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Datasheet for the decision of 7 December 2015

Case Number: T 2059/13 - 3.3.01

Application Number: 06015782.3

Publication Number: 1712225

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Language of the proceedings: EN

Title of invention:
Substituted carbostyril derivatives as 5-HT 1A receptor subtype agonists for the treatment of bipolar disorder

Patent Proprietor:
OTSUKA PHARMACEUTICAL CO., LTD.

Opponents:
STADA Arzneimittel AG
Sanovel Ilaç Sanayi ve Ticaret A.S.
Hexal AG
Teva Pharmaceutical Industries Ltd.
Actavis Group PTC EHF
PENTAFARMA S.A.
CHEMO IBERICA, S.A.
Helm AG

Headword:
Aripiprazole against bipolar disorder/OTSUKA

Relevant legal provisions:
EPC Art. 100(b)
RPBA Art. 13(1)

Keyword:
Late-filed documents - admitted (no)
Sufficiency of disclosure of further medical use - (no)

Decisions cited:
T 0609/02, T 1677/11, T 0063/06, T 0491/08, T 0158/96, T 0801/10, R 0011/08, R 0014/11, T 1253/04, T 0766/91

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

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Case Number: T 2059/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 7 December 2015

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Representative:	UEXKÜLL & STOLBERG Patentanwälte Beselerstrasse 4 22607 Hamburg (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 16 July 2013 revoking European patent No. 1712225 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. Eight oppositions were filed against the grant of European patent No. 1 712 225. They were directed against the patent in its entirety and were based on grounds under Article 100(a)(alleged lack of novelty and of inventive step) (b) and (c) EPC.

II. The documents cited during the opposition proceedings include the following:

(D2) P. E. Keck et al., Medical Clinics of North America, Vol. 85, No. 3 (May 2001), 645-661

(D4) C. L. Bowden, Exp. Opin. Invest. Drugs, Vol. 10, No. 4 (2001), 661-671

(D8) G. S. Sax et al., A Postgraduate Medicine Special Report, April 2000, 1-20

(D9) C. Guille et al., J. Clin. Psychiatry, Vol. 61, No. 9 (September 2000), 638-642

(D11) S. Jordan et al., European Neuropsychopharmacology, Vol. 11, Suppl. 3 (2001), S268

(D12) U.S. patent application No. 09/770,210 filed on 29 January 2001

(D13) T. Kikuchi et al., The Journal of Pharmacology and Experimental Therapeutics, Vol. 274 (1995), 329-336

(D17) WO-A-02/060 423

(D24) I-Shin Shiah et al., Neuropsychobiology, Vol. 38 (1998), 6-12

(D28) C. Cohen et al., The Journal of Pharmacology and Experimental Therapeutics, Vol. 283 (1997), 566-573

(D29) D. S. Robinson et al., Journal of Clinical Psychopharmacology, Vol. 10, No. 3 (Suppl.) (June 1990), 67S-76S

(D42) Comparative Experiments, submitted with patentee's letter dated 13 November 2008, four pages

(D43) N. Haddjeri et al., Journal of Affective Disorders, Vol. 51 (1998), 255-266

(D44) N. Haddjeri et al., The Journal of Neuroscience, Vol. 18, No. 23 (December 1, 1998), 10150-10156

(D45) N. Haddjeri et al., Neuropsychopharmacology, Vol. 22, No. 4 (2000), 346-356

(D46) I. Lucki, J. Clin. Psychiatry, Vol. 52, No. 12 (Suppl.)(December 1991), 24-31

(D47) S. M. Stahl et al., International Journal of Neuropsychopharmacology, Vol. 1 (1998), 11-18

(D48) D. Taylor et al., The Maudsley 2001 Prescribing Guidelines, 6th edn. (2001), Martin Dunitz Ltd., London/GB, 76

(D49) S. Bazire, Psychotropic Drug Directory 2001/02, Quay Books, Mark Allen Publishing Ltd, Dinton/GB, 78-83

(D50) E. Vieta et al., British Journal of Psychiatry, Vol. 187 (2005), 235-242

(D51) Comparative Pharmacological Test, enclosed with patentee's letter dated November 5, 2012, five pages

III. The opposition division revoked the patent; it decided that grounds under Article 100(b) EPC prejudiced the maintenance of the patent.

The opposition division stated that the tests in the application as originally filed indicated only that aripiprazole was a 5-HT_{1A} receptor agonist. Documents (D11) and (D13) described aripiprazole as a partial 5-HT_{1A} receptor agonist and a postsynaptic D_2 receptor

antagonist. It was only known that there was a relationship between 5-HT_{1A}-agonists and depression (see page 4, lines 25-26, of the grandparent application (D17); see also documents (D29), (D46), (D47)). Only document (D24) disclosed the treatment of bipolar depressed persons with a 5-HT_{1A}-agonist. According to document (D2), the relationship between 5-HT_{1A}-agonism and depression could not be extrapolated to bipolar depression. A relationship between D_2 antagonism and bipolar disorders was also not evident.

Additional data provided in documents (D42), (D50), (D51) and in the letter dated 19 August 2010 could not be taken into account since, at the effective date of the patent, the receptor effects (5-HT_{1A} receptor agonism and D_2 antagonism) did not reflect the claimed therapeutic treatment of both the (hypo)manic and depressed phases of bipolar disorders (see page 18, second paragraph of the decision).

IV. The patent proprietor lodged an appeal against this decision.

V. The additional documents cited during the appeal proceedings include the following:

(D58) E. Mutschler, Arzneimittelwirkungen, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart/DE, 7th edn. 1997, 140-145, 152-153

(D59) E. Mutschler, Arzneimittelwirkungen, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart/DE, 8th edn. 2001, 157-172

(D61) Wikipedia Information on Risperidone, http//en.wikipedia.org/wiki/Risperidone, retrieved on 15 January 2014, seven pages

(D62) Wikipedia Information on Aripiprazole, http//en.wikipedia.org/wiki/Aripiprazole, retrieved on 15 January 2014, ten pages

(D63) F. K. Goodwin and K. R. Jamison, Manic-depressive illness, Oxford University Press, Oxford/GB 1990, 420-422

(D64) D. M. Hilty et al., Psychiatric Services, Vol. 50, No. 2 (February 1999), 201-213

(D65) H.-J. Möller et al., Journal of Affective Disorders, Vol. 67 (2001), 141-146

(D66) W. C. Drevets et al., Biol. Psychiatry, Vol. 46 (1999), 1375-1387

(D67) Information on "RISPERDAL®", "Revised: 04/2014", Janssen Pharmaceuticals, Inc., 16 pages

(D68) P. E. Keck et al., Am. J. Psychiatry, Vol. 160 (September 2003), 1651-1658.

VI. The claims under consideration in this decision are the following submitted during the oral proceedings of 13 June 2013 before the opposition division:

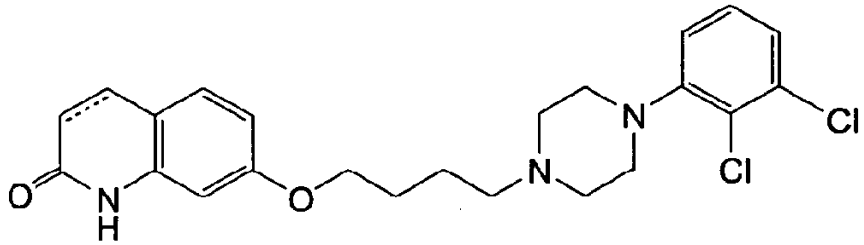
- claims 1 to 4 of the main request;
- claims 1 and 2 of the first auxiliary request;
- claims 1 and 2 of the second auxiliary request;
- claims 1 and 2 of the third auxiliary request;
- claims 1 to 3 of the fourth auxiliary request;
- claim 1 of the fifth auxiliary request;
- claim 1 of the sixth auxiliary request;
- claim 1 of the seventh auxiliary request;

and the following submitted under cover of letter dated 22 May 2015:

- claims 1 to 3 of the eighth auxiliary request;
- claim 1 of the ninth auxiliary request;
- claim 1 of the tenth auxiliary request;
- claim 1 of the eleventh auxiliary request.

a) The independent claim of the **main** request reads as follows:

"1. A compound which is a pharmaceutically acceptable acid-addition salt or solvate of a carbostyril compound of the formula (1):



(1)

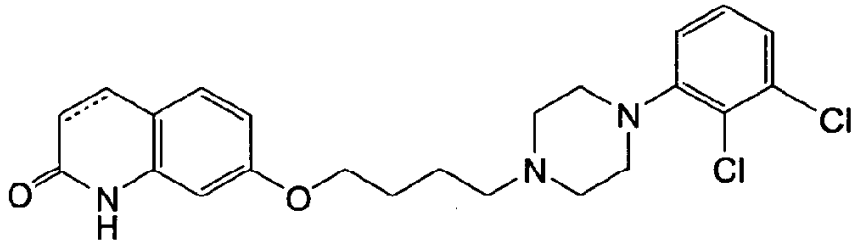
wherein the dotted line represents a single or a double bond, for use in the treatment of disorders of the central nervous system associated with 5-HT_{1A} receptor subtype, selected from

(i) bipolar I disorder with most recent hypomanic, manic, mixed, depressed or unspecific episode, and

(ii) bipolar II disorder with recurrent major depressive episodes with hypomanic episodes, and cyclothymic disorder."

b) The independent claim of the **first** auxiliary request differs from that of the main request in that bipolar II and cyclothymic disorders were deleted. It reads as follows:

"1. A compound which is a pharmaceutically acceptable acid-addition salt or solvate of a carbostyril compound of the formula (1):

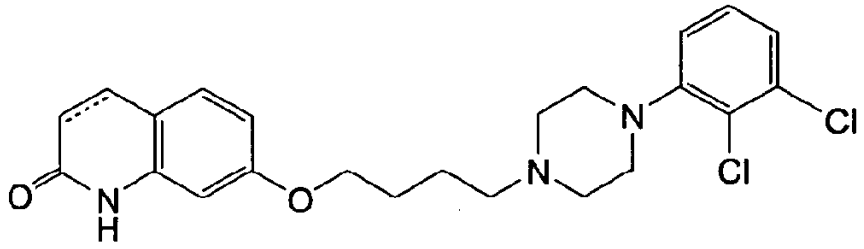


(1)

wherein the dotted line represents a single or a double bond, for use in the treatment of disorders of the central nervous system associated with 5-HT_{1A} receptor subtype, selected from bipolar I disorder with most recent hypomanic, manic, mixed, depressed or unspecific episode."

c) The independent claim of the **second** auxiliary request differs from that of the main request in that bipolar I and cyclothymic disorders were deleted. It reads as follows:

"1. A compound which is a pharmaceutically acceptable acid-addition salt or solvate of a carbostyril compound of the formula (1):

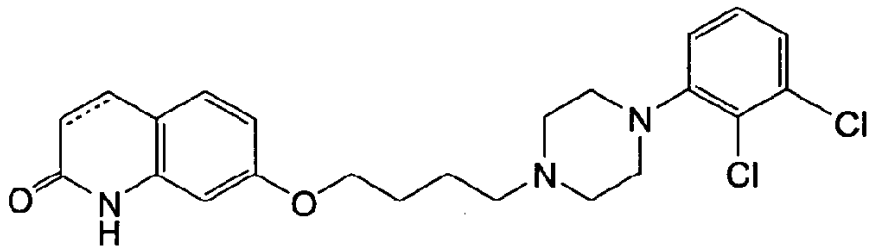


(1)

wherein the dotted line represents a single or a double bond, for use in the treatment of disorders of the central nervous system associated with 5-HT_{1A} receptor subtype, selected from bipolar II disorder with recurrent major depressive episodes with hypomanic episodes."

d) The independent claim of the **third** auxiliary request differs from that of the main request in that the disorders were limited to cyclothymic disorders. It reads as follows:

"1. A compound which is a pharmaceutically acceptable acid-addition salt or solvate of a carbostyril compound of the formula (1):

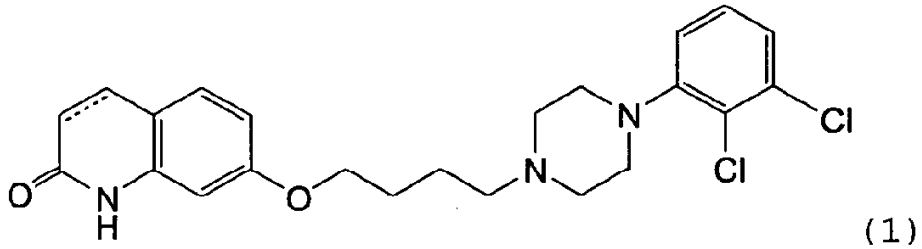


(1)

wherein the dotted line represents a single or a double bond, for use in the treatment of disorders of the central nervous system associated with 5-HT_{1A} receptor subtype, selected from cyclothymic disorder."

e) The independent claims of the **fourth**, **fifth**, **sixth and seventh** auxiliary request differ from those of the main request, first, second and third auxiliary requests, respectively, in that

"1. A compound which is a pharmaceutically acceptable acid-addition salt or solvate of a carbostyril compound of the formula (1):

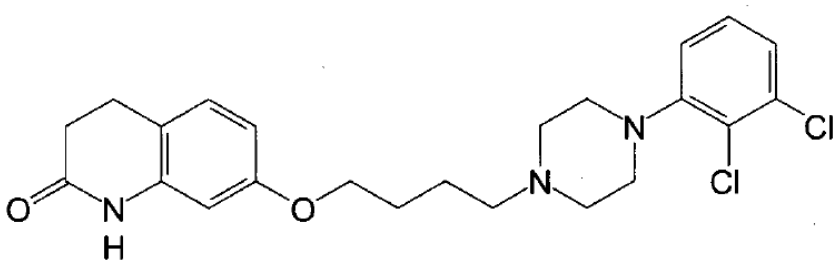


(1)

wherein the dotted line represents a single or a double bond,"

was replaced by

"1. A pharmaceutically acceptable acid-addition salt or solvate of 7-{4-[4-(2,3-dichlorophenyl)-1-piperaziny] butoxyl}-3,4-dihydrocarbostyril of the formula (1):



(1)".

f) The independent claims of the **eighth**, **ninth**, **tenth and eleventh** auxiliary requests differ from those of the fourth, fifth, sixth and seventh auxiliary requests, respectively, only in that the phrase ", wherein the depressive symptoms are reduced" was inserted at the end of each of these claims.

VII. The appellant's arguments as far as relevant for this decision may be summarised as follows:

Late-filed documents

Documents (D63) to (D66) provided information on the role of the 5-HT_{1A} receptor in bipolar disorders, in addition to what was disclosed in document (D43). Documents (D63) to (D68) were filed at such a late stage because the appellant had not been aware of them when submitting the statement setting out the grounds of appeal.

Priority

Bipolar disorders and cyclothymic disorder were not explicitly mentioned in the priority document, but they were implicit options in view of the discussion on postsynaptic D_2 receptor antagonistic and 5-HT_{1A} receptor agonistic activities, as bipolar disorders

belonged to the 5-HT_{1A} receptor related diseases referred to in the priority document.

Sufficiency of disclosure

The facts and circumstances of the present case differed from those underlying T 609/02 in which the chemical structure of the compounds was not identified (see T 1677/11, point 7.2, second paragraph of the reasons).

The patent in suit contained a very detailed description which disclosed in paragraphs [0016], [0022] and [0028] that there was a clear link between 5-HT_{1A} agonism and the suitability of a drug in the treatment of bipolar disorders; the experimental part of the patent in suit demonstrated a high affinity binding of aripiprazole to the 5-HT_{1A} receptor (see paragraph [0040]).

Any information which might be missing in the patent in suit was part of the general knowledge exemplified in documents (D2), (D8), (D43) to (D45) and (D47). The common general knowledge was not restricted to the knowledge contained in text books; it might well be represented by a multitude of scientific articles from different authors. Document (D59) was not the only document reflecting the common general knowledge, nor did this document concern bipolar disorders. Due to its limitations, the study disclosed in document (D24) did not allow the conclusion that there was no relationship between 5-HT_{1A} receptor agonism and bipolar disorder.

The information disclosed in the patent in suit rendered the claimed therapeutic effect plausible which allowed post-published evidence (D42), (D50) and (D51)

to be taken into account. Document (D2) disclosed the efficiency of antidepressants in the treatment of the depressive phase of bipolar disorders, not in the treatment of the manic phase. It was known from documents (D28), (D58) and (D9) that the manic state of a bipolar disorder could be treated with D_2 receptor antagonists. Documents (D63) and (D64) showed that the use of antidepressants was known in the treatment of bipolar disorder. That aripiprazole was indeed effective for that purpose had been demonstrated in document (D50) and in the tests filed with the letter dated 19 August 2010.

Moreover, it was known from documents (D24), (D29), (D43) to (D47) and (D58) that partial 5-HT_{1A} agonists had antidepressant efficacy. Documents (D28) and (D49) showed that D_2 receptor antagonists were effective against mania. The tests (D42), (D51) and those reported in document (D68) showed the activity of aripiprazole as an antidepressant and against bipolar mania.

For these reasons, there was a well-established relationship at the filing date of the patent between

a) D_2 receptor antagonism and the therapeutic effect of the manic state of a bipolar disorder, as well as

b) 5-HT_{1A} receptor agonism and the therapeutic effect on the depressive state of bipolar disorder.

VIII. Respondent 8 did not submit any arguments during the appeal proceedings. The arguments of respondents 1 to 7 as far as relevant for this decision may be summarised as follows:

Late filed documents

Documents (D63) to (D66) were not more relevant than documents (D43) to (D45). Documents (D67) and (D68) were irrelevant as they did not form part of the prior art. The appellant could have submitted these documents much earlier. Therefore, documents (D63) to (D68) should not be admitted into the proceedings.

Priority

The present claims were directed to certain compounds for use in the treatment of bipolar disorder. The priority document did not disclose bipolar disorder directly and unambiguously. Therefore, none of the claims enjoyed the priority claimed.

Sufficiency of disclosure

Sufficiency of disclosure had to be satisfied at the effective date of the patent. It was not satisfied when a second medical use was claimed unless the patent showed that the claimed therapeutic effect was obtained (see T 609/02).

The application as filed did not show that there was a clear and established relationship between the 5-HT_{1A} receptor agonism of aripiprazole and its suitability for the treatment of bipolar disorders. The statement in paragraph [0022] of the patent in suit was merely an assertion and did not suffice to establish sufficiency of disclosure, as was evident from decisions T 609/02 and T 801/10. This was all the more true in view of the disclosure of document (D4), according to which the "inherent complexity of bipolar disorder" had been a

barrier to the study of new agents (see page 668, bottom paragraph of the left-hand column).

Documents (D2), (D8), (D43) to (D45) and (D47) were patent applications or journal articles and did not - in contrast to the general textbook (D59) - reflect the common general knowledge of the skilled person. Tables 1-5 and 1-11 of document (D59) showed that neuroleptica had effects on a multitude of receptors, the 5-HT_{1A} receptor not even being mentioned in this document. The only prior art document cited which dealt with the 5-HT_{1A} receptor and bipolar disorder was (D24) which, however, suggested that the subsensitivity at this receptor only occurred in unipolar, not in bipolar depression. Documents (D43) to (D45) did not relate to 5-HT_{1A} agonism in general, but to tests of certain drugs which had no direct agonistic effect at this receptor. Document (D47) concerned unipolar depression only. As disclosed in document (D2)(see page 650 and the penultimate paragraph on page 657), drugs effective against unipolar depression might induce hypomania, mania and cycle acceleration in bipolar depression. Hence, the therapies of bipolar and unipolar depressions differed considerably. Therefore, it was not generally known at the filing date of the patent that bipolar disorders were linked to the 5-HT_{1A} receptor.

Consequently, the patent in suit, if combined with the knowledge disclosed in the prior art, did not provide the information necessary to carry out the subject-matter of the claims. It was not justified to fill this gap with the disclosure of post-published evidence.

Grounds under Article 100(b) EPC thus prejudiced the maintenance of the patent in suit (see decisions

T 609/02, T 63/06 and T 491/08). As stated under point 7.11 of the decision under appeal, the burden of proof lay with the patentee to show that the disclosure was sufficient.

It was doubtful whether the mechanism of unipolar depression was the same as for bipolar depression (see (D2), page 649, under the heading "Bipolar Depression"). None of the documents (D63) to (D68) disclosed the suitability of 5-HT_{1A} receptor agonists for the treatment of bipolar or unipolar depression. As stated in document (D59), there was no clear relationship between serotonin reuptake inhibition of a drug and its antidepressant activity.

Document (D61) showed that risperidone had effects on a multitude of receptors (see the table on page 4). Hence it was doubtful whether aripiprazole was suitable for treating bipolar depression and bipolar mixed states.

Document (D59) disclosed that neuroleptics used to treat mania not only had a D_2 receptor antagonist component, but also an α_1, 5-HT_2, muscarine and H_1 receptor blocking activity. Thus, there was no clear link between D_2 receptor antagonism and the treatment of mania. Nor did this document show that it belonged to the common knowledge that the therapeutic effect of antipsychotics and antidepressants was based on an affinity to the 5-HT_{1A} receptor.

Document (D24) mentioned that the findings must be interpreted with caution and might mean that 5-HT_{1A} receptor subsensitivity only occurred in unipolar but not in bipolar depression.

None of the further documents cited by the appellant in its grounds for appeal, nor the prior art cited in paragraphs [0009] to [0017] of the patent in suit established a link between the 5-HT_{1A} receptor and bipolar depression.

The invention was that aripiprazole showed 5-HT_{1A} agonism (see the only example). Hence the appellant had to demonstrate that the suitability of this drug for the treatment of bipolar disorder was based on this effect. For this reason, the appellant could not rely on documents (D2), (D9), (D13), (D28), (D48) and (D49) because the effect shown in these documents was based on the D_2 antagonistic effect of the drug, as was evident from (D59).

IX. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the case be remitted to the department of first instance on the basis of the main request or of any of auxiliary requests 1 to 7, filed on 13 June 2013, or of auxiliary requests 8 to 11, filed on 22 May 2015, should the board find one of the requests to comply with the requirements of Article 83 EPC.

Respondents 1 to 7 requested that the appeal be dismissed. Respondent 7 further requested not remit the case to the department of first instance should the board find one of the requests to comply with the requirements of Article 83 EPC. Respondents 1, 3 and 5 further requested that the appellant's request for remittal be rejected and that documents D63 to D68 not be admitted into the appeal proceedings.

Respondent 8 did not take an active part in the proceedings and did not file any requests.

X. Respondent 8 was duly summoned but did not attend the oral proceedings before the board. In accordance with Rule 115(2) EPC, the oral proceedings were continued in the absence of respondent 8.

XI. At the end of the oral proceedings, the Chairman announced the decision of the board.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of documents (D63) to (D68)

2.1 According to Article 13(1) of the Rules of Procedure of the Boards of Appeal (RPBA)

"Any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the Board's discretion. The discretion shall be exercised in view of inter alia the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy." (see the supplementary publication to the OJ EPO 1/2015, 41-50).

2.2 The statement setting out the grounds for appeal is dated 26 November 2013. Documents (D63) to (D68) were filed by the appellant after it had filed its grounds of appeal, namely, as an annex to its letter dated 22 May 2015.

Therefore, it is at the discretion of the board whether or not to admit these documents into the proceedings.

2.3 The appellant declared that it had not been aware of the documents when filing its grounds of appeal.

However, what is decisive is not whether the appellant was aware of the documents when filing its statement setting out the grounds of appeal, but rather whether it could have been aware of them. Documents (D63) to (D66) and (D68) were published in scientific journals during or prior to 2003. Document (D67) is a brochure on the medicament RISPERDAL® which claims copyright of 2007 and was revised in April 2014 (see the right-hand column on the last page). Hence, there is no reason to believe that the appellant could not have retrieved documents (D63) to (D66) and (D68) as well as an earlier version of (D67) well before filing its statement setting out the grounds for appeal.

2.4 The appellant did not argue that the filing of these documents had been a reaction to new facts, arguments or evidence submitted by the respondents or by the board, nor does the board have any reason to believe that this was the case. The respondents essentially relied on arguments, facts and evidence brought forward during the opposition proceedings. Document (D59) was a more recent edition of (D58) previously filed by the appellant; documents (D61) and (D62) are pieces of general information on two drugs. Moreover, the board's communication was issued after the filing of documents (D63) to (D68).

2.5 For these reasons, the board decided not to admit any of the documents (D63) to (D68) into the proceedings.

3. Priority

The independent claims of the twelve requests on file are directed to the use of compounds of formula (1) for use in the treatment of bipolar disorder. Therefore, said use is a technical feature of all these claims.

The priority document (D12) is silent on any of the bipolar disorders mentioned in the present claims. Whether or not bipolar disorders belong to the 5-HT_{1A} receptor related diseases referred to in the priority document is not relevant in the present case. The fact remains that no bipolar disorders of any kind were **directly and unambiguously** disclosed in the priority document.

Hence, the priority is not valid for any of the present claims of any of the requests on file.

Consequently, the relevant date for assessing sufficiency of disclosure under Article 100(b) EPC is the filing date of the patent in suit.

Main Request

4. Article 100(b) EPC

The patent in suit was granted based on a divisional application of EP 05 023 971.4 (parent application), which in turn is a divisional application of European patent application No. 02 716 434.2 (grandparent application). In this section, when assessing what is disclosed in the application as originally filed, reference is made to document (D17), i.e. to the grandparent application as published.

4.1 The present claims relate the compounds of formula (I) for a further medical use (see point VIa) above). It was not contested that in such cases, for the requirement of sufficiency of disclosure to be fulfilled, the suitability of these compounds for the claimed therapeutic application must be disclosed (see point 1.2 of the statement dated 26 November 2013 setting out the grounds of appeal; see also the reference to "Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, section II.C.6.2, cited under this point).

4.2 T 609/02

4.2.1 Under point 7.2 of the decision under appeal, the opposition division relied on the following statement in point 9 of the Reasons of decision T 609/02 of 27 October 2004:

"The boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical. It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously

reflects such a therapeutic application (T 241/95, OJ EPO 2001, 103, point 4.1.2 of the reasons, see also T 158/96 of 28 October 1998, point 3.5.2 of the reasons) or, as decision T 158/96 also put it, if there is a "clear and accepted established relationship" between the shown physiological activities and the disease (loc. cit.). Once this evidence is available from the patent application, then post-published (so-called) expert evidence (if any) may be taken into account, but only to back-up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on their own."

4.2.2 The appellant argued that the facts and circumstances of the present case differed from those underlying T 609/02 in which the chemical structure of the compounds was not identified (see point VII above).

4.2.3 In this regard the board agrees with the appellant. However, such differences are normal and the usefulness of case law is not confined to similar or identical facts, but lies in the principles or guidance which can be extracted from earlier cases (see R 11/08 of 6 April 2009, point 11 of the reasons; R 14/11 of 5 July 2012, point 2.9.1 of the reasons). As stated by the respondents, the statement relied upon by the opposition division is

- of a more general nature, not limited to cases where the chemical structure of the compounds was not identified; it relates to the therapeutic use of chemical compound in general; and is
- confirmed by other decisions of the boards of appeal

(see, e.g., respondent 7's letter dated 5 March 2014, section 3 b; respondent 5's letter dated 20 March 2014, section 2.3, first paragraph; respondent 4's letter dated 14 April 2014, page 2, the section under the heading "Decision T609/02"; see decision T 801/10 of 8 July 2014 cited by Respondent 7 during the oral proceedings before the board, point 4.1 of the reasons).

4.2.4 Therefore, for a patent claiming a compound for use in therapy, grounds under Article 100(b) EPC will prejudice the maintenance if the application does not disclose the suitability of the product for the claimed therapeutic application to the skilled person using its common general knowledge. Only once this evidence is available from the patent application, may post-published evidence be taken into account when assessing sufficiency of disclosure.

4.3 For these reasons, assessing sufficiency of disclosure in the present case requires to determine

- to what extent the disclosure in the patent in suit and, more importantly, in the application as filed reveals the suitability of these compounds for the claimed therapeutic application,
- to what extent the person skilled in the art was able to supplement this disclosure with its common general knowledge,
- to what extent the pre-published documents cited by the parties were to be considered as common general knowledge, and
- whether, in the present case, any alleged deficiency of the disclosure of the patent could be cured by post-published evidence.

4.4 The disclosure in the patent in suit

4.4.1 The applicant argued that the patent in suit disclosed in paragraphs [0016], [0022] and [0028] that there was a clear link between 5-HT_{1A} agonism and the suitability of a drug against bipolar disorders, and that paragraph [0040] demonstrated a high affinity binding of aripiprazole to the 5-HT_{1A} receptor.

4.4.2 It was not contested that the patent in suit and the respective application as filed showed that aripiprazole binds to the 5-HT_{1A} receptor. The respondents did, however, contest that the patent in suit disclosed that there was a clear relationship between 5-HT_{1A} agonism and the suitability of a drug against bipolar disorders.

4.4.3 The patent in suit cites prior art as demonstrating that 5-HT_{1A} receptor agonists might be useful

- "for the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events" in paragraph [0010];
- to produce "neuroprotective, anxiolytic-and antidepressant-like effects" (see paragraph [0012]);
- as "broad spectrum antiemetic agents" (see paragraph [0013];
- "in the treatment of cognitive impairment in Alzheimer's disease, Parkinson's disease or senile dementia"(see paragraph [0015];
- "in the treatment of depression" (see paragraph [0016]; and
- in reversing "neuroleptic-induced catalepsy in rodents, which mimic movement impairments observed in Parkinson's disease" (see paragraph [0017].

The patent in suit mentions the 5-HT_{1A} receptor in connection with bipolar disorders in paragraphs [0022] and [0028]

In paragraph [0022] of the patent in suit it is stated that bipolar disorder was a "disorder of the central nervous system associated with the 5-HT_{1A} receptor subtype, and more precisely bipolar disorders as defined in the claims". This statement does not refer to any prior art. Moreover, as respondent 7 remarked, a corresponding statement is missing in the application as filed (see document (D17), page 15, lines 5-9). The same applies to the reference to documents (D1) and (D2) in paragraphs [0020] and [0021] of the patent in suit (see (D17), page 15, lines 4-5).

Paragraph [0028] corresponds to (D17), page 16, line 23, to page 17, line 2. The paragraph reads as follows:

"The potent, partial 5-HT_{1A} receptor agonist in the present invention is useful for various disorders of the central nervous system associated with the 5-HT_{1A} receptor subtype that induces bipolar disorders, such as bipolar I disorder with most recent hypomanic, manic, mixed, depressed or unspecified episode; bipolar II disorder with recurrent major depressive episodes with hypomanic episodes, and cyclothymic disorder."

4.4.4 The prior art cited in paragraphs [0012] to [0017] does not concern bipolar disorders.

Both paragraphs [0022] and [0028] provide mere statements; the patent does not support these by reference to any evidence or conclusive line of argument rendering the general suitability of 5-HT_{1A}

receptor agonists for the treatment of bipolar disorders plausible.

4.4.5 Therefore, the sections of the patent as disclosed at its filing date do not render the suitability of any of the compounds of formula (1) for the treatment of any type of bipolar disorder plausible. Nor do they provide the information that there is a clear relationship between 5-HT_{1A} receptor agonism and the suitability for the treatment of bipolar disorder.

4.5 The common general knowledge

4.5.1 According to the established jurisprudence of the Boards of Appeal, common general knowledge is represented by basic handbooks and textbooks on the subject in question; it does not normally include patent literature and scientific articles (see T 766/91 of 29 September 1993, point 8.2 of the reasons; T 1253/04 of 7 June 2005, point 10 of the reason).

4.5.2 The appellant argued that documents (D2), (D8), (D43) to (D45) and (D47) reflected the common general knowledge and that these documents showed that there was a direct relationship between 5-HT_{1A} agonism and the suitability of a drug for the treatment of bipolar disorders.

The respondents argued that theses documents were not basic handbooks and textbooks and thus insufficient as evidence that their disclosure reflected the common general knowledge.

Document (D2) is the publication of a patent application. Document (D8) is a postgraduate medicine

special report. Documents (D43) to (D45) and (D47) are articles published in scientific journals.

As is apparent from T 1253/04 cited above, these documents do not generally reflect the common general knowledge. The appellant did not provide any argument why, in the present case, such documents could exceptionally be regarded as common general knowledge. Nor is it apparent to the board that the field of bipolar disorder treatment is such a new field of research that common general knowledge is solely reflected in patent documents and scientific articles.

4.5.3 For these reasons, there is no evidence on file showing that the person skilled in the art was in the possession of common general knowledge at the filing date of the patent in suit which, together with the disclosure of the application as filed, led to the direct and unambiguous conclusion that 5-HT_{1A} agonists in general, or any of the compounds of formula (1) in particular, were useful in the treatment of any type of bipolar disorder.

4.6 Hence, the application as filed in combination with the common knowledge at the filing date did not disclose the suitability of any of the compounds of formula (1) in the treatment of any type of bipolar disorder. Consequently, the minimum requirements set out in T 609/02 for taking into account post-published evidence are not met.

4.7 Therefore, grounds under Article 100(b) EPC prejudice the maintenance of the patent on the basis of the main request.

5. Auxiliary requests

The auxiliary requests likewise cover the therapeutic use of the compounds of formula (1) against bipolar disorders (see under point VI above). The phrase "wherein the depressive symptoms are reduced" inserted into each of the claims 1 of the eighth to eleventh auxiliary requests is a comment on the mechanism of action, and not a feature qualifying the therapeutic use specified in these claims.

Hence, the auxiliary requests share the fate of the main request.

6. As grounds under Article 100(b) EPC (corresponding to a deficiency under Article 83 EPC) prejudice the maintenance of the patent based on any of the present requests, the condition under which the appellant requested remittal of the case is not met. Hence, the board did not have to decide on this request.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated