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Datasheet for the decision of 30 July 2019

Case Number: T 1491/14 - 3.3.01

Application Number: 08850935.1

Publication Number: 2219647

IPC: A61K31/495, A61P25/00

Language of the proceedings: EN

Title of invention:
THERAPEUTIC USES OF COMPOUNDS HAVING COMBINED SERT, 5-HT3 AND 5-HT1A ACTIVITY

Patent Proprietor:
H. Lundbeck A/S
Takeda Pharmaceuticals U.S.A., Inc.

Opponent:
SANDOZ AG

Headword:
Vortioxetine/LUNDBECK

Relevant legal provisions:
EPC Art. 100(a), 54, 56, 83

Keyword:

Novelty - main request (yes) - new group of patients
Inventive step - auxiliary request 1 (yes) - no one-way-street situation
Sufficiency of disclosure - auxiliary request 1 (yes)

Decisions cited:

G 0003/14, T 0619/02

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Case Number: T 1491/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 30 July 2019

Appellant: (Patent Proprietor 1)	H. Lundbeck A/S Ottiliavej 9 2500 Valby (DK)
Appellant: (Patent Proprietor 2)	Takeda Pharmaceuticals U.S.A., Inc. One Takeda Parkway Deerfield, IL 60015 (US)
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Appellant: (Opponent)	SANDOZ AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Best, Michael Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstrasse 2 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 May 2014 concerning maintenance of the European Patent No. 2219647 in amended form.**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 2 219 647 was granted with four claims. Independent claims 1 and 3 read as follows:

"*1. A use of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl] piperazine and pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of a disease selected from depression, anxiety, abuse or chronic pain, wherein said medicament is for use in a patient who has previously received another medication for the treatment of said disease which medication was ceased or reduced due to sleep or sexually related adverse events.*"

"*3. 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine and pharmaceutically acceptable salts thereof for use in the treatment of a disease selected from depression, anxiety, abuse or chronic pain in a patient who has previously received another medication for the treatment of said disease which medication was ceased or reduced due to sleep or sexually related adverse events.*"

In the following, the compound cited in claims 1 and 3 will be referred to by its common name "vortioxetine".

II. The following documents are referred to in the present decision:

D2: WO 03/029232
D4: WO 2007/144005
D8: D. Spinks et al., Curr. Med. Chem., 9, 2002, 799-810

D9: E.K. Moltzen et al., Curr. Top. Med. Chem., 6, 2006, 1801-1823

D18: I.M. Anderson et al., J. Psychopharmacol., 22(4), June 2008, 343-396

D20: A. To et al., BCMJ, 44(9), 2002, 479-484

D22: Declaration of Prof Volz dated 24 April 2013

D23: Declaration of Dr Parmentier dated 6 June 2013

D27: D. Antai-Otong, Perspectives Psych. Care, 40(1), 2004, 29-33

D30: Guidelines for Phase 1 Clinical Trials, The Association of the British Pharmaceutical Industry, London, 2007 edition

D31: C. Buoen et al., J. Clin. Pharmacol., 45, 2005, 1123-1136

D32: S.H. Preskorn et al., Antidepressants: Past, Present and Future, Volume 157, Springer, 2004, 250-252

D34: E. Alvarez et al., Int. J. Neuropsychopharmacol., 15, 2012, 589-600

D36: M. Dragheim, Clinical Study Results, NCDEU Annual Meeting, 2013, Hollywood, Florida, USA

D43: Assessment report for an initial marketing authorisation application, Procedure No. EMEA/H/C/002717, European Medicines Agency, 24 October 2013

D45: ICD-10 depression diagnostic criteria, General Practice Notebook, web page downloaded on 25 March 2014

D46: J.P. Griffin et al., The Textbook of Pharmaceutical Medicine, 5th edition, Blackwell Publishing Ltd., 2006, 144-161

D47: A. Sharma et al., J. Clin. Pharmacol., 40, 2000, 161-167

D48: C. Chan et al., Br. J. Clin. Pharmacol., 63(3), 2006, 310-314

D49: B. Søgaard et al., J. Clin. Pharmacol., 45, 2005, 1400-1406

D50: FDA label for Cymbalta®, no available date

D51: FDA label for Lexapro™, no available date

D52: M.S. Jacobsen et al., Poster presented at the 29th CNIP World Congress of Neuropsychopharmacology, 22-26 June 2014, Vancouver, Canada

D52a to D52d: expanded sections of D52

D56a: M.E. Thase, J. Clin. Psychiatry, 76(1), 2015, 120-121

D56b: J. Zhang et al., J. Clin. Psychiatry, 76(1), 2015, 8-14

D58: A. Cleare et al., J. Psychopharmacol., 29(5), 2015, 1-67

III. The decision under appeal is the interlocutory decision of the opposition division finding that the patent as amended in the form of auxiliary request 1 filed during the oral proceedings of 26 March 2014 met the requirements of the EPC.

The opposition division held that the invention claimed in the patent as granted was novel and sufficiently disclosed. However, it was not inventive starting from document D4 as the closest prior art. In contrast, the invention claimed in auxiliary request 1 was novel, inventive and sufficiently disclosed, and did not add subject-matter.

IV. Each of the patent proprietors and the opponent filed an appeal against the decision. As both parties are appellants (and thus also respectively respondents), they will be referred to in the following as "patent proprietors" and "opponent".

V. With their statement of grounds of appeal, the patent proprietors filed several documents and six claim sets as auxiliary requests 1 to 6. These claim sets were identical to those pending in the opposition proceedings.

Claims 1 and 3 of auxiliary request 1 differ from claims 1 and 3 of the patent as granted in that the reason for ceasing or reducing medication has been limited to sleep related adverse events.

With its reply to the opponent's statement of grounds of appeal and with a letter dated 3 July 2015, the patent proprietors filed further documents. Subsequently, with a letter dated 17 June 2019, they filed additional claim sets as auxiliary requests 2a to 6a.

VI. With its statement of grounds of appeal, the opponent substantiated why, in its opinion, the request held patentable by the opposition division did not fulfil the requirements of Articles 83, 54 and 56 EPC.

With its reply to the patent proprietors' statement of grounds of appeal, the opponent filed documents D56a and D56b.

VII. Oral proceedings were held before the board on 30 July 2019.

VIII. The opponent's arguments, where relevant to the present decision, may be summarised as follows:

Novelty - main request

The group of patients defined in claims 1 and 3 is not limiting because it does not reflect a new clinical situation. Patients who received a first-line treatment for depression and ceased it after some time cannot be distinguished from other patients, neither physiologically nor pathologically; they all suffer from depression and their treatment with vortioxetine is exactly the same (vortioxetine is administered in the same manner for achieving the same effect through the same mode of action).

This results from the fact that the patient group is characterised by a mental act (i.e. the decision to cease or reduce medication due to the occurrence of sleep or sexually related adverse events) motivated by non-technical factors such as the patient's social and personal circumstances. This lack of technical character precludes the distinction of the patients of claims 1 and 3 from other patients, e.g. by measuring a physical or chemical parameter. This case is analogous to the one underlying the decision T 619/02.

In addition, there is no functional link between the patients' decision and the pharmacological effect of vortioxetine, i.e. the treatment of depression.

Thus, in accordance with the established case law that features of a mere mental nature are not technical features for the purposes of Article 54 EPC (Case Law of the Boards of Appeal of the EPO, 8th edition, 2016, I.C.5.2.8, page 121, paragraph 5), the group of patients of claims 1 and 3 cannot be taken into consideration for the assessment of novelty. As a

result, the subject-matter of claims 1 and 3 lacks novelty over the uses of vortioxetine disclosed in documents D4 and D2.

Inventive step - main request

Document D4 is the closest prior art because it is directed to the treatment of depression, anxiety, abuse and chronic pain with vortioxetine. Moreover, in the passage bridging pages 12 and 13, D4 refers to the low occurrence of sexually related side effects caused by vortioxetine in clinical trials.

The use of claims 1 and 3 differs from the closest prior art in that it is directed to a specific patient group. However, the selection of that patient group is arbitrary and has no effect. The evidence on file does not allow the opposite to be concluded. On the one hand, the clinical tests on file have not been carried out on patients according to claims 1 and 3; those involved in the clinical tests in the patent were patients in general, and those in document D52 did not discontinue their first-line treatment because they experienced sexually related adverse events but because they wished to take part in the clinical tests with vortioxetine (see D52a, heading "Methods"). On the other hand, the tests in paragraph [0032] of the patent are not suitable to assess sleep related side effects; the Hamilton Rating Scale for depression is a standardised method to evaluate the severity of depression based on the occurrence of specific symptoms such as insomnia, it is not intended to assess the side effects of medication. Furthermore, as sleep related problems are symptoms associated with depression which diminish when the patient's depressive state improves,

a reduction of insomnia cannot be univocally attributed to a low level of sleep related side effects.

In fact, vortioxetine does not cause fewer adverse events than other serotonine reuptake inhibitors (SRIs), as concluded by the US Food and Drug Administration (FDA) after an analysis of all the clinical studies available (see D56b, heading "Conclusions" in the abstract, and page 12, left-hand column, paragraph 3). In particular, in relation to the incidence of sexually related adverse events, the FDA found that vortioxetine was not better than duloxetine (see D56a, page 2, left-hand column, paragraph 2). The European Medicines Agency (EMEA) came to the same conclusion (see D43, page 156, paragraph 5).

If the board nevertheless acknowledges that vortioxetine causes fewer sleep and sexually related adverse events than other antidepressants, then the objective technical problem may be formulated as finding a patient group which particularly benefits from the treatment of depression with vortioxetine.

The solution proposed in claim 1 is obvious because document D4 discloses clinical trials with vortioxetine where the level of sexual dysfunction was found to be surprisingly low. Contrary to the patent proprietors' opinion, the skilled person would have relied on that finding because it came from scientists from a reputed pharmaceutical company who knew all the details on the clinical tests and the conclusions that could be drawn from their results. It is therefore immaterial whether the tests in document D4 were phase I or II. This situation is not comparable with that of the clinical trials in documents D47 to D49, where the corresponding

authors did not draw any conclusion in relation to the level of sexually related side effects.

With respect to the incidence of sleep related adverse events, the skilled person would have continued the study of side effects started in document D4 and would have found that the level of sleep disturbances caused by vortioxetine was also low. This is a direct consequence of the fact that authorities require the establishment of the side-effect profile of drugs before issuing a marketing authorisation. Thus, as SRI antidepressants were known to cause sleep related side effects at the priority date, their assessment was compulsory for the marketing of vortioxetine. This put the skilled person in a one-way-street situation which led inevitably to the claimed invention.

Inventive step - auxiliary request 1

The arguments of inventive step in relation to claims 1 and 3 of the main request also apply to claims 1 and 3 of auxiliary request 1 to the extent that they refer to sleep related adverse events.

Sufficiency of disclosure - auxiliary request 1

The invention of claims 1 and 3 is insufficiently disclosed in two respects: the patent does not disclose how to identify the patients belonging to the claimed group, and it does not prove that vortioxetine is suitable for effectively treating anxiety, abuse and chronic pain.

With regard to the identification of the patients belonging to the group of claims 1 and 3, the patent fails to specify the kind (e.g. early, middle or late

insomnia) and the severity of the sleep related adverse events and how to distinguish between the sleep related adverse events caused by medication and those which are a symptom of the treated disease. Contrary to the patent proprietors' arguments, questioning the patient cannot be sufficient because there is no standard questionnaire for this purpose and the patent does not specify which questions have to be asked to reliably clarify the mentioned issues. Furthermore, the decision to cease or reduce medication is often motivated by several factors, not just by one side effect, and the patent does not explain how to deal with patients who had several reasons for reducing or ceasing their previous medication.

As regards the effectiveness of vortioxetine to treat anxiety, abuse and chronic pain, the patent contains no data on the treatment of anxiety and abuse, and the treatment of chronic pain is supported only by limited animal experiments.

IX. The patent proprietors' arguments, where relevant to the present decision, may be summarised as follows:

Novelty - main request

The patient group in claims 1 and 3 is defined by technical features. Depression, anxiety, abuse and chronic pain are technically established using diagnostic criteria, questioning the patients about their mental state (see documents D22, D23 and D45). In this context, the patient's perception of side effects falls within the patient's pathological status and is a technical criterion of diagnosis for future treatment since the patient's attitude towards medication and side effects conditions their adherence to the

treatment (see D18, page 368, right-hand column, paragraph 2).

Thus, the patients' decision in claims 1 and 3 reflects a specific pathological status and is not arbitrary. Life circumstances and the patients' perception have an impact on mental diseases which can be determined by the treating physician for prescribing a change of treatment or additional intervention (see D18, points 2.3, 2.4 and 3.2). In particular, a failure in a previous treatment conditions the patients' attitude, putting them at risk of relapse. This circumstance characterises the patients' pathological mental status, making them different from other patients; the physician would also treat them differently (see D18, point 2.3, last black dot). Accordingly, the patients' decision in claims 1 and 3 is technical and cannot be compared with the purely aesthetic choice that was discussed in decision T 619/02.

Furthermore, there is a link between the pathological mental status of the patients in claims 1 and 3 and the treatment of depression, anxiety, abuse or chronic pain with vortioxetine. Those patients particularly benefit from the claimed treatment because vortioxetine minimises the side effects which led the patients to reduce or cease their previous medication.

Following the above, the patient group effectively limits the breadth of claims 1 and 3. Moreover, this limitation renders the use of claims 1 and 3 novel because it defines a narrow selection in relation to the patients treated in documents D4 and D2; the patients were treated with a first-line medication, suffered specific side effects during that treatment,

and ceased or reduced the treatment due to those specific side effects.

Inventive step - main request

Document D4 is not a suitable starting point because it is directed to the treatment of cognitive impairment in depressed patients rather than to the treatment of the patients of claims 1 and 3. The choice of this document is based on hindsight and leads to the formulation of an arbitrary, unrealistic technical problem.

Should document D4 nevertheless be taken as the closest prior art, then the use of claims 1 and 3 differs in the specific patient group treated.

The treatment with vortioxetine is particularly suitable for the claimed patient group because its incidence of sleep and sexually related adverse events is at the level of placebo. This is demonstrated by the results of the clinical tests presented in paragraphs [0032] and [0033] and Figures 6 to 8 of the patent, as well as in documents D34 (see Figure 3 and Table 5), D52a (see heading "Introduction"), D52d (see heading "Conclusions"), D43 (see pages 134 and 156) and D58 (see Table 5).

In this connection, the conclusions of the EMEA in document D43 regarding the incidence of sexually related adverse events are more accurate than those of the FDA in documents D56a and D56b, because the methodology used by the EMEA for identifying the level of such adverse events is more sensitive than that of the FDA.

Further, contrary to the opponent's opinion, the tests reported in paragraph [0032] and Figures 6 to 8 of the patent are suitable to assess the level of sleep related side effects because it is possible to discriminate between sleep related side effects and sleep related symptoms; the latter require weeks of treatment to decrease, while the former typically emerge from the start of the treatment. Thus, the fact that the patients in Figures 6 to 8 experienced fewer sleep related adverse events than placebo from the beginning of the treatment revealed that vortioxetine produces low levels of sleep related side effects. This was confirmed by international authorities in documents D43 (see page 134, paragraph 3) and D58 (Table 5).

On the basis of these effects, the technical problem solved is finding a patient group which particularly benefits from the treatment with vortioxetine.

The solution proposed in claims 1 and 3 was not obvious because document D4 teaches that vortioxetine belongs to the family of SRI antidepressants, which is generally associated with the emergence of sleep and sexually related side effects.

Regarding the incidence of sexually related adverse events, the skilled person would not have relied on the conclusion on page 13, lines 1-2 of document D4 that vortioxetine was associated with few sexually related adverse events, since the clinical tests on which that conclusion was based had been carried out under phase I conditions, which are unsuitable for establishing the levels of sexually related adverse events. Therefore, the skilled person had no reasonable expectations that, contrary to the general knowledge in relation to SRI

antidepressants, vortioxetine would produce few sexually related adverse events.

The fact that the clinical trials were carried out under phase I conditions is derivable from the low number of subjects (rather than patients) involved and the fact that they were exposed to vortioxetine rather than treated with it. The reason why the phase I trials are unsuitable to assess the level of sexually related side effects is that they are carried out in a hospital-like environment (which makes it difficult for patients to engage in sexual activity), for a relative short time (while sexually related adverse events arise in the mid term, see D32, page 251, paragraph 2), on healthy subjects (who are inherently different from patients, see D46, page 159, right-hand column, paragraph 1), and not all subjects are necessarily exposed to doses as high as those expected to be used in therapy.

A proper assessment of sexually related side effects would have required at least phase II clinical tests, as is demonstrated by the case of the SRI antidepressants duloxetin and escitalopram, which in phase I did not produce sexually related side effects (see D47, section "Clinical adverse events"; D48, section "Results"; and D49, section "Safety and Tolerability"), but their labelling information shows that they indeed produce such side effects (see D50, Table 3 and D51, Table 3).

As to the sleep related adverse events, there was no pointer in the prior art suggesting that vortioxetine was advantageous. The opponent's view that the skilled person was in a one-way-street situation is tainted by hindsight and by the unrealistic situation arising from

the choice of document D4 as the starting point, which distorts the state of the art.

Inventive step - auxiliary request 1

The arguments of inventive step put forward in relation to claims 1 and 3 of the main request also apply to claims 1 and 3 of auxiliary request 1 to the extent that they relate to sleep related adverse events.

Sufficiency of disclosure - auxiliary request 1

The skilled person can identify the patients of claims 1 and 3 by anamnesis, which is the normal tool for a physician in the area of mental health to establish a diagnosis. In this field, it is standard practice to ask patients about their treatment history, including their previous medication, the adverse events they experienced and their adherence to the treatment (see expert declarations D22, points 9 to 15, and D23, points 7 to 13). Thus, a physician always knows whether a patient has taken another medication, whether they ceased or reduced it, and whether they did so because of the occurrence of sleep related adverse events. This situation is analogous to that of the diagnosis of depression, which is established by identifying symptoms through direct questioning (see D45). The fact that the symptoms of depression are subjective in their nature (loss of interest and pleasure, poor concentration or indecisiveness, low self-confidence, etc.) does not preclude the establishment of a valid diagnosis. The same applies to the establishment of the pathological state of the patients in claims 1 and 3. Furthermore, the physician working in the field of mental health can routinely identify the patients of claims 1 and 3 without the need of a standardised

questionnaire (see D18, section 3.2, second black dot, and D20, heading "Managing adverse effects of antidepressants").

X. The final requests of the parties were as follows.

The patent proprietors requested that the decision under appeal be set aside and that the opposed patent be maintained without amendment. Alternatively, they requested that the opposed patent be maintained on the basis of the set of claims of auxiliary request 1 as upheld by the opposition division (implying that the appeal of the opponent be dismissed), or, on the basis of the set of claims of one of auxiliary requests 2 to 6, submitted with the statement of grounds of appeal, or auxiliary requests 2a to 6a, submitted with the letter dated 17 June 2019.

The opponent requested that the decision under appeal be set aside and that the patent be revoked, or, alternatively, that the appeal of the patent proprietors be dismissed. The opponent furthermore requested that documents D56a and D56b (submitted by the opponent as document D53) be admitted into the proceedings.

XI. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. Documents on file

The parties have either withdrawn their objections or not objected (see minutes of the oral proceedings held on 30 July 2019) to the admission of the documents filed by the other party during the appeal proceedings. The board sees no reason to raise any objection in this respect either. Hence, all the documents filed in the appeal proceedings are admitted into the proceedings.

2. Novelty - main request (patent as granted)

The opponent contested the novelty of the subject-matter of claims 1 and 3 over the content of documents D4 and D2.

Document D4 is an international patent application published after the two older priority dates and before the filing date of the contested patent. It was nevertheless undisputed that the claimed invention does not enjoy those older priority dates and that document D4 belongs to the prior art within the meaning of Article 54(2) EPC.

2.1 Document D4 discloses (see claims 1 and 15) the use of vortioxetine for the treatment of depression, anxiety, abuse and chronic pain. Similarly, document D2 discloses (see fifth compound in claim 11, and claim 13) the use of vortioxetine for the treatment of depression and anxiety.

It was common ground that documents D4 and D2 disclose the use of the same compound for the treatment of the same diseases as claims 1 and 3 of the patent in suit. It was also common ground that the claimed uses differ from those in D4 and D2 only by the fact that they are directed to a specific patient group. The board needs then to assess whether that patient group is suitable to render the claimed use novel over the disclosures of D4 and D2, which do not specify any subgroup among the patients suffering from depression, anxiety, abuse or chronic pain.

2.2 In the course of the oral proceedings before the board, the patent proprietors put forward that the criteria for a patient group rendering a previously known therapeutic method novel are that:

i) The patient group is not disclosed in the relevant prior art.

ii) The patients belonging to the group can be distinguished from those of the prior art by their physiological or pathological status.

iii) There is a functional relationship between their characterising physiological or pathological status and the therapeutic treatment and thus the selection of the patients is not arbitrary.

The opponent did not contest this, and the board agrees that - although the case law of the board of appeal does not seem to provide fixed criteria for a patient group - a patient group fulfilling those three criteria is anyhow suitable to render the claimed subject-matter novel. In addition, the board holds that the three

criteria are fulfilled by the patient group of claims 1 and 3, as explained below.

2.2.1 Documents D4 and D2 do not specify the condition of the treated patients beyond the fact that they are suffering from depression, anxiety, abuse or chronic pain. The patients of claims 1 and 3 are characterised by the fact that, in addition to suffering from depression, anxiety, abuse or chronic pain, they were previously treated for any of those diseases with a medicament other than vortioxetine, and they discontinued or reduced medication due to the occurrence of sleep or sexually related adverse events. As such patients have not been disclosed in documents D4 and D2, they constitute an undisclosed sub-group which fulfils criterion i).

2.2.2 The patients in claims 1 and 3 are characterised by the fact that they decided to cease or reduce their first-line medication for depression, anxiety, abuse or chronic pain following the incidence of sleep or sexually related adverse events experienced during the treatment. Contrary to the opponent's view, the patients' decision to continue or reduce or cease medication due to adverse effects cannot be regarded as a non-technical feature. In fact, this decision is covered by the more general concept of patient compliance, which concept is accepted in the case law as being of a technical nature. Such a decision is driven by the patients' perception that the burden of the sleep or sexually related side effects experienced is unbearable or at least as limiting as the disease itself. This failure of the previous treatment certainly affects the patients' mental health and their attitude towards antidepressants, making them different

from other patients from a pathological point of view, in particular from naive patients.

This becomes even more evident considering that attitude is an important factor in mental diseases and that patients' adherence to the treatment is closely linked to their favourable attitude to the medication and the confidence in managing side effects (see D18, page 368, right-hand column, paragraph 2). Thus, the patients of claims 1 and 3 are conditioned by a potential lack of confidence in the management of side effects or the fear that there might not be an acceptable treatment for them. This circumstance exposes patients to a higher risk of relapse and makes them potentially more difficult to treat. In fact, those patients would be treated differently by their physician, since, as noted in document D18 (page 347, point 2.3, last black dot), one of the factors to consider in choosing an antidepressant is the tolerability and the adverse effects of a previously given drug and the likely side effects of the new drug.

The opponent argued that the patients of claims 1 and 3 are only distinguished from those of the prior art by a mental act and that this situation would be analogous to the one underlying decision T 619/02.

The board disagrees. The case of decision T 619/02 concerns a method of odour selection which involves a purely aesthetic choice deprived of technical character. This situation can in no way be equated with that of the patients of claims 1 and 3, who had to weigh the benefits and drawbacks of their prescribed medication and take a decision between two options, both of which entailed serious consequences for their daily life. Such a decision was, as considered above,

not an arbitrary choice based on the patients' free will but rather a technical decision comparable to that of a physician selecting the most suitable treatment for a patient. Hence, the conclusions of decision T 619/02 are not applicable to the present case.

The board therefore holds that the particular history of the patients of claims 1 and 3 makes them pathologically different from other patients, in particular from naive patients, and that criterion ii) is fulfilled too.

In this connection, the issue of whether the patients may in practice be effectively distinguished from other patients will be addressed in the discussion of sufficiency of disclosure (section 6).

2.2.3 With regard to criterion iii), the fact that vortioxetine produces sleep and sexually related adverse events at (or close to) the level of placebo (see e.g. D34, Table 5; D58, Table 5; D36; and D43, page 134, paragraph 3) makes it particularly suitable for treating depression, anxiety, abuse or chronic pain in patients who took the decision to reduce or cease a previous medication due to the occurrence of such adverse events (this issue will be discussed in more detail in the context of inventive step). The functional link between the pathological status of the patients and their therapeutic treatment is therefore clear.

2.3 The board therefore concludes that the subject-matter of claims 1 and 3 is novel over the content of documents D4 and D2.

3. Inventive step - main request (patent as granted)

3.1 The opponent considered document D4 to be the closest prior art. The patent proprietors contested this view with the argument that D4 did not deal with the central problem of the patent, namely the reduction or cessation of a first-line therapy due to the incidence of sleep or sexually related adverse events.

In the board's view, the patent proprietors' argument must fail because document D4 is concerned with the treatment of depression, anxiety, abuse and chronic pain with vortioxetine (see claims 1 and 15, and page 12, lines 12 to 24), which is the primary aim of the patent. In addition, the document mentions in the passage bridging pages 12 and 13 that antidepressants frequently cause sexually related adverse events which may lead to discontinuation of the treatment, and that the occurrence of sexually related adverse events observed in patients treated with vortioxetine was surprisingly low. Hence, it is apparent from its technical field, its aim and its information on vortioxetine side effects that D4 is particularly close to the invention. Document D4 is therefore a highly suitable starting point for the assessment of inventive step.

3.2 It was undisputed that the use of claims 1 and 3 differed from the closest prior art in the specific group of patients to which it was directed.

3.3 In relation to the effect produced by this difference, the board is satisfied that, for the reasons explained in sections 3.3.1 and 3.3.2 below, the evidence on file demonstrates that vortioxetine causes sleep and

sexually related side effects at the level of placebo (i.e. at the lowest possible level) or slightly above it. It has also been shown that vortioxetine produces lower sleep and sexually related adverse events than reference SRI antidepressants such as duloxetine and venlafaxine. Accordingly, vortioxetine is particularly suitable for treating patients who could not bear the occurrence of sleep or sexually related adverse events of a previous treatment.

3.3.1 The low incidence of sexually related adverse events caused by vortioxetine is derivable from the results of the clinical tests reported in paragraph [0033] of the patent, where placebo and vortioxetine produced practically no cases of anorgasmia, delayed ejaculation, erectile dysfunction, decreased libido, abnormal orgasm, loss of libido, or decreased orgasmic sensation. This observation was confirmed by the clinical trials reported in documents D34 (see Table 5) and D36 (Table), where the occurrence of sexually related side effects (anorgasmia, delayed ejaculation and erectile dysfunction) at increasing daily doses of vortioxetine from 5 mg to 20 mg was again as low as that of placebo. Lastly, these results were corroborated by the EMEA in its assessment report for marketing authorisation (D43), which concluded on pages 134 (paragraphs 5 and 6) and 156 (paragraph 5) that, although there is an increase in the occurrence of sexual dysfunction going from the 5mg to the 20mg group, the overall incidence during the treatment with vortioxetine was low (38%) and slightly higher than that in the placebo group (32%). Even at the higher daily dose of 20mg, the incidence of sexually related adverse events caused by vortioxetine (43%) was below that of duloxetine (46%).

The opponent contested this conclusion with reference to the publications by the FDA, D56a and D56b, which stated that the occurrence of sexual side effects with vortioxetine was higher than with placebo, appeared to be dose-related, and was similar to duloxetine (see D56a, page 2, left-hand column, paragraph 2; and D56b, page 13, left-hand column, last paragraph). In particular, the opponent referred to Table 3 of document D56b, which showed that the incidence of sexual dysfunction in patients treated with 20mg vortioxetine (34-29%) was higher than with the active control, 60mg duloxetine (28-26%).

As noted by the patent proprietors, this slightly higher incidence of sexual dysfunction for vortioxetine reported by the FDA, which seems to contradict the conclusions of the EMEA, may be explained by the different methodology used by the agencies in their analysis of clinical tests; while the FDA assessed the incidence of sexual side effects on the basis of a positive reporting at two consecutive visits (see the text below Table 3 of D56b), the EMEA noted each incidence of the side effect. Hence, the methodology of the EMEA appears to be more sensitive for the identification of the levels of adverse events, and its conclusions can be considered to be more accurate in this respect. The board therefore holds that documents D56a and D56b do not invalidate the results and conclusions of the patent or documents D34, D36 and D43 in relation to the low incidence of sexually related adverse events of vortioxetine.

3.3.2 Concerning the sleep related adverse events, the results of the clinical tests reported in the patent in paragraph [0032] and depicted in Figures 6 to 8 display the incidence of insomnia in patients treated for

depression with vortioxetine. In particular, Figures 6 to 8 show that the incidence of early, middle and late insomnia during the treatment was lower than that of placebo.

The opponent questioned whether these results were suitable to conclude that vortioxetine produces few sleep related side effects, because insomnia is not only a side effect of antidepressants but also a symptom of depression which diminishes along with the treatment, due to the improvement of the patient's state. However, the board is convinced by the patent proprietors' argument that the difference in timing between the onset of an effective level of the treatment for depression and the appearance of the sleep related adverse events allows the discrimination between a low incidence of sleep related side effects and a reduction of sleep related symptoms.

As argued by the patent proprietors, the onset of the antidepressant effect of SRIs often requires weeks of treatment (see D8, page 801, right-hand column, last paragraph, and D9, page 1801, left-hand column, last paragraph), while sleep related adverse events typically occur immediately following the initiation of treatment (see D20, page 2, heading "Central nervous system side effects"). In this context, Figure 2 of document D34 shows that, before the second week of treatment, there is no statistically significant difference between the depressive state of the patients treated with vortioxetine and those treated with placebo. In other words, the antidepressant effect of vortioxetine is not significant during the first two weeks of treatment. The board therefore holds that the low levels of insomnia (below placebo) observed in Figures 6 to 8 of the patent during the first two weeks

of treatment necessarily imply a low incidence of sleep related adverse events. Furthermore, this effect has been confirmed by the British Association for Psychopharmacology and the EMEA in documents D58 and D43, respectively. The British Association indicated in Table 5 of document D58, which depicts the side effect profile of commonly used antidepressants, that vortioxetine does not produce insomnia or agitation. Similarly, the EMEA stated on page 134 (see paragraph 3) of document D43, with reference to vortioxetine, that "*[t]he incidence of insomnia and somnolence were similar to placebo*".

3.4 Based on these effects, the board agrees with the parties that the objective technical problem may be formulated as finding a patient group which particularly benefits from the treatment with vortioxetine.

3.5 The board is also satisfied that the patient group of claims 1 and 3 is a suitable solution to that problem. The question of whether or not that solution was obvious depends first and foremost on the value that the skilled person would have attached to the conclusion drawn by the inventors of document D4 on page 13, lines 1-2, that:

"*[t]hese data suggest that clinical intervention using compounds of the present invention is associated with surprisingly few deficits in sexual functioning.*"

This conclusion was drawn in relation to clinical trials where 114 subjects had been exposed to vortioxetine and only one reported sexual dysfunction.

The patent proprietors considered that this conclusion would not have given the skilled person any expectation of success in relation to the low levels of sexually related adverse events produced by vortioxetine because it was based on phase I clinical trials which, by their nature, are unsuitable for assessing the level of side effects, especially sexually related side effects. The fact that the tests were phase I trials was apparent from the low number of (healthy) subjects involved and the fact that they were not treated with the drug, but exposed to it. The reasons why such tests would be unsuitable are multiple. Firstly, only a small proportion of the subjects is exposed to doses that would be used in therapy. Secondly, the trials are carried out in a clinical environment, which makes the subject's ability to engage in sexual activity difficult. And thirdly, the tests are carried out for a reduced time period, while sexually related adverse events generally emerge after weeks of treatment (see document D32, page 251, paragraph 2).

The board is not convinced by those arguments. The inventors of D4 were aware that vortioxetine was an SRI antidepressant (see page 1, lines 4 to 7) and could then expect it to produce sexually related adverse events, also in healthy subjects (phase I trial). In fact, they recorded the occurrence of such events and found them to be surprisingly low. This conclusion was drawn by clinical experts on the basis of the results obtained from clinical trials carried out on a considerable number of subjects and of which they had all the relevant information. So, they knew exactly which conclusions could be validly drawn from those trials. Accordingly, irrespective of the phase of the trials and the level of detail disclosed in D4, the

skilled person would not have considered the conclusion of the inventors of D4 to be unfounded.

3.6 The board therefore holds that at the relevant date of the patent it was obvious to the skilled person that patients who had suffered sexually related adverse events in a previous treatment for depression, and who had reduced or ceased that treatment due to those adverse events, were patients who could particularly benefit from the treatment for depression with vortioxetine. Hence, the subject-matter of claims 1 and 3 as granted does not involve any inventive step.

4. Novelty - auxiliary request 1

In claims 1 and 3 of auxiliary request 1, the patients of the main request have been limited to those who reduced or ceased the previous medication due to the occurrence of sleep related adverse events. Thus, the reasons why the subject-matter of the granted claims is novel apply *mutatis mutandis* to the subject-matter of the claims of auxiliary request 1.

5. Inventive step - auxiliary request 1

5.1 As for the main request, starting from document D4, the subject-matter of claims 1 and 3 differs in the group of patients treated.

5.2 Also like the main request, the technical problem to be solved may be formulated as finding a patient group which particularly benefits from the treatment with vortioxetine.

5.3 It has already been discussed in section 3.3.2 that vortioxetine produces sleep related side effects at the

level of placebo. The board is therefore satisfied that the solution proposed in claims 1 and 3 effectively solves the problem posed.

5.4 With regard to the issue of obviousness, the board notes that no document on file suggests that vortioxetine produces particularly low levels of sleep related adverse events or that it is particularly suitable for treating patients who reduced or ceased their previous medication due to the occurrence of such adverse events. The solution proposed in claims 1 and 3 of auxiliary request 1 was therefore not obvious to the skilled person.

5.5 In this context, the opponent argued that the skilled person would have arrived at the subject-matter of claims 1 and 3 as a result of a one-way-street situation. In order to obtain a marketing authorisation for vortioxetine, the skilled person would have been obliged to carry out clinical tests assessing its level of side effects, especially those known for SRI antidepressants, e.g. sleep disturbances. By doing so, the skilled person would have necessarily observed the low level of sleep related adverse events produced by vortioxetine and, hence, they would have inevitably arrived at the use of claims 1 and 3 without the involvement of an inventive step.

This argument has to be rejected for being fundamentally flawed; it confuses the applicant of document D4 with the skilled person, assuming that the skilled person would be prompted to bring vortioxetine into the market rather than to solve the problem posed.

As established in the case law, a one-way-street situation arises when the skilled person inevitably

arrives at a particular combination of technical features due to a lack of alternatives (see Case Law of the Boards of Appeal of the EPO, 8th edition, 2016, I.D.10.8, paragraph 2). This is not the situation in the case at hand, however. The skilled person confronted with the problem of finding a patient group which particularly benefits from the treatment with vortioxetine had multiple choices, e.g. testing patients of different age ranges, with specific concomitant conditions such as depression associated to chronic pain, with particular genetic or physiological features, etc. Hence, the opponent's view that the skilled person inevitably had to carry out clinical tests for assessing the side effects of vortioxetine cannot be accepted.

6. Sufficiency of disclosure - auxiliary request 1

The opponent argued that the invention of auxiliary request 1 was not sufficiently disclosed in two respects.

- The skilled person was not able to identify the patients belonging to the group of claims 1 and 3.

- It had not been proven that vortioxetine was suitable for treating anxiety, abuse and chronic pain.

6.1 With regard to the identification of the patients who belong to the group of claims 1 and 3, it was common ground that the diagnostic of depression, anxiety, abuse and chronic pain is generally made by anamnesis using standard criteria, for example the ICD-10 depression diagnostic criteria disclosed in document D45, where patients are questioned on symptoms of subjective nature like persistent sadness, low mood,

loss of interest or pleasure, fatigue, low energy, etc. The validity of the clinical diagnostic obtained in this manner has not been contested.

The board agrees with the patent proprietors that, in a similar way, a physician in the field of mental health is able to establish, by questioning, whether new patients received a previous medication, whether they experienced adverse events during that previous medication and of which nature, and, where applicable, the reasons why they reduced or ceased medication. In this respect, contrary to the opponent's arguments, the measurement of a physical or chemical parameter is not required for identifying the patients. This view is confirmed by the expert declarations D22 (point 9) and D23 (point 8), which state that a physician who treats a patient for the first time will as standard practice question the patient not only on the nature and duration of their symptoms but also on their treatment history. It is also noted that the assessment of sleep related adverse events in patients treated with antidepressants is common practice as also follows from the fact, recognised by the opponent in its arguments of inventive step, that such an assessment is required for obtaining a marketing authorisation.

Thus, the board has no doubts that a physician in the field of mental health can identify patients who have previously received medication for depression, anxiety, abuse or chronic pain, who experienced sleep related adverse events, and who reduced or ceased medication due to those sleep related adverse events. The fact that there are no standard questionnaires for this purpose does not represent an impasse, since gathering that information is part of the aim of anamnesis, which is a generally accepted means for diagnosis and

identification of issues in the field of mental health where conditions can mostly only be assessed on the basis of the patient's perception.

6.2 The board acknowledges that in particular cases where the patient had more than one reason for reducing or ceasing medication, there might be some uncertainty about whether the reduction or cessation of medication could be assigned to the sleep related adverse events. This uncertainty, however, amounts to a lack of clarity rather than a lack of sufficiency. As the technical features in question (definition of the patient group) were already present in the claims as granted, and the cause of uncertainty is not the amendment of claims 1 and 3 with respect to their corresponding granted claims (i.e. the deletion of sexually related adverse events from claims 1 and 3), this issue is not within the scope of the opposition appeal proceedings (see Enlarged Board decision G 3/14, catchword).

6.3 With regard to the suitability of vortioxetine to treat abuse and chronic pain, the opposition division acknowledged that the invention was sufficiently disclosed and based its decision on the tests of Examples 1 and 4 in the patent and on the knowledge at the priority date that vortioxetine was SRI, 5-HT_{1a} agonist and 5-HT_3 antagonist (see contested decision, last half of page 12). Although the opposition division did not explicitly mention the treatment of anxiety, it was apparent from the patent (paragraphs [0001] and [0002]) that the opposition division's argument also applied to anxiety; the fact that vortioxetine was SRI, 5-HT_{1a} agonist and 5-HT_3 antagonist made it suitable for the treatment of anxiety, as confirmed by documents D4 (page 1, lines 4-7 and 10-12) and D2 (page 1, lines 3-5).

In its statement of grounds of appeal, the opponent did not challenge this aspect of the decision. It did so for the first and sole time in section 3.3.5 of its reply to the patent proprietors' statement of ground of appeal. In that section, however, the opponent did not provide any reasons why the contested decision was wrong; it merely stated that the patent did not contain sufficient evidence, ignoring the explanation given by the opposition division of why the invention was sufficiently disclosed. Accordingly, the board considers that the opponent has not substantiated this aspect of its objection and therefore sees no reason to reverse this part of the decision under appeal.

6.4 In conclusion, the board holds that the skilled person is able to carry out the invention of claims 1 and 3 without undue burden.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated