proceedings which was not so late as to cause delay. The scope of the claims of the new request was also the scope of the previous requests. Moreover, the transfer of ownership should also count in favour of the new amendments.

As regards clarity, the term "*acetylated metabolic derivative thereof*" related to a particular compound corresponding to the acetylated derivative of *triethylenetetramine.* On page 21, line 23, the description gave a precise definition of the acetylated derivative, which was an active metabolite of *triethylenetetramine.* This was to be compared with the passage of the description relating to the inactive acetylated product of hydralazine, on page 17, line 11.

As regards inventive step, document (2) was considered to be the closest prior art. Document (4) could not be used to assess inventive step, since it was publicly available on 24 September 1999, which was the filing date of the application.
Document (2) related to a different medical indication and the problem should be seen as the provision of a product for treating or preventing a specific disease, namely cardiomyopathy. As shown by documents (7) or (8), cardiomyopathy was a specific and distinct complication of diabetes, for which there was no incentive to use the claimed compound.

XIII. The appellant requested that the first-instance decision be set aside and a patent be granted on the

basis of the main request or one of auxiliary requests 1, 2 or 3 filed with the letter dated 26 January 2013.

Reasons for the decision

1. The appeal is admissible.

2. Admission of a new document into the proceedings

A new document was submitted during oral proceedings, thus at a very late stage of the proceedings.
This document consisted of the front page and the table of contents of the journal "Free Radical Biology & Medicine, Vol. 27, Nos. 5/6, (1999)", accompanied by a letter specifying the date of receipt of the journal by the British Library. This specific edition contains in its pages 536-543 the non-patent literature document (4). According to this document, the date of public availability at the British Library of document (4) was 24 September 1999, which is the filing date of the present application.

The board does not consider the teaching of document (4) to be relevant for the assessment of inventive step in the present case. Thus, the knowledge of its date of public availability at the British Library, let alone its actual and effective publication date, which might be different, has no bearing on the present proceedings.

The board exercises its power of discretion and admits this evidence into the proceedings.

3. Main request - Admission into the proceedings

The main request was filed with the letter dated 26 January 2013 after oral proceedings had been arranged and thus at a late stage in the proceedings. It comprises amended independent claims 1 and 8 containing an additional feature regarding the claimed medical indication, namely "*for treating or reducing the likelihood of diabetic nephropathy*".

This amendment originates from the description, and was not present in any claim of any request during the search phase and examination or appeal proceedings. It amends the appellant's case within the meaning of Article 13(1) and (3) RPBA. The amendment is such as to constitute a new technical case.

Since this substantive amendment introduces for the first time new subject-matter into the main claim of a request and constitutes a substantial shift of the invention which cannot be justified at such a late stage in the proceedings, the board decides not to admit the main request into the proceedings.

4. Auxiliary request 1 - Admission into the proceedings

The subject-matter of claims 1 and 8 of auxiliary request 1, which was filed with the same letter as the main request, comprises the same additional feature regarding the claimed medical indication, namely "*for treating or reducing the likelihood of diabetic nephropathy*", as claims 1 and 8 of the main request.

The reasoning applied to the main request applies *mutatis mutandis* to auxiliary request 1, and the board decides to not admit it into the proceedings.

5. Auxiliary request 2 - Article 84 EPC

5.1 Article 84 EPC requires that the claims must define the matter for which protection is sought. They must be clear and concise and supported by the description.

5.2 Claims 1 and 7 of auxiliary request 2 are respectively in the form of a Swiss-type claim and of a purpose-related product claim. In particular, they both relate to the compound "*triethylenetetramine dihydrochloride, or acetylated metabolic derivative thereof*", used for or for use in "*treating or reducing the likelihood of diabetic cardiomyopathy*".

The expression "*or acetylated metabolic derivative thereof*" adds to the specific compound defined in claims 1 and 8 those which are "*acetylated metabolic derivative*" of said specific compound. There is, however, no definition of how and to what extent the compounds according to claims 1 or 8 may be acetylated while still being regarded as compounds which could be used for "*treating or reducing the likelihood of diabetic cardiomyopathy*". This has the effect that the person skilled in the art cannot decide clearly which compounds are to be covered by the claims and which are not.

Thus, claims 1 and 7 of auxiliary request 2 do not clearly define the matter for which protection is sought.

5.3 In the applicant's view, the "*acetylated metabolic derivative*" of triethylenetetramine dihydrochloride is a particular compound which is obtained by acetylation of triethylenetetramine dihydrochloride when administered to the patient. The description gives a precise definition of this derivative, since it mentions that most of the drug is cleared in the urine within the first 6 hours of oral dosing, mainly as an acetyl derivative (see page 21, lines 23-26). It was obvious for the applicant that this compound should be an active metabolite of triethylenetetramine dihydrochloride.

5.4 The board could not however follow this opinion.
The claims must be clear as such. This implies that the claims be clear in themselves when read with the normal skills, but not including knowledge derived from the description of the patent application.
Therefore, the appellant's argument that it was clear from the description of the application what was to be understood by "*acetylated metabolic derivative*" cannot support clarity of the claims.

In any case, the description does not give further evidence or details about the claimed "*acetylated metabolic derivative*". From the passage cited by the applicant it can neither be deducted what the structure of the "*acetylated metabolic derivative*" may be, and in particular how and to what extent the acetylation takes place, nor that the said "*acetylated metabolic derivative*" mentioned in the description has a real pharmacological activity, namely that it is an active

metabolic derivative which could be used for "*treating or reducing the likelihood of diabetic cardiomyopathy*".

5.5 Auxiliary request 2 does not meet the requirements of Article 84 EPC.

6. Auxiliary request 3

6.1 Auxiliary request 3 - Article 123(2) EPC

The subject-matter of claims 1-6 of auxiliary request 3 meets the requirements of Article 123(2) EPC.

6.2 Auxiliary request 3 - Article 56 EPC

The present invention as claimed in claim 6 of auxiliary request 3 relates to a specific compound, namely triethylenetetramine dihydrochloride, for use in a method of treating or reducing the likelihood of diabetic cardiomyopathy. This specific compound is a copper chelating agent, acting as a fructosamine oxidase inhibitor or antagonist (see page 4, lines 5-12; page 7, lines 7-8; page 9, lines 24-27; Example 3, in particular point e) and Table 8).

6.2.1 Document (2) is concerned with the use of triethylenetetramine dihydrochloride as a transition metal chelating agent, to prevent auto-oxidation and thus correct nerve conduction and blood flow changes in streptozocin-diabetic rats (see abstract). The document shows the restoration of nutritive endoneurial blood flow reduced by diabetes, and proves that compounds with an action as chelating agents correct the perfusion deficits in diabetic rats (see pages 1160-

1161, "Results"; page 1161, right-hand side, 1st and 2nd par.). Document (2) suggests that chelators may have a therapeutic role in micro- and macro-vascular changes, and thus of vasculopathies, in diabetic patients (see page 1162, last par.).

One other cited document relates to triethylenetetramine for use in a therapeutic method. Document (4) concerns the effect of chelator treatment with triethylenetetramine on endothelium-dependent relaxation of the aorta and corpus cavernosum of diabetic rats (see abstract). The teaching of this document is more remote than the teaching of document (2).

Document (2) constitutes the closest prior art, since it refers to triethylenetetramine and to its general potential therapeutic role in the micro- and macro-vascular changes in diabetic patients. This choice was not contested by the appellant.

6.2.2 The problem underlying the present invention may be seen as the provision of a new product for use in treating or reducing the likelihood of diabetic cardiomyopathy.

6.2.3 The proposed solution to this problem is the specific compound as defined in claim 6, namely triethylenetetramine dihydrochloride.

6.2.4 Example 3 of the description provides a comparative study on myocardial fibrosis in diabetic STZ rats. It appears from the study that triethylenetetramine is highly effective in inhibiting the development of

diabetic cardiomyopathy, since no evidence of myocardial fibrosis was observed after 24 weeks of treatment. This example therefore establishes the credibility of the presence of the claimed technical effect of triethylenetetramine.
The board is thus convinced that the above problem has been plausibly solved.

6.2.5 Thus, the question to be answered is whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

Document (2) does not suggest that triethylenetetramine might be active in a method of treating or reducing the likelihood of diabetic cardiomyopathy. This document does not show any relationship between the therapeutic role of triethylenetetramine in micro- and macro-vascular changes in diabetic patients, and thus of diabetic vasculopathies, and the treatment of diabetic cardiomyopathy.

Moreover, document (8) explicitly discloses that cardiomyopathy is a specific complication of diabetes, independent of other complications, such as coronary artery disease, hypertension or valvulopathies. The pathogenic bases of diabetic cardiomyopathy are linked with the metabolic alterations of diabetes (see document (8), Abstract and page 135).

A link between a potential therapeutic effect in vasculopathy, such as nutritive endoneurial blood flow, and cardiomyopathy is therefore not known from the cited prior art.

Thus, the effect of triethylenetetramine on cardiomyopathy is unexpected.

6.2.6 The subject-matter of claim 6 of auxiliary request 3 is therefore inventive over document (2).

This reasoning also applies to the subject-matter of claim 1, which is a Swiss-type use claim relating to the same compound and the same medical indication.

The requirements of Article 56 EPC are therefore met for auxiliary request 3.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of the claims according to the third auxiliary request filed with the letter of 26 January 2013, and a description adapted thereto.

The Registrar: The Chairman:

N. Maslin U. Oswald