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Datasheet for the decision of 18 December 2009

Case Number: T 0478/05 - 3.3.02

Application Number: 98925875.1

Publication Number: 1001755

IPC: A61K 31/19

Language of the proceedings: EN

Title of invention:
Carboxylic acids and derivatives thereof and pharmaceutical compositions containing them

Applicant:
Syndrome X Limited

Headword:
Dyslipoproteinemia/SYNDROME X LIMITED

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)

Relevant legal provisions (EPC 1973):
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Keyword:
"Main request: novelty, inventive step, sufficiency, clarity, allowability of the amendments (yes): treatment of dislipoproteinemia not disclosed or rendered obvious by the available prior art"

Decisions cited:
-

Catchword:
-

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Case Number: T 0478/05 **-** 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 18 December 2009

Appellant: Syndrome X Limited
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 16 November 2004 refusing European patent application No. 98925875.1 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: J. Riolo
Members: A. Lindner
K. Garnett

Summary of Facts and Submissions

I. European patent application No. 98 925 875.1 was refused by a decision of the examining division of 22 October 2004 on the basis of Article 97 EPC on the grounds that the subject-matter of the main and sole request did not involve an inventive step.

II. The decision was based on claims 1-2 of the main request filed at the oral proceedings before the examining division on 22 October 2004.

Independent claim 1 of the main request before the examining division reads as follows:

"1. Use of a xenobiotic compound of the formula R-COOH, or a salt or an ester or amide of such compound, in the manufacture of a pharmaceutical composition for the treatment of dyslipopropteinemia (combined hypertriglyceridemia, hyper-cholesterolemia, low HDL-cholesterol) wherein said compound is capable of being endogenously converted to its respective coenzyme A thioester, RCOSCoA, and wherein said compound inhibits HNF-4α transcriptional activity by the binding of its coenzyme A thioester to HNF-4α; wherein R designates a saturated or unsaturated alkyl chain of 10-24 carbon atoms, one or more of which may be replaced by heteroatoms, where one or more of said carbon or heteroatom chain members optionally forms part of a ring, and where said chain is optionally substituted by a hydrocarbyl radical, heterocyclyl radical, lower alkoxy, hydroxyl-substituted lower alkyl, hydroxyl, carboxyl, phenyl, or (hydroxy-, lower alkyl-, lower alkoxy-, lower alkenyl or lower alkynyl)-substituted

phenyl, C3-C7 cycloaklyl or or (hydroxy-, lower alkyl-, lower alkoxy-, lower alkenyl- or lower alkynyl)-substituted C3-C7 cycloalkyl."

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

(4) R. Hertz et al.: "Mode of action of peroxisome proliferators as hypolipidemic drugs: Suppression of apolipoprotein C-III", J. Biol. Chem., vol. 270, no. 22, 1995, pages 13470-13475

(8) J. Bar-Tana et al.: "Hypolipidemic effect of ß,ß-methyl-substituted hexadecanedioic acid (medica 16) in normal and nephrotic rats", J. Lipid. Res., vol. 29, no. 4, 1988, pages 431-441

IV. The arguments in the decision may be summarised as follows:

In connection with novelty, the examining division reasoned that the nephrotic rats in the animal model of document (8) did not suffer from low HDL cholesterol. As a consequence, document (8) did not anticipate the subject-matter as claimed in the main request. Regarding inventive step, the examining division reasoned that the rat model of document (8), which was defined as closest prior art, showed that Medice 16 (= 3,3,14,14-tetramethyl-hexadecane-1,16-dioic acid) was able to treat all three symptoms of dyslipoproteinemia. As a consequence, it was obvious to use Medice 16 for the treatment of human dyslipoproteinemia.

V. The appellant (applicant) lodged an appeal against this decision.

VI. In the official communication of 1 December 2009, the board raised objections under Articles 83 and 84 EPC and noted that the claims still contained unsearched subject-matter.

VII. At the oral proceedings of 18 December 2009, the appellant filed a new main request. Independent claim 1 reads as follows:

"1. A xenobiotic compound of the formula R-COOH, or a salt or an ester or amide of such compound, for use in the treatment of dyslipoproteinemia having the symptoms of hypertriglyceridemia, hyper-cholesterolemia and low HDL-cholesterol, wherein said compound is capable of being endogenously converted to its respective coenzyme A thioester, RCOSCoA, wherein said compound inhibits HNF-4α transcriptional activity by the binding of its coenzyme A thioester to HNF-4α; and wherein the compound of the formula R-COOH is selected from:
1,16 Hexadecanedioic acid
1,18 Octadecanedioic acid
2,2,15,15-tetramethyl-hexadecane-1,16-dioic acid
2,2,17,17-tetramethyl-octadecane-1,18-dioic acid
3,3,14,14-tetramethyl-hexadecane-1,16-dioic acid
3,3,16,16-tetramethyl-octadecane-1,18-dioic acid
4,4,13,13-tetramethyl-hexadecane-1,16-dioic acid and
4,4,15,15-tetramethyl-octadecane-1,18-dioic acid."

VIII. The appellant's submissions can essentially be summarised as follows:

Dyslipoproteinemia as defined in claim 1 was known to only affect humans. The rat model of document (8) was not pertinent, as it involved a different mechanism of action including activation via PPAR, which did not occur in the human liver. Moreover, the rat model of document (8) did not show that low HDL-cholesterol could be treated with Medice 16. As a consequence, the subject-matter as claimed was not obvious in the light of document (8).

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed at the oral proceedings of 18 December 2009.

Reasons for the decision

1. The appeal is admissible.

2. Admissibility of the new main request:

The main request filed at the oral proceedings is admissible since it is a fair attempt to overcome the objections raised in the board's communication of 1 December 2009.

3. Amendments - Article 123(2) EPC:

In claim 1 of the present main request the xenobiotic compounds of the formula R-COOH are now limited to

eight specific substances. These compounds are disclosed on page 5, lines 21-26 and in claim 7 of the original application. In addition, claim 1 was reformulated from the "Swiss-type" format to the new format according to Article 54(5) EPC. The requirements of Article 123(2) EPC are therefore met.

4. Functional features:

Due to the limitation of the xenobiotic compounds to eight specific substances, the functional features of claim 1, which serve to define the compounds of the formula R-COOH by means of their capability to inhibit HNF-4α transcriptional activity, do not cause any unclarity. Moreover, the skilled person no longer needs to carry out tedious tests in order to determine whether or not a given compound inhibits HNF-4α transcriptional activity. As a consequence, the requirements of Article 83 and 84 EPC are met.

5. Novelty:

Claim 1 is directed to a xenobiotic compound for use in the treatment of dyslipoproteinemia having the symptoms of hypertriglyceridemia, hyper-cholesterolemia and low HDL-cholesterol.

Document (8) describes an animal model in which both normal and PAN-nephrotic rats were treated with Medice 16, which corresponds to the compound as defined in present claim 2. The PAN-nephrotic rats were used as a hyperlipidemic model system for studying the potential of hypolipidemic agents. Tables 1 and 3 show that the treatment resulted in a noticeable decrease in the

triglycerol and cholesterol contents of both the normal and PAN-nephrotic rats. However, the PAN-nephrotic rats do not serve as a model for low HDL-cholesterol, as the HDL-cholesterol concentration before administration of Medice 16 was considerably increased as compared to the concentration found in normal rats (121.8 mg/dl vs. 30.4 mg/dl; see tables 1 and 3). Moreover, administration of Medice 16 did not further increase the HDL-cholesterol concentration in the PAN-nephrotic rats. Medice 16 reduced the VLDL and LDL contents of cholesterol in the nephrotic rat and thereby the HDL : (VLDL + LDL) ratio. However, it did not increase HDL-cholesterol in absolute terms, which would be necessary for low HDL-cholesterol treatment. It is noted that the slight increase from 121.8 mg/dl to 125.1 mg/dl is within the margin of error and therefore not significant. As a consequence, document (8) does not disclose the treatment of dyslipoproteinemia as defined in present claim 1.

Document (4) discloses Medica 16 for the treatment of combined hypertriglyceridemia/hypercholesterolemia in humans (see page 13470, lower part of the left-hand column). Document (4) does not relate to an increase of low HDL-cholesterol.

In view of the fact that neither document (4) nor document (8) nor any of the other available prior art documents disclose the treatment of dyslipoproteinemia having the symptoms of hypertriglyceridemia, hyper-cholesterolemia and low HDL-cholesterol, the subject-matter of the main request meets the requirements of Article 54 EPC.

6. Inventive step:

The present invention concerns the provision of a xenobiotic amphiphatic carboxylate for the treatment of dyslipoproteinemia having the symptoms of hyperglyceridemia, hyper-cholesterolemia and low HDL-cholesterol (see page 5, lines 14-15, page 6, lines 5-7 and page 9, lines 27-29 of the original application).

As for the closest prior art, both documents (4) and (8) disclose the use of Medice 16 in the treatment of combined hypertriglyceridemia/hypercholesterolemia (see point 5 above). In view of the fact that dyslipoproteinemia having the three symptoms defined above is only known to affect humans and taking into consideration that only the former document refers to the treatment of humans, document (4) constitutes the closest prior art. The problem to be solved with regard the closest prior art can be defined as the provision of Medice 16 and other dicarboxylic acids for the treatment of a further disease. It was solved by the provision of the eight compounds according to claim 1 for use in the treatment of dyslipoproteinemia having the three symptoms defined above.

In view of the disclosure on page 5, lines 14-15 and 22-26, page 16, lines 23-28 and figure 4b, the board accepts that the problem has been plausibly solved. It is noted that none of the available prior art documents suggests that low HDL-cholesterol can be treated with Medice 16 or any of the other compounds of present claim 1. As low HDL-cholesterol is an integral part of dyslipoproteinemia, the subject-matter of claim is not obvious in the light of the available prior art. As a

consequence, the requirements of Article 56 EPC are met.

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 claims 1 and 2 of the main request filed during the oral proceedings and any necessary consequential adaptation of the description.

The Registrar: The Chairman

N. Maslin J. Riolo