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Datasheet for the decision of 27 November 2014

Case Number: T 0094/11 - 3.3.10

Application Number: 02718949.7

Publication Number: 1360169

IPC: C07C215/64, A61K31/137, A61P25/00, A61P13/00

Language of the proceedings: EN

Title of invention:
SUCCINATE SALT OF O-DESMETHYL-VENLAFAXINE

Patent Proprietor:
Wyeth LLC

Opponents:
EGIS Gyógyszergyár Nyrt
Lammert, Roland, Dr.
SEPRACOR Inc

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step -
(yes) surprising properties of particular salt forms

Decisions cited:

Catchword:

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Case Number: T 0094/11 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 27 November 2014

Appellant: (Patent Proprietor)	Wyeth LLC Five Giralda Farms Madison, NJ 07940 (US)
Representative:	Dörries, Hans Ulrich df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Appellant: (Opponent 2)	Lammert, Roland, Dr. Hermanstr. 25d 86150 Augsburg (DE)
Representative:	Vossius & Partner Siebertstrasse 3 81675 München (DE)
Party as of right: (Opponent 1)	EGIS Gyógyszergyár Nyrt 1106 Budapest Keresztúri út 30-38 (HU)
Representative:	Motsch, Andreas Patentanwälte Motsch & Seitz St.-Anna-Platz 4 80538 München (DE)
Party as of right: (Opponent 3)	SEPRACOR Inc 84 Waterford Drive Marlborough, MA 07152 (US)
Representative:	Jones Day Rechtsanwälte, Attorneys-at-Law, Patentanwälte Prinzregentenstrasse 11 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on**

15 November 2010 concerning maintenance of the European Patent No. 1360169 in amended form.

Composition of the Board:

Chairman	P. Gryczka
Members:	J. Mercey
	C. Schmidt

Summary of Facts and Submissions

I. Appellant I (Patent proprietor) and Appellant II (Opponent 2) lodged appeals against the interlocutory decision of the Opposition Division which found that European patent No. 1 360 169 in amended form met the requirements of the EPC.

II. Notice of Opposition had been filed by *inter alia* Appellant II requesting revocation of the patent as granted in its entirety on the grounds of *inter alia* lack of inventive step (Article 100(a) EPC). *Inter alia* the following documents were submitted in opposition proceedings:

(9) WO-A-00/59851,
(16) Byrn et al., Pharmaceutical Research, 1995, Vol. 12, No. 7, pages 945 to 954 and
(22) Declaration of Dr. Aeri Park with Exhibits 1 to 12, filed by Appellant I with letter dated 1 October 2010.

III. Opponents 1 and 3 withdrew their oppositions before the Opposition Division.

IV. The Opposition Division found that the claims of the then pending main request did not fulfil the requirements of Article 123(2) EPC and that the subject-matter of claim 1 of the then pending auxiliary request 1, directed to crystalline O-desmethyl venlafaxine (ODV) succinate, was novel, but not inventive, document (9) being considered to represent the closest prior art. The subject-matter of the then pending auxiliary request 2, directed to crystalline Forms I and II of ODV succinate was, however, found to involve an inventive step.

V. With letter dated 26 September 2014, Appellant I submitted a main request and auxiliary requests 1 to 3, claim 1 of the the main request reading as follows:

"A compound which is a crystalline hydrate of O-desmethyl venlafaxine succinate."

VI. Appellant I submitted that the claimed subject-matter was inventive, since document (9) taught that inorganic acid salts, most particularly the hydrochloride salt, of the venlafaxine derivatives disclosed therein, were preferred. The succinate salt was merely disclosed in a general list, the skilled person being unable to predict if a crystalline form thereof might exist, let alone a crystalline hydrate with desirable properties. The experimental data provided in the patent in suit and in document (22) showed that the claimed crystalline hydrates had surprisingly favourable properties, such as stability under unusually high heat, low humidity and mechanical stress conditions, and were non-hygroscopic. Furthermore, the succinate salt had good solubility, permeability and bioavailability. *Inter alia* document (16) taught that it was not possible to predict whether a crystalline and/or hydrate form of a particular salt might even exist, let alone what its properties would be if it did.

VII. Appellant II argued that crystalline Forms I and II of ODV succinate, said forms both being monohydrates, were not inventive. More particularly, the person skilled in the art was obliged in view of regulatory reasons to search for and characterise polymorphic forms of a known pharmaceutical compound, citing document (16) in this respect. Any alleged surprising and/or beneficial

property of the claimed forms was merely a bonus effect.

VIII. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or auxiliary request 1, alternatively that the appeal of Appellant II be dismissed and the patent thus be maintained on the basis of auxiliary request 2, or, subsidiarily, that the patent be maintained on the basis of auxiliary request 3, all requests filed with letter dated 26 September 2014.

Appellant II requested that the decision under appeal be set aside and the patent be revoked.

IX. Oral proceedings were held on 27 November 2014 in the absence of Appellant II, who, after having been duly summoned, did not attend. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeals are admissible.

Main request

2. Amendments (Article 123(2) and (3) EPC)

2.1 Claim 1 is based on original claims 1, 4 and 6. Hence, its subject-matter does not extend beyond the content of the application as filed, such that the requirements of Article 123(2) EPC are satisfied.

2.2 These amendments bring about a restriction of the scope of the claims as granted, namely from a succinate of O-desmethyl venlafaxine (ODV) to a crystalline hydrate of ODV succinate, and therefore of the protection conferred thereby, which is in keeping with the requirements of Article 123(3) EPC.

3. Inventive step (Article 56 EPC)

The sole objection raised by Appellant II against the subject-matter of the patent in suit during appeal proceedings is lack of inventive step.

3.1 Claim 1 of the main request is directed to a crystalline hydrate of ODV succinate.

3.1.1 Document (9) discloses ODV and pharmaceutically acceptable salts, solvates, and clathrates thereof (see claim 22). It further defines "pharmaceutically acceptable salts" as salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. It then lists 26 suitable non-toxic acids, including succinic acid, four inorganic acids being described as "particularly preferred" and the hydrochloride salt as "most particularly preferred" (see page 4, lines 8 to 15).

3.1.2 Thus, the Board considers, in agreement with the Opposition Division and both Appellants, that document (9) represents the closest state of the art and, hence, takes it as the starting point when assessing inventive step.

3.2 In view of this state of the art, the problem underlying the patent in suit, as formulated by Appellant I and indicated in paragraphs [0003] to

[0005] of the patent in suit, was the provision of a salt of ODV that exhibits a suitable combination of properties for development into a solid dosage form such as desirable hygroscopicity, stability, solubility, permeability and bioavailability.

3.3 As the solution to this problem, claim 1 of the main request proposes a crystalline hydrate of ODV succinate.

3.4 To demonstrate that the claimed salts have the alleged desirable properties, Appellant I relied upon the experimental evidence in the patent in suit and in the declaration (22), including Exhibits 1 to 12. This evidence relates to specific crystalline forms of hydrates of ODV succinate, Forms I and II both being monohydrates (see paragraphs [0023] to [0028] of the patent in suit) and Form III being a crystalline hydrate of ODV containing less than one but more than half a mole of water (see paragraph [0037] of the patent in suit).

3.4.1 Example 1 of the patent in suit shows that Form I has a desirable solubility, namely of 32.2 mg/ml at 25°C. Example 14 shows that whether formulated as an intravenous or oral solution, tablets or capsules, Form I is essentially completely absorbed in beagle dogs. Example 13 is a test of regional absorption in the gastrointestinal tract of rats, the rat perfusion data showing that ODV succinate has much better absorption in the small intestine and in the colon that ODV fumarate, several publications having demonstrated that there is a high correlation between the rat perfusion model and *in vivo* human absorption. Figure 8 of the patent in suit (thermogravimetric analyses) and Exhibits 5 and 9 (variable temperature X-ray powder

diffractograms) show that Forms I and II are stable up to 105°C. Figure 7 of the patent in suit and Exhibit 6, both X-ray powder diffractograms, show that Form I exhibits stability under grinding. Exhibits 7 and 10 shows that Forms I and II are non-hygroscopic. More particularly, during a dynamic vapour sorption/ desorption experiment, virtually no change in sample weight was observed when the samples were exposed from 5% relative humidity (RH) to 95% RH, than back to 5% RH conditions. According to paragraph 9 of document (22), when the formulated drug containing Form I was evaluated under accelerated stability study conditions (25°C/60% RH and 30°C/75% RH) in a blister package for up to 24 months, no change in the crystalline form of the drug was detected on all three batches investigated. Exhibit 12 (variable temperature X-ray powder diffractogram) shows that Form III is also stable and non-hygroscopic when held at 75% RH for one week at both ambient temperature and 40°C.

3.4.2 In view of these extensive data, the Board is satisfied that the problem underlying the patent in suit has been successfully solved, the Board considering that in the absence of any evidence to the contrary and in view of the narrow scope of the claim, the data for the crystalline monohydrates (Forms I and II) and the hydrate containing less than one but more than half a mole of water (Form III) may be extrapolated to any crystalline hydrates of ODV succinate.

3.5 Finally, it remains to be decided whether or not the proposed solution to this problem is obvious in view of the cited prior art.

3.5.1 Document (9) is not concerned with any of the properties of crystallinity, hygroscopicity, stability,

solubility, permeability or bioavailability of ODV, but is rather concerned with examining different derivatives of venlafaxine, of which ODV is only one, for their biological potency and specificity and thus avoidance of side effects (see page 2, lines 30 to 37 and Example 6). In document (9), particular inorganic salts, namely hydrochlorides, hydrobromides, phosphates and sulphates are described as being preferred, crystalline forms not being mentioned at all, nor succinate hydrates. Since *inter alia* document (16) teaches that solid drug substances display a wide and largely unpredictable variety of solid state properties (see page 945, left hand column, third paragraph, first sentence), it not being even clear if hydrates of a particular salt will even be formed, let alone what properties they would then have (see pages 949 to 950), it could not have been expected that crystalline hydrates of ODV succinate would possess the exceptional stability under heat, mechanical stress and humidity, as well as good solubility, permeability and bioavailability demonstrated, and thus be capable of solving the ambitious technical problem underlying the patent in suit.

3.6 Appellant II submitted that the claimed subject-matter was not inventive exclusively on the basis of the combination of the teachings of documents (9) and (16). It argued that the person skilled in the art was obliged in view of regulatory reasons to search for and characterise polymorphic forms of a known pharmaceutical compound, citing page 945, left hand column, first paragraph of document (16) in this respect, said search being a routine task. The characterisation of the forms by routine measures such as X-ray powder diffraction and thermogravimetric analysis, as well as the identification of hydrates,

were also addressed by document (16). Thus, any alleged surprising and/or beneficial property of the claimed forms was merely a bonus effect.

However, in the present case, the Board holds that starting from the list of salts suggested by document (9), the choice of a crystalline, hydrate of the succinate of ODV in order to achieve a form that had good stability, solubility, permeability and bioavailability, as well as low hygroscopicity, involved more than routine experimentation in view of the complexity of the technical problem to be solved especially in the light of the chemical structure of ODV. As indicated in paragraph 4 of document (22), the stability of the claimed crystalline hydrates at high temperatures (105°C) and low humidity (5% RH) is unexpected in view of the fact that in general hydrates tend to lose the water of crystallisation under elevated temperatures or dry conditions and convert either to an anhydrous crystalline form or non-crystalline material as a result of dehydration (see Exhibit 3). In addition, ODV succinate contains a tertiary amine group which is less likely to form hydrogen bonds with water molecules due to the steric hindrance of the amine. This renders it even more surprising that the hydrates thereof are stable at such high temperatures and under extremely dry conditions. This physical stability is particularly advantageous during processing of the pharmaceutical, especially during drying of bulk material.

3.7 The Board thus holds that the crystalline hydrates of ODV succinate represent a purposive selection from within a vast number of alternative salts of ODV which would certainly not be equally suitable candidates for development into a solid dosage form, there being no

pointer in document (9), or in any of the other cited documents, to the crystalline hydrates of the succinates thereof.

3.8 For these reasons, the Board concludes that a compound according to claim 1, a pharmaceutical composition comprising such a compound according to claim 11, and the use of such a compound in the manufacture of a medicament according to claim 23, together with the subject-matter of dependent claims 2 to 10 and 12 to 22, involves an inventive step within the meaning of Articles 52(1) and 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Opposition Division with the order to maintain the patent on the basis of the main request as filed with letter dated 26 September 2014 and a description to be adapted.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated