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Datasheet for the decision of 10 August 2015

Case Number: T 2266/11 - 3.3.01

Application Number: 05766869.1

Publication Number: 1768976

IPC: C07D401/06, A61K31/454, A61P5/06

Language of the proceedings: EN

Title of invention:

CRYSTAL FORMS OF (3R)-1-(2-METHYLALANYL-D-TRYPTOPHYL)-3-(PHENYLMETHYL)-3-PIPERIDINECARBOXYLIC ACID 1,2,2-TRIMETHYLHYDRAZIDE

Applicant:

Helsinn Healthcare S.A.

Headword:

anamorelin/HELSINN

Relevant legal provisions:

EPC Art. 56

Keyword:

Main Request:
Inventive step - (yes) -
crystallisation of the base not obvious under the present circumstances

Decisions cited:

Catchword:

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Case Number: T 2266/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 10 August 2015

Appellant: (Applicant)	Helsinn Healthcare S.A. Via Pian Scairolo, 9 6912 Lugano / Pazzallo (CH)
Representative:	Zardi, Marco M. Zardi & Co. SA Via G. B. Pioda 6 6900 Lugano (CH)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 16 May 2011 refusing European patent application No. 05766869.1 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	C. M. Radke
	L. Bühler

Summary of Facts and Submissions

I. European patent application No. 05 766 869.1 relates to a crystalline (3R)-l-(2-methylalanyl-D-tryptophyl)-3-(phenylmethyl)-3- piperidinecarboxylic acid 1,2,2-trimethylhydrazide, i.e. a crystalline form of the compound known by the International Nonproprietary Name (INN) anamorelin.

II. During the oral proceedings of 16 December 2010, the examining division decided that the subject-matter of the claims of the main request then on file was not inventive, whereas the claims of the auxiliary request submitted during said oral proceedings met the requirements of the EPC. The applicant was given a period of two months to file a description adapted to the claims of the auxiliary request.

In the communication dated 18 March 2011, the examining division granted an extension of this period to a total of four months.

In its reply dated 21 April 2011, the applicant indicated that it disagreed with the decision concerning the main request and that it would not limit the application according to the auxiliary request.

III. With its decision posted on 16 May 2011, the examining division refused the application.

In particular, the examining division decided that the subject-matter of the claims of the only request then on file was not inventive in view of document (D1), especially in view of step j of its example 1. It was obvious to recrystallise the amorphous form obtained in that step.

IV. The following documents were cited during examination and appeal proceedings:

(D1) US-B-6 576 648
(D2) Lab journal, project no. B-3289/3290, book no. BOP-T, 12 to 16 January 2006, pages 100-103
(D3) Declaration of Mr. Neal G. Anderson dated 21 September 2011, filed under cover of a letter dated 22 September 2011, eleven pages including Annexes 1 and 2 and the CV of Mr Anderson.

V. The applicant appealed this decision.

VI. In its communications dated 5 June 2014 and 10 April 2015, the board informed the appellant of deficiencies in the claims of the main request and in the description. Once these were overcome, the main request was likely to be considered allowable.

VII. With the replies dated 12 February and 21 May 2015, the appellant submitted amended claims of the main request and amended pages 1, 7, 23, 35, 35a and 35b of the description. In its letter dated 28 May 2015, the appellant requested the deletion of page 35b.

VIII. The present claims are
- claims 1 to 15 of the main request, filed with the letter dated 21 May 2015; and
- claims 1 to 6 of the auxiliary request, submitted during the oral proceedings of 16 December 2010.

The independent claims 1, 6, 14 and 15 and dependent claim 4 of the main request read as follows:

"1. A crystalline (3R)-l-(2-methylalanyl-D-tryptophyl)-3-(phenylmethyl)-3-piperidinecarboxylic acid 1,2,2-trimethylhydrazide."

"4. The crystalline composition of Claim 3, wherein the hydrate is a dihydrate."

"6. A process for preparing crystalline (3R)-1-(2-methylalanyl-D-tryptophyl)-3- (phenylmethyl)-3-piperidinecarboxylic acid 1,2,2-trimethylhydrazide as set forth in claim 4, comprising the steps of:

a) combining (3R)-1-(2-methylalanyl-D-tryptophyl)-3-(phenylmethyl)-3-piperidinecarboxylic acid 1,2,2-trimethylhydrazide with a solvent; wherein the solvent is selected from the group consisting of methanol and mixtures thereof with water;

b) precipitating the crystals from the solvent; and

c) isolating the crystals."

"14. A pharmaceutical composition comprising the crystalline (3R)-1-(2-methylalanyl-D-tryptophyl)-3-(phenylmethyl)-3-piperidinecarboxylic acid 1,2,2-trimethylhydrazide of claim 4 and at least one pharmaceutically acceptable carrier or diluent."

"15. Use of a therapeutically effective amount of the crystalline (3R)-1-(2-methylalanyl-D-tryptophyl)-3-(phenylmethyl)-3-piperidinecarboxylic acid 1,2,2-trimethylhydrazide of claim 4 in the manufacture of a medicament for stimulating the release of growth hormone from the pituitary of a mammal."

The main request comprises the following amended pages of the description:

- pages 1, 35 and 35a, enclosed with the letter dated 21 May 2015 and
- pages 7 and 23, enclosed with the letter dated 12 February 2015.

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 or, as a subsidiary measure, on the basis of the claims of the auxiliary request. Oral proceedings were requested in case the main request was not allowed,.

X. As the appellant's main request is granted, there was no need to hold oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

Main Request

2. Novelty

Annex 1 of document (D3) (which is based on the respective lab protocol (D2)) shows that the repetition of example 1, step j, of document (D1) yields **amorphous** anamorelin. This was acknowledged under point 2 of the reasons of the decision under appeal.

As the anamorelin referred to in the present claims is restricted to a **crystalline** form, their subject-matter differs from the disclosure of example 1, step j, of document (D1). Example 1 is the only example of document (D1), and its step j the only step in which anamorelin is formed. No other prior art document was cited during examination proceedings. Therefore, the

subject-matter of these claims is novel. This corresponds to the conclusion drawn under point 2 of the reasons of the decision under appeal.

3. Inventive step

3.1 Document (D1) represents the closest prior art.

3.2 The objective problem to be solved was to provide an alternative pure form of anamorelin (see page 2, lines 12-15, of the application as filed). The examples of the present application show that this problem was solved; a purity of 99.8% is reported in example 4 (see page 30, lines 21-24 of the application as filed).

3.3 Step j of example 1 of document (D1) yields

(i) first **anamorelin hydrochloride** as a "non-crystalline precipitate" (see column 19, line 59);

(ii) then **anamorelin base** by dissolving the precipitate in methylene chloride (CH_2Cl_2), adding soda to set free anamorelin base, from which the solvent is subsequently evaporated (see column 19, line 59, to column 20, line 5),

(iii) finally **anamorelin fumarate** as a "white crystalline salt" by dissolving the base in ethyl acetate and adding fumaric acid (see column 20, lines 5-10).

The examining division was of the opinion that it was obvious to recrystallise the base obtained in step (ii) mentioned above by cooling a hot solution thereof in ethyl acetate (in view of the fact that, according to step (iii) mentioned above, the base was dissolved in this solvent).

In ANNEX 2 of the declaration (D3) the appellant summarised the following 16 crystallisation experiments (the polarities of the solvents indicated below being disclosed on page 4 of (D3)):

(1) By vapour diffusion of an antisolvent (hexane or diisopropyl ether (IPE)) into a solution in THF (polarity: 0.21), **ethyl acetate** (E.A.)(polarity: 0.23), acrylonitrile (MeCN)(polarity: 0.46) or acetone (polarity: 0.36);
(2) by slow evaporation of the solvent from the solution in ethanol (polarity: 0.65), methanol (polarity: 0.76), THF (polarity: 0.21), acetone (polarity: 0.36), 1-butanol (polarity: 0.60), acrylonitrile (polarity: 0.46); a 2:1 mixture of ethanol, methanol, THF, acetone or acrylonitrile (MeCN) with water; and from a ternary mixture of 1-butanol/ethanol/water.

In each of the four tests (1) a powder was obtained which, according to page 6, third paragraph, of the letter dated 15 November 2010, was amorphous in each case. The fact that precipitation in these tests was effected by vapour diffusion of an antisolvent rather than by cooling a hot solution (as suggested in the fourth and sixth paragraphs on page 4 of the decision under appeal) is not considered to be relevant, as both precipitation processes are based on a gradual decrease in solubility of anamorelin in the solvent (as do tests (2) where the solvent is evaporated slowly). Hence, the board does not share the view of the examining division that crystallisation experiments by cooling hot solutions in ethyl acetate might have been helpful.

In the twelve tests (2) only the two tests in methanol and its mixture with water yielded crystals.

Hence, no crystallisation from a solution in ethyl acetate (polarity: 0.23) was observed, nor from THF (0.21) which has a similar polarity. The other solvent used according to (D1) in dissolving the base is methylene chloride (CH_2Cl_2; polarity: 0.31). The solubility of a solid in a solvent depends on the polarity of the solvent; polar solvents tend to dissolve polar solids, whereas unpolar solvents tend to dissolve unpolar solids. Therefore, the person skilled in the art would have looked for a solvent of a similar polarity when trying to crystallise the base. ANNEX 2 of document (D3) rather shows that, when doing so, the person skilled in the art would not have obtained crystals. Therefore, the person skilled in the art was not likely to obtain the crystalline base as he would not have expected that solvents of an extremely high polarity such as 0.76 (methanol) or of its aqueous solutions (water: polarity: 1.0) were necessary.

For these reasons, the person skilled in the art would have failed when trying to crystallise anamorelin base in the solvents suggested in document (D1) or in solvents of similar polarity.

Moreover, he would not have deemed it necessary to crystallise anamoreline **base** at all cost because document (D1) offers an alternative path to an anamorelin derivative which is likely to be crystalline, and thus to be purified easily; its claim 1 is directed to anamorelin "or a pharmaceutically acceptable **salt** thereof". The fumarate salt obtained in step j of example 1 was **crystalline**. Hence, the person skilled in the art looking for an alternative pure form of anamorelin was more likely to try to crystallise a salt thereof comparable to the fumarate.

Thus, the subject-matter of the claims of the main request is based on an inventive step.

4. The examining division did not raise any additional objections as to the claims, nor did the board see any reason to raise an objection of its own.

5. The board made sure that the amended description meets the requirements of the EPC, in particular that it was properly adapted to the amended claims.

6. Since the main request was allowable, it was not necessary to consider the auxiliary request.

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 in the following version:

Description:

Pages 2-6, 8-22, 24-34 as originally filed
Pages 1, 35 and 35a, filed with the letter dated 21 May 2015;
Pages 7 and 23, filed with the letter dated 12 February 2015.

Claims:

Nos. 1-15 filed with the letter dated 21 May 2015.

Drawings:

Nos. 1/5-5/5 as originally filed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated