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Datasheet for the decision of 28 October 2022

Case Number: T 0387/21 - 3.3.07

Application Number: 10796399.3

Publication Number: 2515887

IPC: A61K9/70, A61K31/381

Language of the proceedings: EN

Title of invention:
POLYVINYLPYRROLIDONE FOR THE STABILIZATION OF A SOLID DISPERSION OF THE NON-CRYSTALLINE FORM OF ROTIGOTINE

Patent Proprietor:
UCB Biopharma SRL
LTS LOHMANN Therapie-Systeme AG

Opponents:
Luye Pharma Switzerland AG
Generics [U.K.] Limited

Headword:
Solid dispersion of Rotigotine / UCB BIOPHARMA

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main request (yes)

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Case Number: T 0387/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 28 October 2022

Appellant: (Patent Proprietor 1)	UCB Biopharma SRL Allée de la Recherche 60 1070 Brussels (BE)
Appellant: (Patent Proprietor 2)	LTS LOHMANN Therapie-Systeme AG Lohmannstrasse 2 56626 Andernach (DE)
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Party as of right: (Opponent 2)	Generics [U.K.] Limited Station Close Potters Bar Herfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on**

3 March 2021 concerning maintenance of the European Patent No. 2515887 in amended form.

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	A. Jimenez

Summary of Facts and Submissions

I. European patent 2 515 887 (hereinafter "the patent") was granted on the basis of 13 claims.

Claim 1 of the patent read as follows:

"A method for stabilizing rotigotine, the method comprising providing a solid dispersion comprising a dispersing agent and a dispersed phase, said dispersing agent comprising at least one silicone pressure sensitive adhesive and said dispersed phase comprising polyvinylpyrrolidone and a non-crystalline form of rotigotine, wherein the weight ratio of rotigotine to polyvinylpyrrolidone is in a range from 9:4 to 9:6, rotigotine is rotigotine free base, and the solubility of rotigotine in the dispersing agent is below 1 w-%."

Claim 4 of the patent read as follows:

"A solid dispersion comprising a dispersing agent and a dispersed phase, said dispersing agent comprising at least one silicone pressure sensitive adhesive and said dispersed phase comprising rotigotine and polyvinylpyrrolidone, wherein the weight ratio of rotigotine to polyvinylpyrrolidone is in a range from 9:4 to 9:6, rotigotine is rotigotine free base, and the solubility of rotigotine in the dispersing agent is below 1 wt-%."

II. Two oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed.

III. The opposition division took the interlocutory decision that, on the basis of auxiliary request 2, the patent met the requirements of the EPC. The decision was based on the patent as granted as the main request, on auxiliary request 1 filed on 18 November 2020 and on auxiliary request 2 filed on 18 March 2020.

IV. The decision of the opposition division cited among others the following documents:

D1: US2009/0299304
D2: US2005/0260254
D3: WO03/092677
D8: US2005/0079206
D10: EP0737066
D13: Analytical development report - Tg

V. With regard to the main request (patent as granted), the opposition division decided as follows:

(a) It complied with the requirements of Article 123(2) EPC, of sufficiency of disclosure and of novelty.

(b) However, it did not comply with Article 56 EPC.

D2 represented the closest prior art. The subject-matter of claim 1 differed from D2 in that the solubility of rotigotine in the dispersing agent was below 1 wt%. The problem was the provision of an alternative method for stabilizing rotigotine in a solid dispersion. The claimed solution did not involve an inventive step because the solubility of rotigotine in the dispersing agent was arbitrarily selected.

VI. The patent proprietors (appellants P) and opponent 1 (appellant O1) each lodged an appeal against the interlocutory decision of the opposition division.

VII. With the statement setting out the grounds of appeal, appellants P defended their case on the basis of the patent as granted as the main request, and filed auxiliary requests 1-10.

VIII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

IX. Oral proceedings were held before the Board on 28 October 2022. During the oral proceedings, appellant O1 withdrew the objections against the main request under Article 123(2), 83 and 54 EPC.

X. Appellant O1's arguments regarding inventive step can be summarised as follows:

(a) Starting from D1

D1 disclosed a transdermal drug delivery system having an adhesive layer comprising in particular an adhesive, the therapeutic agent in amorphous form and a polymeric stabilizing and a dispersing agent (see paragraphs [0002] and [0020]). The polymeric stabilizer was most preferably PVP (see paragraph [0049]). The adhesive material was most preferably a polysiloxane (see paragraph [0044]). Paragraph [0063] indicated that rotigotine was used in a stabilizer : rotigotine weight ratio of 0.5:1 (4.5:9) or greater. The reference to "rotigotine" in this passage meant rotigotine free base. Furthermore, the solubility of rotigotine in the dispersing agent in D1 was necessarily the same as in

the patent, namely below 1 wt%, because the same silicone (polysiloxane) dispersing agent was used.

To the extent that the feature "the solubility of rotigotine in the dispersing agent is below 1 wt%" was not shown in D1, no technical effect had been shown to arise from this difference. The objective technical problem was to provide an alternative solid dispersion of rotigotine. The claimed solubility in the dispersing agent was an arbitrarily selected feature. Hence the claimed subject-matter was obvious.

(b) Starting from D2

Starting from formulation 20011036 of D2, the subject-matter of claim 4 differed in that the solubility of rotigotine in the dispersing agent was below 1 wt%. No technical effect had been shown to arise from this difference. The objective technical problem starting from document D2 was the provision of an alternative solid dispersion of rotigotine. The solubility of rotigotine in the dispersing agent defined in claim 4 had been arbitrarily selected, and therefore could not confer an inventive step. Furthermore, D2 neither taught away from using the solvent-based technology known from D1, nor indicated that a dispersing agent with a solubility for rotigotine below 1 wt% would be incompatible with the hot melt technology used in D2.

(c) Starting from D3 or D8

D3 and D8 disclosed transdermal therapeutic systems produced by a solvent-based process and containing rotigotine free base, PVP and a silicone pressure-sensitive adhesive, wherein the rotigotine to PVP

weight ratio was 9:3 or 9:2 (see examples 2 and 4 or D3, and Invention Example 1 of D8).

The subject-matter of claim 4 of the main request differed from the teaching of D3 and D8 in terms of:
- the weight ratio of rotigotine to PVP in the range from 9:4 to 9:6, and
- the solubility in the dispersing agent below 1 wt%.

No effect had been shown for the solubility feature. As to the rotigotine to PVP ratio, the contested patent essentially found that a higher relative amount of rotigotine favored crystallization, whereas as lower relative amount of rotigotine lead to insufficient drug release.

Even if the problem starting from D3 or D8 was seen in the provision of a transdermal therapeutic system with reduced crystallization tendency and sufficient drug release, the claimed solution was obvious. Since PVP was a known crystallization inhibitor, it was obvious for the skilled person to increase the amount of PVP in relation to rotigotine in order to reduce the tendency for crystallization. Furthermore, both D1 and D2 disclosed rotigotine to PVP weight ratios as claimed without reporting any insufficient drug release or crystallization problems. Hence, the claimed subject-matter did not involve an inventive step.

XI. The arguments of appellants P regarding inventive step can be summarised as follows:

(a) Starting from D1

The claimed subject-matter differed from the teaching of D1 at least in the solubility of rotigotine in the

dispersing agent of below 1 wt.-% and the use of rotigotine free base with a rotigotine to PVP weight ratio of 9:4 to 9:6. In particular, paragraph [0063] of D1 as such left open whether rotigotine free base or a salt thereof was meant. To be consistent with the general teaching of D1 (especially paragraphs [0030] and [0031]), paragraph [0063] necessarily related to rotigotine HCl having a glass transition temperature (Tg) of 76°C (see D13), and thus did not disclose a rotigotine free base to stabilizing weight ratio of 9:4 to 9:6 as defined in claim 1. Furthermore, there was no basis for concluding that any silicone or polysiloxane covered by the general definition of the adhesive material in paragraph [0044] of D1 had a solubility of rotigotine free base below 1 wt%.

The objective technical problem was the provision of an improved transdermal therapeutic system containing rotigotine as active ingredient preventing rotigotine from crystallization and providing for a sufficient drug release.

The claimed solution was not obvious for the skilled person, because D1 taught away from a rotigotine free base to PVP ratio of 9:4 to 9:6. Based on the low Tg of rotigotine free base, D1 called for a therapeutic agent to stabilizing agent ratio of 0.5 or less.

(b) Starting from D2

The claimed subject-matter differed from formulation example 20011036 of D2 by the solubility of rotigotine in the dispersing agent of below 1 wt.-% and the production of the claimed transdermal therapeutic system by a solvent-based process. The objective technical problem was the provision of an alternative

albeit stable solid dispersion of rotigotine as part of a transdermal therapeutic system characterized by suitable drug release properties.

The claimed solution was not obvious because D2 not only advocated the preparation of hot melt patches, but also expressly taught away from the use of a solvent-based transdermal therapeutic system as a simple replacement of the hot melt-based systems described therein. Hot melt and solvent-based processes were two different technologies, which could not be used interchangeably for preparing the adhesive matrix of a transdermal patch. In particular, the plain silicone adhesives used in the claimed transdermal therapeutic system were not hot-meltable.

(c) Starting from D3 or D8

D3 and D8 disclosed the preparation of a rotigotine patch via a solvent-based process, using a rotigotine to PVP weight ratio of 9:3 or 9:2 (see example 4 of D3 or invention example 1 of D8). Starting from D3 or D8, the distinguishing feature was the rotigotine to PVP weight ratio of 9:4 to 9:6. The objective technical problem was to provide an improved transdermal therapeutic system containing rotigotine as active ingredient preventing rotigotine from crystallization and providing for a sufficient drug release. Neither D3 nor D8 provided a pointer to the claimed solution. No incentive was to be found in D1 or D2 either. In particular, the method of D1 was predicated on a correlation between the Tg of the therapeutic agent and the amount of crystallization inhibitor. Thus, D1 taught away from the claimed rotigotine free base to PVP ratio of 9:4 to 9:6.

XII. Appellants P request that the decision under appeal be set aside and that the patent be maintained as granted, or, alternatively, that the patent be maintained on the basis of one of auxiliary requests 1-10 filed with the grounds of appeal.

XIII. Appellant O1 requests that the decision under appeal be set aside and that the patent be revoked in its entirety.

XIV. Respondent O2 (opponent 2) made no request during the appeal proceedings.

Reasons for the Decision

Main request (patent as granted), inventive step

1. Following appellant O1's withdrawal, at the oral proceedings, of the objections of added subject-matter, insufficiency of disclosure and lack of novelty, the sole issue to be addressed is inventive step. In the following, inventive step is assessed for the subject-matter of claim 4, which is the broadest claim of the main request.

The invention seeks to address the problems of stabilizing a solid dispersion of non-crystalline rotigotine for use in the preparation of a transdermal therapeutic system (TTS) having increased long term storage stability due to the reduced formation of rotigotine crystals (see paragraph [0001] of the patent). To solve these problems, the claimed solid dispersion comprises a dispersed phase comprising PVP and rotigotine free base in defined ratios, and a

dispersing agent containing at least one silicone pressure sensitive adhesive and having defined solubility for rotigotine.

Appellant O1 raised objections of lack of inventive step starting alternatively from D1, D2 or D3/D8.

2. Starting from D1

2.1 D1 discloses a solid dispersion transdermal drug delivery system (TTS) including an adhesive layer which comprises an adhesive, a therapeutic agent in amorphous form and a combination polymeric stabilizing and dispersing agent and a protective release liner (see paragraphs [0002] and [0020]). The therapeutic agent is present in a stable amorphous form (i.e. non-crystalline) and forms a solid dispersion with a polymer stabilizer (see paragraph [0051]). The therapeutic agent may, in one of several alternatives, be rotigotine (see paragraphs [0057]-[0068]). The adhesive material is most preferably one or more polysiloxanes (i.e. silicones; see paragraph [0044]). The stabilizer is most preferably polyvinyl-pyrrolidone (i.e. PVP; see paragraph [0049]).

The weight ratio of the stabilizing agent to rotigotine is 0.5 or greater, or, in other words, the weight ratio of rotigotine to stabilizing agent is 9:4.5 or lower (see paragraph [063]).

Thus, D1 discloses a TTS solid dispersion comprising one or more polysiloxanes as adhesive material, PVP as stabilizer, and rotigotine, with a rotigotine : stabilizer weight ratio of 9:4.5 or lower.

2.2 However, for the following reasons, D1 neither discloses this ratio in combination with the use of rotigotine free base, nor that the solubility of rotigotine in the dispersing agent is below 1 wt%.

2.2.1 Firstly, D1 does not explicitly disclose that "the solubility of rotigotine in the dispersing agent is below 1 wt%".

Appellant O1's position is that, if the solubility of rotigotine in a silicone dispersing agent is below 1 wt% according to the contested patent, then the same must be true for the same material (polysiloxane adhesive) in D1.

The Board does not share this position. There is no indication, in the patent or otherwise, that all silicones or polysiloxane adhesives generally stated in paragraph [0044] of D1 are characterized by a solubility for rotigotine free base below 1 wt%. In the patent, the formulation examples (see the examples and table 1) contain specific silicone adhesives as dispersing agent, namely a mixture of the Dow Corning silicone adhesives BIO-PSA Q7-4301 and 4201. In contrast, D1 neither discloses the claimed solubility, nor specific polysiloxane adhesives (such as those exemplified in the patent) leading implicitly to this solubility.

2.2.2 Secondly, paragraph [0063] of D1 does not disclose the rotigotine : PVP ratio of 9:4.5 in the context of rotigotine free base.

D1 generally indicates that the "references to the therapeutic agents also include their salts" (see paragraph [0053]). In light of this general indication,

the mention of rotigotine in paragraph [0063] cannot be assumed to refer specifically to the free base, but must be regarded as being unspecific as to which form of rotigotine is meant.

2.2.3 Furthermore, D1 discloses that "if the therapeutic agent has a low glass transition temperature, the weight ratio of the polymeric material to the amorphous form of a therapeutic agent required to disperse the amorphous form of the therapeutic agent is 2 or greater", a low glass transition temperature (Tg) being less than 50° C (see paragraph [0030]). Thus D1 indicates that, if the therapeutic agent (here: rotigotine) has a low Tg, a weight ratio of polymeric stabilizing/dispersing agent (here: PVP) to rotigotine of at least 2 is not just preferable, but mandatory to obtain a dispersion. A weight ratio of PVP to rotigotine of at least 2 corresponds to a rotigotine : PVP ratio below 9:18, which is outside the claimed range of 9:4 to 9:6.

Appellant O1 points out that the weight ratio of polymeric stabilizing/dispersing agent to therapeutic agent in D1 is generally at least 0.5 according to claims 2 and 14 of D1. However, in the Board's view, the broad definition of the invention in claims 2 and 14 of D1 does not lead to a different reading of D1. This broad definition covers both alternatives, namely a polymer : therapeutic agent ratio above 0.5 for high Tg therapeutic agents, and above 2 for low Tg therapeutic agents. However it does not imply that a ratio of 0.5 is possible in the specific case of low Tg therapeutic agents. This is also not derivable from paragraphs [0058]-[0060] of D1, since these passages are limited to different therapeutic agents (namely scopolamine, oxybutynin or naltrexone). On the

contrary, paragraph [0057] reiterates that therapeutic agents with lower Tg "require an increased amount of stabilizing agent, by weight, to disperse and stabilize the therapeutic agent" (i.e. in a ratio of 2 or greater).

2.2.4 As shown in D13, rotigotine free base has a low Tg of 9° C (see section 5). Accordingly, the disclosure in paragraph [0063] of D1, relating to a weight ratio of stabilizing agent to rotigotine of 0.5, is not only unspecific as to the form of rotigotine referred to (i.e. salt or free base), but is in fact incompatible with rotigotine free base having a low Tg. This passage is rather consistent with a form of rotigotine with a high Tg (see paragraph [0031] of D1), such as a rotigotine salt. Rotigotine HCl for instance has a Tg=76° C (see D13).

2.3 The Board comes to the conclusion that, even if the problem to be solved is the provision of an alternative solid dispersion of rotigotine, an inventive step is to be acknowledged, because the skilled person, starting from D1, would not consider the use of rotigotine free base in combination with the claimed rotigotine : stabilizer weight ratio.

As explained above (see 2.2.3), in D1 (see paragraph [0030]), a ratio polymeric material : therapeutic agent of 2 or greater, corresponding to a rotigotine : PVP ratio of 9:18 or lower, is "required" for therapeutic agents with low Tg, e.g. less than 50°C. The combination of rotigotine free base (having a low Tg) with the much higher ratio of from 9:4 to 9:6 is thus not compatible with the teaching of D1.

2.4 Accordingly, the skilled person, starting from D1, would not consider a rotigotine : PVP ratio of 9:4-9:6 in combination with the use of rotigotine free base as an obvious solution to the problem.

3. Starting from D2

3.1 D2 is concerned with the provision of a TTS encompassing a rotigotine containing adhesive matrix. TTS Formulation 20011036 of D2 (see page 10, table 1) is a solid dispersion comprising a silicone pressure sensitive adhesive (silicone-based hot melt adhesive containing Bio-PSA 7-4300 Bio adhesive), 10 wt% PVP and 15 wt% free-base rotigotine, hence with a rotigotine : PVP ratio of 9:6.

Considering the similarity of the general purpose (the preparation of rotigotine TTS) and in terms of features, D2 is a suitable starting point for the assessment of inventive step.

3.2 The subject-matter of claim 4 differs from the TTS formulation 20011036 of D2 in that the solubility of rotigotine in the dispersing agent is below 1 wt%.

3.3 Considering that no effect has been shown to be associated with the differentiating feature, the technical problem starting from D2 is the provision of an alternative solid dispersion of rotigotine.

3.4 The Board agrees with appellant O1 that the claims of the main request are not limited to any particular process for the preparation of the dispersion, and cover both solvent-based or hot-melt processes. The relevant question is however whether the skilled person, starting from D2, would consider using a

dispersing agent in which rotigotine (free base) has a solubility below 1 wt%.

3.4.1 The crux of D2 is to avoid the drawbacks associated with solvent-based processes, and in particular to allow for larger amounts of rotigotine. To this end, D2 proposes a TTS with a rotigotine-containing adhesive matrix, characterized in that the adhesive matrix is produced in a hot-melting process, whereby the adhesive matrix contains a hot-meltable adhesive in which rotigotine is dispersed and partly or completely dissolved (see paragraphs [0010] and [0018]). In the Board's view, the skilled person, starting from D2, would not realistically take a step back and consider solvent-based processes. Hence the skilled person starting from D2 would consider the use of dispersing agents only to the extent that they are compatible with the hot-melt process of D2.

3.4.2 In this respect, D2 requires the use of specific hot-meltable dispersing agents (see paragraphs [0052]-[0055]) in which rotigotine is partly or completely dissolved. This statement must be read in the context of the purpose of D2, which is to allow for higher charges of rotigotine such as up to over 40%. In particular, the chosen starting point (formulation 20011036 of D2) contains 15 wt% rotigotine. Accordingly, the skilled person is explicitly instructed by the starting point D2 not to choose dispersing agents with a low solubility for rotigotine, and would be deterred from choosing a dispersing agent with a solubility for rotigotine below 1 wt%.

Contrary to appellant O1's opinion, there is no indication that the skilled person could regard a dispersing agent in which rotigotine has a solubility

below 1 wt% as compatible with these limitations set in D2. Appellant O1 referred to paragraphs [0139]-[0141] of D2, which allow for the adhesive matrix to contain 50-99 wt% of hot-meltable adhesive and 1-40 wt% rotigotine. However, even if this broad disclosure covers, at one end-point, the presence of rotigotine in an amount of 1 wt% in the adhesive matrix, it does not mean that this low amount of 1 wt% rotigotine could be only partially soluble in the matrix.

Accordingly, the skilled person, starting from D2, would not consider the use of a dispersing agent with a solubility for rotigotine below 1 wt% as an obvious solution to the problem.

4. Starting from D3 or D8

Both D3 (see examples 2 and 4 on pages 15-16 and 20-22) and D8 (see Invention example 1 on page 4) show TTSs containing rotigotine free base, PVP and at least one silicone pressure-sensitive adhesive, wherein the rotigotine : PVP ratio is 9:3 or 9:2. The compositions of D3 and D8 correspond to the (comparative) 9:2 composition of the patent (see table 1) and use the same mixture of BIO-PSA® Q7-4301 and 07-4201 as dispersing agent.

The sole distinguishing feature is the rotigotine to PVP weight ratio of 9:4 to 9:6.

According to the appellants P, the technical effect resulting from this difference is an improvement in stability in combination with an unchanged drug release. In the Board's view, this effect is supported by the experimental data of the patent (see paragraph [0129] and table 3): increasing the amount of PVP to a

rotigotine : PVP ratio of 9:4 or 9:6 prevents the crystallization of rotigotine which occurs for a ratio of 9:2. At the same time, the drug release profiles for ratios of 9:4 and 9:6 remain similar to, or better than, those for ratios of 9:2 and 9:3 (see figure 1 and paragraph [0142]).

Accordingly, the objective technical problem is the provision of an improved transdermal therapeutic system containing rotigotine as active ingredient preventing rotigotine from crystallization and providing for a sufficient drug release.

Appellant O1 considers that the claimed solution is obvious in light of D1 or D2, or taking into account the known properties of PVP. The Board does not concur and considers that the skilled person could not expect that the claimed subject-matter would solve the above problem. In D1, a rotigotine : stabilizer ratio within the claimed range of 9:4-9:6 is not considered in the context of rotigotine free base (see 2.2.4 above). In D2, a rotigotine : PVP ratio of 9:6 is shown in the context of hot-meltable dispersing agents, and is not associated with the improvement observed in the patent. Lastly, PVP is known as a crystallization inhibitor for transdermal preparations, but is also known to be detrimental to other properties such as permeation rates for delivery (see D10, paragraphs [0008] and [0017]). Hence, the skilled person would not expect that the release profile would remain satisfactory.

In conclusion, the main request meets the requirement of inventive step.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is maintained as granted.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated