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Datasheet for the decision of 5 April 2022

Case Number: T 2344/19 - 3.3.01

Application Number: 11749331.2

Publication Number: 2608789

IPC: A61K31/495, A61P25/00

Language of the proceedings: EN

Title of invention:
THERAPEUTIC USES OF 1-[2-(2,4-DIMETHYL-PHENYLSULFANYL)PHENYL]PIPERAZINE

Patent Proprietor:
H. Lundbeck A/S

Opponent:
Hexal AG

Headword:
Vortioxetine/LUNDBECK

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - new patient group (yes)
Inventive step - (yes)

Decisions cited:
T 1491/14

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Beschwerdekammern

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Case Number: T 2344/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 5 April 2022

Appellant: (Patent Proprietor)	H. Lundbeck A/S Ottiliavej 9 2500 Valby (DK)
Representative:	Potter Clarkson The Belgrave Centre Talbot Street Nottingham NG1 5GG (GB)
Respondent: (Opponent)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 June 2019 revoking European patent No. 2608789 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	M. Pregetter
	R. Romandini

Summary of Facts and Submissions

I. European patent No. 2608789 is based on European patent application No. 11749331.2, filed as an international application published as WO2012/025123.

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(1) WO03/029232

(2) WO2007/144005

(3) WO2009/062517

(6) Artigas et al., Eur. Neuropsychopharmacol., 2009, 19, S426-S427

(7) P.S. Masand, Exp. Opin. Pharmacother., 2000, 1(3), 377 to 389

(14) J.M. Ferguson, Primary Care Companion J. Clin. Psychiatry, 2001, 3(1), 22-27

(15) Kelly et al., Dialogues Clin. Neurosci., 2008, 10(4), 409-18

(17) Cassano et al., Ann. Clin. Psychiatry, 2004, 16, 15-25

(24) Summary of Product Characteristics (SmPC) of Brintellix, submitted on 1 June 2018, 101 pages

(30) Guidelines for ATC classification and DDD assignment 2019, WHO Collaborating Centre for Drug

Statistics Methodology, 57 pages

(30a) Internet page from WHO Collaborating Centre for Drug Statistics Methodology from 28 January 2010, 4 pages

(30b) ATC alterations from 2005-2019, last updated 2018-11-28, obtained from www.whocc.no, 4 pages

(31) Stahl et al., J. Clin. Psychiatry, 2003, 64 (suppl. 13), 13-17

(32) M. Millan, Neurotherapeutics, 2009, 6(1), 53-77

(32a) Internet page from WHO Collaborating Centre for Drug Statistics Methodology relating to classification of vilazodone, 1 page

(33) Lanni et al., Cell. Mol. Life Sci., 2009, 66, 2985-3308

(34) Schwartz et al., Obes. Rev., 2004, 5, 115-21

(35) Raeder et al., J. Clin. Psychiatry, 2006, 67, 1974-82

(36) Cascade et al., Psychiatry (Edgemont), 2009, 6(2), 16-18

(37) British National Formulary, March 2010, pages 225-38

(38) Hayes et al., Am. J. Physiol. Regul. Integr. Comp. Physiol., 2004, 287, R817-R823

(39) Daughters et al., Peptides, 2001, 22, 1331-8

(40) G. Curzon, Ann. N.Y. Acad. Sci., 1990, 600(1), 521-31

(41) C. Dourish, Obes. Res., 1995, 3 (Suppl. 4 Nov.), 449S-462S

III. The patent was opposed under Article 100(a) and (b) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

In the course of the opposition proceedings, the patent proprietor requested that the opposition be rejected, and submitted auxiliary requests 1 and 2, both filed on 14 March 2019.

The opposition division revoked the patent. The subject-matter of all the requests was found not to involve an inventive step.

IV. The patent proprietor appealed against this decision. With the statement setting out the grounds of appeal, it re-submitted auxiliary requests 1 and 2 and submitted documents (30), (30a), (30b), (31), (32), (32a), and (33) to (41).

V. Oral proceedings before the board took place on 5 April 2022.

In the course of the oral proceedings, the appellant withdrew its main request and auxiliary request 1. Auxiliary request 2, submitted with the statement setting out the grounds of appeal, became the new main request.

Claims 1 and 3 of the main request (former auxiliary request 2) read as follows:

"1. 1-[2-(2,4-dimethyl-phenylsulfanyl)phenyl]piperazine and pharmaceutically acceptable salts thereof for use in the long-term treatment of depression or anxiety in a patient who has previously received medication for the treatment of said disease which medication was ceased due to weight gain related adverse events, wherein long-term treatment refers to a treatment period above 12 weeks.

3. Use of 1-[2-(2,4-dimethyl-phenylsulfanyl)phenyl]piperazine and pharmaceutically acceptable salts thereof in the manufacture of a medicament for the long-term treatment of depression or anxiety in a patient who has previously received medication for the treatment of said disease which medication was ceased due to weight gain related adverse events, wherein long-term treatment refers to a treatment period above 12 weeks."

VI. The patent proprietor's (appellant's) arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Novelty

The patient group had to be considered as a technical feature of the claims under consideration and was to be assessed according to the usual requirements for novelty (see decision of the Enlarged Board of Appeal G 2/08). None of the documents invoked by the respondent disclosed the patient group defined in the claims.

Inventive step

Document (7) represented the closest prior art. This document suggested switching patients to alternative psychotropic drugs if their weight increased during treatment despite various measures. The difference between the claims under consideration and the disclosure of document (7) was the use of 1-[2-(2,4-dimethyl-phenylsulfanyl)phenyl]piperazine (vortioxetine) as the switch drug. The data in the patent in suit demonstrated that vortioxetine could be used in long-term treatment of depression or anxiety with low rates of weight related adverse events. The technical problem was thus to provide a treatment for depression or anxiety in patients who could not tolerate weight related adverse events. The use of vortioxetine was not obvious. Vortioxetine was not an SSRI (selective serotonin re-uptake inhibitor), a class of compounds that had been disclosed as not having, in its majority, weight gain related adverse events in short-term treatments. Vortioxetine acted on several receptors, being a 5-HT_3 receptor antagonist, a 5-HT_{1A} receptor agonist and a 5-HT enhancer, rendering its effect on weight unpredictable. The only document on file relating to vortioxetine and mentioning weight was document (6). However, document (6) was confined to a short-term study and mentioned weight merely by indicating that "no clinically relevant changes" had been observed. It was not clear whether this result was statistically relevant. Furthermore, it was known that weight related adverse events could differ considerably in the short and in the long term (see document (7)). Short-term studies had no predictive value for weight related adverse events (see documents (14), (15) and (17)). In addition, the 5-HT_3 receptor and the 5-HT_{1A}

receptor, on both of which vortioxetine acted, had both been shown to increase food uptake or to reduce satiety, and were therefore associated with weight gain. Therefore the person skilled in the art would not have had any expectation of success when using vortioxetine to solve the problem stated above.

Starting from document (3), the problem could be formulated as the provision of a treatment for depression or anxiety in patients who could not or would not tolerate weight related adverse events. The solution to this problem was not obvious, for the same reasons as given above.

VII. The opponent's (respondent's) arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Novelty

Patients' decisions to cease a previous medication upon occurrence of adverse events did not make them different in terms of their physiological and pathological status from other patients experiencing the same adverse events but not deciding to cease the previous medication. A physiological and pathological status of a patient was determined by the treatment as such and not by the patient's attitude towards it. A patient's decision to cease or not to cease a line of treatment was the mere result of a mental act which was not suitable to distinguish the claimed subject-matter from the prior art.

Decision T 1491/14 should not be followed. The facts differed in particular in that a patient's decision to cease medication due to weight gain was purely

subjective. Some patients with weight gain might accept this side-effect and not cease medication, while others with weight gain might cease medication due to the occurrence of other side-effects. It was thus not necessarily their pathological status but merely subjective decisions taken by the patients themselves or by their physicians that linked and/or limited the group of patients defined in the claims. Such a patient group could not constitute a technical feature which was suitable for delimiting the subject-matter from the prior art.

Thus the technical feature relating to the group of patients as defined in claims 1 and 3 could not be taken into consideration for assessing novelty. As a result, the subject-matter of claims 1 and 3 lacked novelty over the uses of vortioxetine disclosed in documents (1)-(3) and (6).

Inventive step

Documents (3) and (7) could be seen as the closest prior art.

Document (7) disclosed psychotropic drugs for the treatment of depression and anxiety, including SSRIs, which were discussed in view of their propensity to induce clinically significant weight gain. The document taught that if weight increase could not be reversed by other means the medication should be switched. The subject-matter of claims 1 and 3 under consideration differed in that it specifically defined vortioxetine, which was not identified in document (7). No comparative data had been provided to show that vortioxetine was better suited as switch medication than other agents, in particular other SSRIs. The data

in the patent in suit merely showed that vortioxetine led to weight gain similar to placebo, but not that vortioxetine led to no weight gain. The technical problem was the provision of a further active for long-term second-line treatment of depression or anxiety in a patient group suffering from weight gain related adverse events.

The person skilled in the art would have selected vortioxetine as this further active. Vortioxetine was a member of the class of SSRIs which was known to have in general no weight gain related side-effects. Also, document (7) suggested that effects on the 5-HT_{2c} receptor were responsible for weight gain, and it was known that vortioxetine had no effect on this receptor. In addition, vortioxetine was undergoing phase III clinical studies, where any adverse effects related to weight would have been automatically found, rendering the claimed invention obvious. Furthermore, document (6) already disclosed that administration of vortioxetine did not lead to any clinically relevant changes of weight. There was thus a clear expectation of success for the person skilled in the art, all the more so as a treatment of 12 weeks could not be considered a long-term treatment.

Document (3) disclosed the use of vortioxetine hydrobromide for use in the treatment of depression and anxiety. The subject-matter of claims 1 and 3 under consideration differed in the specific group of patients to which the treatment was directed. The technical problem was to identify an arbitrary patient group which could be treated with the known antidepressant and anti-anxiety agent vortioxetine. As there was no reason for the skilled person to assume that the patient group specified in claims 1 and 3

could not be treated with vortioxetine, the claimed solution did not involve an inventive step.

VIII. The parties' final requests were as follows:

The appellant (patent proprietor) stated that it withdrew the main request and auxiliary request 1, and therefore requested that the decision be set aside and the patent be maintained based on the claim requests of the new main, and now sole, request filed as auxiliary request 2 with the statement of grounds of appeal.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Novelty (Article 54 EPC)*

2.1 The patient's decision to cease medication for the treatment of depression or anxiety as such is not defined in the claims under consideration. The claims (merely) define a group of patients who had previously received medication which was ceased due to weight gain related adverse events. Thus the claims are directed to patients in the following factual situation: their (previous) medication was stopped due to weight gain related adverse events (irrespective of the decision-making process underlying the stop). Consequently, no mental act or thought process forms part of the claimed subject-matter.

The indication that the previous treatment was stopped

due to weight gain related adverse events establishes the fact that the group of patients under consideration is known to develop weight gain related side-effects when administered medication active in the treatment of depression or anxiety. The development of certain side-effects reflects a certain physiological and/or pathological status of the patients concerned. The development of these side-effects during treatment for depression or anxiety creates a link between the patients, their physiological and/or pathological status, and the therapeutic treatment.

The patient group under consideration is thus a technical feature of the claims.

2.2 The technical feature defining the patient group under consideration is not disclosed in any of the documents cited by the respondent in the context of novelty, i.e. documents (1), (2), (3) and (6).

2.3 The subject-matter of the claims of the main request is novel within the meaning of Article 54 EPC.

3. *Inventive step (Article 56 EPC)*

3.1 The patent in suit relates to the use of 1-[2-(2,4-dimethyl-phenylsulfanyl)phenyl]piperazine (vortioxetine) and pharmaceutically acceptable salts thereof in the treatment of CNS diseases. Long-term treatment with vortioxetine has been found not to be associated with weight increase. The patent aims at using this compound in the treatment of depression or anxiety in a patient who has previously received medication for the treatment of this disease which was ceased or reduced due to weight related adverse events

(paragraphs [0001] and [0016]).

3.2 It was common ground that document (7) represented the closest prior art. The respondent additionally relied on document (3).

3.3 *Problem-solution approach starting from document (7)*

3.3.1 Document (7) describes weight gain as a common adverse effect of psychotropic drugs (abstract). In the concluding passages, it states that medication should be switched to another drug if weight increase due to a psychotropic drug cannot be stopped or reversed by measures relating to proper nutrition and eating habits, physical exercise and behaviour modification (paragraph bridging pages 386 and 387).

The difference between the subject-matter of claims 1 and 3 as granted and the disclosure of document (7) is the use of vortioxetine as the switch drug.

3.3.2 *Data in the patent in suit*

There is no indication on file that weight gain as a side-effect of therapeutic treatment of depression or anxiety is related exclusively to factors such as individual genetic predispositions. Therefore weight gain is considered to be due to various causes, as is also insinuated by the countermeasures of document (7) (paragraph bridging pages 386 and 387, see point 3.3.1 above). Consequently, there is no need for data to be obtained from patients having been treated by (other) actives before switching to vortioxetine. All experimental data relating to weight gain can be taken into account, including the data in the patent in suit.

This data (Tables 1 to 4) does not show that no weight at all is gained by the patients receiving vortioxetine. However, in view of the relatively small relative weight differences and taking into account the percentages of patients displaying a weight gain above 7%, the conclusion can be drawn that in the first year of treatment no weight gain above what can be expected in the population under consideration (= "placebo-like") is found after administration of vortioxetine. The qualitative information provided in the SmPC of Brintellix (active agent vortioxetine hydrobromide) confirms this finding (document (24), page 12, paragraph 4).

However, the data in the patent does not show a comparison with another potential switch drug, which fact has to be reflected in the formulation of the technical problem.

3.3.3 The technical problem is thus the provision of a further active for long-term second-line treatment of depression or anxiety in a patient group prone to weight gain related adverse events.

3.3.4 *Obviousness of the solution*

3.3.5 *Long-term side-effects versus short-term side-effects*

Document (7), which is the closest prior art and a document dedicated to weight gain associated with psychotropic drugs (see title), explicitly discloses that short-term clinical trials, which last 6 to 8 weeks, may underestimate the long-term effects (> 18 months) on weight gain (page 379, left-hand column, paragraph 2). This is confirmed by document (14) (page 26, paragraph 2), document (15) (page 411, right-hand

column, paragraph 2), and document (17) (page 17, left-hand column, last paragraph). Consequently, the board considers that the person skilled in the art, in the case at hand, would have been aware of the issue and would have sought to provide an alternative psychotropic drug for which it was well established that no long-term weight gain related side-effects were to be expected.

It seems to be a general consensus in literature that the initial period of treatment by psychotropic drugs is up to 3 months. Furthermore, as stated by the respondent, problems with treatment usually tend to arise in the first 5 to 7 weeks. Consequently, a period of above 12 weeks, as defined in claim 1 under consideration, can be considered as long-term treatment in the field concerned.

3.3.6 *Vortioxetine - an SSRI?*

The respondent based their line of argument, *inter alia*, on the classification of psychotropic drugs and the side-effects known for drugs of a certain class. In this context they argued that the person skilled in the art would have considered vortioxetine to belong to the class of SSRIs since vortioxetine was known to act on SERT (serotonin transporter).

The classification of vortioxetine in activity schemes of psychotropic drugs is not crucial to the present decision and can therefore be left open. It has been established that not all SSRIs have no weight related side-effects, and furthermore doubts have been raised as to the long-term weight related side-effects of SSRIs. This can be seen from document (7). Document (7) discloses that accumulating evidence suggests that in

the short term SSRI treatment may cause weight loss, but may induce weight gain during long-term use, possibly related to serotonin receptor 5-HT_{2c} hyposensitivity (page 383, left-hand column, paragraph 2).

As there seems to be no well-established and generally recognised long-term side-effect profile for the actives belonging to the class of SSRIs, the skilled person dealing with patients known to be susceptible to weight gain would have focused entirely on the side-effect profiles of the individual actives. The classification of vortioxetine (e.g. as an SSRI) is thus irrelevant.

3.3.7 *Side-effect profile of vortioxetine*

Several documents on file disclose the use of vortioxetine as a psychotropic drug and thus as a drug suitable for use in the treatment of depression or anxiety. Documents (1) to (3) disclose vortioxetine for this treatment. However, they are silent on side-effects. Document (6) relates to a proof-of-concept study to evaluate the efficacy and tolerability of vortioxetine. This study lasted 6 weeks and included 429 patients. Nausea, headache, hyperhidrosis and dry mouth are identified as the most common side-effects. No clinically relevant changes are seen in, *inter alia*, weight over the course of the study. Document (6) consequently establishes that vortioxetine has no short-term side-effects related to weight. No disclosure of long-term side-effects of vortioxetine made before the effective date of the patent in suit is on file.

Vortioxetine has been described as having or not having

activity on various receptors, such as SERT, 5-HT_3, 5-HT_{1A} and 5-HT_{2c}. However, the person skilled in the art receives no guidance from the documents on file on how to predict weight gain related side-effects from these activities. Consequently, no conclusion on the occurrence of weight related side-effects in the treatment with vortioxetine may be drawn that goes beyond mere speculation.

3.3.8 *Expectation of success versus hope to succeed*

The case at hand relates to the treatment of depression or anxiety. As clearly established in document (7), weight gain related adverse effects put the patients at considerable risk - coronary heart disease, hypertension, type II diabetes, dyslipidaemia and cancer being mentioned - but, and this is also of the utmost importance, they may also lead to non-compliance, with the probability of relapse and subsequent (re)hospitalisation (abstract).

In view of the disclosure of document (7) (see paragraph above and points 3.3.1 and 3.3.5) and the objective technical problem, it is clear that the person skilled in the art would have avoided the administration of any psychotropic drug for which long-term weight gain related side-effects had not been excluded. They would also have avoided any treatment potentially worsening the overall physiological condition of the patient, or, when leading to non-compliance, worsening the underlying psychiatric condition and potentially leading to relapse, hospitalisation or even fatal consequences.

In summary, the person skilled in the art would have needed to count on success or, put differently, have a

strong expectation of success. Any treatment undertaken with a mere hope to succeed, in the present case a treatment where short-term side-effects had been excluded but nothing was known on long-term side-effects, would not have been envisaged by the person skilled in the art.

3.3.9 Consequently, since no information on long-term weight gain related side-effects was known for vortioxetine, the person skilled in the art would not have considered vortioxetine for solving the technical problem stated above, and thus would not have arrived at the claimed subject-matter.

3.4 *Problem-solution approach starting from document (3)*

3.4.1 Document (3) discloses the use of vortioxetine hydrobromide for the treatment of depression and anxiety.

The subject-matter of claims 1 and 3 differs in the specific group of patients to which it was directed.

The technical problem is the provision of a further specific use of vortioxetine in the treatment of depression or anxiety.

3.4.2 *Obviousness*

As established above, see point 3.3.7, the person skilled in the art had not been aware that vortioxetine had a favourable side-effect profile concerning weight gain in long-term treatments. Consequently, the person skilled in the art would have had no incentive to administer vortioxetine as second-line treatment to a group of patients known to have had issues with weight

gain related adverse events in a previous treatment of depression or anxiety.

3.5 The subject-matter of claims 1 and 3 of the main request involves an inventive step within the meaning of Article 56 EPC.

3.6 *Further arguments*

The respondent argued that a clinical phase III study involving vortioxetine was taking place and the presence and absence of adverse events would have been known from this study and therefore could not form the basis for acknowledging the presence of an inventive step.

As stated in T 1491/14, this argument is fundamentally flawed. In addition to the arguments provided in T 1491/14, the person skilled in the art, as a matter of principle, could not have been aware of the outcome of an incomplete study at the effective date of the patent in suit. The future outcome of such a study as such does not represent prior art in the sense of Article 54(2) EPC, and consequently cannot be included in the assessment of inventive step. Concerning the expectation of success of the person skilled in the art for a successful outcome of such a study, the following applies: such expectation has to be assessed for each case separately, as has been done for vortioxetine and long-term weight gain related side-effects, see points 3.3.5 to 3.3.9 above.

Order

For these reasons it is decided that:

- The decision under appeal is set aside;

- The case is remitted to the opposition division with the order to maintain the patent in amended form with the following claims and a description possibly adapted thereto:

Claims 1 to 4 of the main request submitted as auxiliary request 2 with the statement of grounds of appeal.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated