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Datasheet for the decision of 1 July 2008

Case Number: T 1391/05 - 3.3.02

Application Number: 00920922.2

Publication Number: 1171129

IPC: A61K 31/445

Language of the proceedings: EN

Title of invention:
Use of glucosylceramide synthesis inhibitors in therapy

Applicant:
Actelion Pharmaceuticals Ltd.

Opponent:
-

Headword:
Glucosylceramide inhibitors/ACTELION PHARMACEUTICALS LTD.

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step - no: obvious combination of two prior art documents linked by a cross-reference"

Decisions cited:
-

Catchword:
-

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Case Number: T 1391/05 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 1 July 2008

Appellant: Actelion Pharmaceuticals Ltd.
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Representative: Ruhlmann, Eric
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted ??? refusing European application No. 00920922.2 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
P. Mühlens

Summary of Facts and Submissions

I. European patent application No. 00 920 922.2 entitled "Use of glucosylceramide synthesis inhibitors in therapy" was refused by a decision of the examining division of 1 June 2005 on the grounds of lack of inventive step.

II. The following documents, cited during the proceedings before the examining division and the board of appeal, remain relevant for the present decision:

(1) WO 98/02161
(3) Journal of inherited metabolic disease, 18(6), 1995, 717-722

III. The decision was based on claims 1 to 3 of the request filed on 4 May 2004.

Independent claim 1 of this request read as follows:

"1. The use of an imino sugar-structured inhibitor of glucosylceramide synthesis in the manufacture of a medicament for use in the treatment of Niemann-Pick type C disease."

IV. The examining division considered that the subject-matter of the set of claims of the request filed on 4 May 2004 did not fulfil the requirements of inventive step vis-à-vis document (1) (WO 98/02161) in the light of document (3) (Journal of inherited metabolic disease, 18(6), 1995, 717-722).

In its view, document (1) disclosed that N-butyldeoxynojirimycin (NB-DNJ), an inhibitor of glucosylceramidase, is useful for the treatment of diseases characterised by elevated plasma chitotriosidase such as the Niemann-Pick (NP) disease (page 23, lines 14 to 19).

Moreover, document (3), which is referred to in document (1), confirmed that NP-C, like NP-A and NP-B, is characterised by an elevated chitotriosidase activity (table 2).

It accordingly concluded that this prior art suggested using NB-DNJ in order to solve the problem of finding new drugs for the treatment of NP-C disease, so that the claimed subject-matter, which concerned the use of NB-DNJ in the manufacture of a medicament for the treatment of NP-C disease, was not inventive.

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

It filed auxiliary requests 1 and 2 with its letter dated 7 March 2008.

The sole claim of auxiliary request 1 reads:

"1. The use of N-butyldeoxynojirimycin in the manufacture of a medicament for use in the treatment of Niemann-Pick type C disease."

The sole claim of auxiliary request 2 reads:

"1. The use of N-butyldeoxynojirimycin in the manufacture of a medicament for reducing neuronal glycolipid storage in Niemann-Pick type C disease patients."

VI. Oral proceedings were held before the board on 1 July 2008.

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

It first stressed the differences between Gaucher disease and Niemann-Pick C disease as to etiology, visceral manifestation, neurological manifestations, life expectancy and chitotriosidase plasma levels.

Having regard to the fact that these two diseases were different and that document (1) did even not provide concrete evidence that Gaucher disease could be effectively treated by inhibiting glucosylceramide synthesis, it concluded that the skilled person would not consider the inhibitor of glucosylceramide synthesis disclosed in document (1) for the treatment of Niemann-Pick C disease.

That was the more so because the significance of chitotriosidase in plasma in both diseases was not understood, chitotriosidase being merely a known marker for these diseases.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis

of the set of claims of the main request (set of claims filed on 4 May 2004) or, alternatively, of auxiliary requests 1 or 2 filed with the letter of 7 March 2008.

Reasons for the decision

1. The appeal is admissible.

2. *Main request*

2.1 Inventive step

2.1.1 The board considers that document (1), which discloses the use of inhibitors of glucosylceramidase (deoxynojirimycin derivatives, e.g. N-butyldeoxynojirimycin) for the treatment of diseases characterised by elevated plasma chitotriosidase such as Gaucher disease, can be considered as the closest prior art (page 1, lines 2 to 5; page 14, line 21, to page 15, line 36; page 30 to 32, compound N-butyldeoxynojirimycin).

This document moreover discloses that "a benefical effect might also be exerted by inhibitors of glucosylceramidase activity in case of other disease states that are characterized by elevated plasma chitotriosidase, such as the Niemann-Pick disease ..." (page 23, lines 15 to 19).

The application concerns the use of inhibitors of glucosylceramide synthesis, in particular N-butyldeoxynojirimycin, in the manufacture of a

medicament for use in the treatment of Niemann-Pick type C disease (page 1, lines 3 to 6).

Therefore, starting from document (1), the technical problem to be solved is that of providing a new application for inhibitors of glucosylceramide synthesis, in particular N-butyldeoxynojirimycin.

The proposed solution is the subject-matter of independent claim 1, i.e. the use of inhibitors of glucosylceramide synthesis, in particular N-butyldeoxynojirimycin, in the manufacture of a medicament for use in the treatment of Niemann-Pick type C disease.

From the description, in particular the animal models, the board is satisfied that the problem is plausibly solved.

The question to be answered is thus whether the proposed solution, i.e. the treatment of Niemann-Pick type C disease, is obvious to the skilled person faced with the problem defined above in the light of the available prior art documents.

In that respect, document (1) in the sentence quoted above contains a reference to document (3) in connection with the type of other diseases which might be treated having regard to their elevated plasma chitotriosidase level.

It appears from this latter document, which investigates the presence of an elevated plasma chitotriosidase in various diseases, that Niemann-Pick

C has a plasma value which is elevated (i.e. 304 to 940 nmol/h per ml) since it is clearly greater than the highest reference value of 195 nmol/h per ml.

Having regard on the one hand to the suggestion in document (1) with respect to the use of inhibitors of glucosylceramide synthesis, in particular N-butyldeoxynojirimycin, in the treatment of diseases characterised by elevated plasma chitotriosidase, such as Niemann-Pick diseases in general, and on the other hand to document (3), to which document (1) refers in that respect, which discloses that Niemann-Pick C like the other types of Niemann-Pick disease, namely A and B, also has an elevated plasma chitotriosidase, the board is convinced that the skilled person, faced with the problem as defined above, would consider the use of inhibitors of glucosylceramide synthesis, in particular N-butyldeoxynojirimycin, as a promising solution to the above-mentioned problem.

2.1.2 In the appeal proceedings, the appellant stressed the various differences between Gaucher disease, which is the main topic of document (1), and Niemann-Pick C disease, which is the subject of the present claims.

The board does not contest that the two illnesses are distinct.

The board also agrees that, in the light of this difference, the skilled person would *prima facie* not expect a drug useful for treating Gaucher disease to be also useful in the treatment of Niemann-Pick C disease.

The present situation is different however because of the disclosure in prior art document (1), which made precisely this inventive contribution to the art, namely that inhibitors of glucosylceramide synthesis, such as N-butyldeoxynojirimycin, might be useful for both indications.

Accordingly, this line of argumentation is no longer relevant for the assessment of inventive step in the present case, i.e. in answering the question whether the skilled person would have envisaged the use of inhibitors of glucosylceramide synthesis, such as N-butyldeoxynojirimycin, in the treatment of Niemann-Pick C disease.

Neither does the board disagree with the appellant that document (1) merely suggests that these compounds "might" exert a beneficial effect and that the effect on Gaucher disease is tested only via enzymatic *in vitro* tests.

The board however does not agree that, for all the above reasons, the skilled person would not have tried these molecules for treating Niemann-Pick C disease because it had no reasonable expectation of success.

In fact, assessment of the question whether the skilled person would try the suggestion of document (1) is also influenced by the difficulties it would encounter when putting the teaching into practice and by the severity of the considered illness and urgent need to find a treatment for it.

In the present case, the board observes that the molecules to be tested were already available, so that no complicated and costly structure research programs were necessary. Indeed, the priority of the present application was filed only about a year after the publication of document (1).

In addition, as emphasised by the appellant itself during the oral proceedings, there is as yet no accepted treatment for Niemann-Pick C disease, which is a severe disease (life expectancy of 8-10 years for the infantile forms, 20-30 years for the later forms).

For these reasons, the board remains convinced that the skilled person would in any case have tried the promising suggestion of document (1) despite the correct considerations raised by the appellant.

As to the last point raised by the appellant concerning the experimental data in document (1), the appellant is reminded that *in vitro* data is, as a rule in the field of pharmacy, accepted as *prima facie* evidence of the claimed effect.

In that respect, the board notes that the application also does not contain clinical data and the appellant did not contest the validity of the *in vitro* results.

For these reasons, the board concludes that the subject-matter of claim 1 lacks inventive step as required by Article 56 EPC.

Under these circumstances, there is no need to consider the remaining claims.

3. *Auxiliary request 1*

The only argument put forward by the appellant with respect to this request during the oral proceedings was that, according to the results shown in document (1), N-butyldeoxynojirimycin was not the most promising molecule.

This consideration does not change anything as to the fact that the skilled person could choose said compound without inventive activity as it remains within the various alternatives disclosed in document (1).

Accordingly, the above analysis and conclusion apply *mutatis mutandis* to this claim.

4. *Auxiliary request 2*

The only argument put forward by the appellant with respect to this request during the oral proceedings was that document (1) was totally silent about any effect on reducing neuronal glycolipid storage in the treatment of Niemann-Pick C disease.

This feature in claim 1, which is merely the description of one of the consequences of the successful treatment of Niemann-Pick C disease, cannot as such add anything to the assessment of inventive step.

Accordingly, the above analysis and conclusion apply *mutatis mutandis* to this claim.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chairman

N. Maslin U. Oswald