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**Datasheet for the decision  
of 8 July 2014**

**Case Number:** T 0801/10 - 3.3.01

**Application Number:** 05023971.4

**Publication Number:** 1621198

**IPC:** A61K31/496, A61K45/06,  
A61P25/18, A61P25/28

**Language of the proceedings:** EN

**Title of invention:**  
Substituted carbostyryl derivatives as 5-HT 1A receptor  
subtype agonists

**Patent Proprietor:**  
OTSUKA PHARMACEUTICAL CO., LTD.

**Opponents:**  
Teva Pharmaceutical Industries Ltd.  
STADA Arzneimittel AG

**Headword:**  
Use of aripiprazole/OTSUKA

**Relevant legal provisions:**  
EPC 1973 Art. 100(b)  
RPBA Art. 12(4), 13(1)

**Keyword:**  
Main, first auxiliary requests: lack of sufficiency of  
disclosure of purpose claimed

**Decisions cited:**  
T 0609/02, T 0433/05, T 0801/06



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Case Number: T 0801/10 - 3.3.01

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.01**  
**of 8 July 2014**

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**Decision under appeal:** **Interlocutory decision of the Opposition  
Division of the European Patent Office posted on  
19 February 2010 concerning maintenance of the  
European Patent No. 1621198 in amended form.**

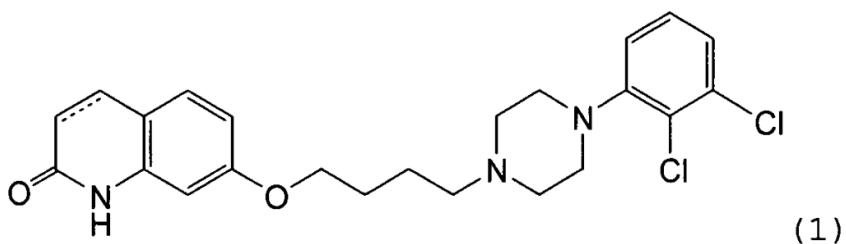
**Composition of the Board:**

**Chairman**           A. Lindner  
**Members:**         L. Seymour  
                      T. Karamanli

## Summary of Facts and Submissions

I. The present appeals lie from the interlocutory decision of the opposition division maintaining European patent No. 1 621 198 in amended form based on auxiliary request 1 filed with letter dated 17 December 2009. Claim 1 of this request reads as follows:

"1. Use of a carbostyryl compound of the formula (1):



wherein the dotted line represents a single or a double bond, or a pharmaceutically acceptable salt or solvate thereof, for the production of a medicament for the treatment of disorders of the central nervous system associated with 5-HT<sub>1A</sub> receptor subtype, which disorder

(i) is selected from cognitive impairment caused by treatment-resistant schizophrenia, cognitive impairment caused by inveterate schizophrenia, or cognitive impairment caused by chronic schizophrenia,  
and

(ii) fails to respond to

(a) 1-3 typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine,  
and

(b) one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride."

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

- (1) EP-A-0 367 141
- (2) J A Lieberman, J. Clin. Psychiatry, 1996, 57(suppl. 11), 68-71
- (6) M J Millan, J. Pharmacol. Exp. Therap., 2000, 295(3), 853-861
- (7) R S E Keefe et al., Schizophr. Bull., 1999, 25(2), 201 - 222
- (8) Affidavit of Alexander Rudolf Cools, dated 25 January 2008
- (9) A R Saha et al., Schizophr. Res., 1999, 36(1-3), 295
- (23) J M Kane, J. Clin. Psychiatry, 2007, 68(2), 213-223
- (24) D W Heinrichs et al., Schizophr. Bull., 1984, 10(3), 388-398
- (25) R S Kern et al., Psychopharmacol., 2006, 187, 312-320
- (28) S Jordan et al., Eur. J. Pharmacol., 2004, 483, 45-53

- (29) C U Correll, *J. Clin. Psychiatry*, 2008, 69  
(suppl. 4), 26-36
- (30) M J Cuesta et al., *Schizophr. Res.*, 1 March 2001,  
48, 17-28
- (31) PS Goldman-Rakic et al., *Brain Res. Rev.*, 2000,  
31, 295-301
- (32) H Y Meltzer et al., *Prog. Neuro-Psychopharm. Biol.  
Psych.*, 2003, 27, 1159-1172
- (33) A. Abi-Dargham, *World Psychiatry*, 2:3 - October  
2003, 166-171
- (34) A Newman-Tancredi, *Curr. Opin. Investig. Drugs*,  
2010, 11(7), 802-812
- (35) Affidavit of Bryan L. Roth, dated 23 May 2011
- (36) C P Lawler et al., *Neuropsychopharmacol.*, 1999,  
20(6), 612 - 627
- (37) N Iqbal, *Jap. J. Clin. Psychopharmacol.*, 2006,  
9(12), 2503-2511, and English translation of  
excerpts thereof
- (38) A Farah, *Prim. Care Companion J. Clin. Psychiatry*,  
2005, 7, 268-274
- (39) A Newman-Tancredi et al., *Curr. Opin. Investig.  
Drugs*, 2007, 8(7), 539-554
- (40) Center for Drug Evaluation and Research,  
Application Number 21-436, Statistical Review(s),  
pages 1-3, 20-22

III. In the decision under appeal, the opposition division considered that, taking into consideration the amendments made in auxiliary request 1, the patent and the invention to which it related met the requirements of the EPC.

In particular, the opposition division was of the opinion that the invention was sufficiently disclosed to be put into practice, in the sense that the skilled person knew which compound to use and which diseases to treat.

Furthermore, the opposition division considered the claimed subject-matter to be novel, since a subgroup of patients failing to respond to both typical antipsychotic drugs (TADs) and atypical antipsychotic drugs (AADs) was not disclosed in document (2).

With respect to the issue of inventive step, the opposition division identified document (9) as representing the closest prior art, which related to the treatment of relapsing hospitalised schizophrenic patients. An inventive step was recognised because there was no pointer in the prior art that aripiprazole would also be efficient in schizophrenic patients resistant to other AADs, as had been demonstrated in post-published document (23).

IV. Opponents 1 and 2 (appellants I and II) each lodged an appeal against this decision.

V. With its reply of 18 February 2011, the respondent (patentee) filed documents (28) to (34). This was followed by document (35) with letter of 27 May 2011,

and documents (36) to (39) with letter of 16 January 2014.

- VI. In a communication sent as annex to the summons to oral proceedings, the board *inter alia* noted that the question of whether document (23) could be seen as providing support for a successful treatment of cognitive impairment as expressed in the present claims should be discussed under the heading of Article 100(b) EPC 1973 rather than Article 56 EPC 1973. In addition, attention was drawn to the fact that the admissibility of the large number of additional documents filed during the written appeal proceedings might have to be discussed.
- VII. With letter of 6 June 2014, the respondent filed an auxiliary request.
- VIII. Oral proceedings were held before the board on 8 July 2014.

During the course of the oral proceedings, the respondent replaced its auxiliary request filed with letter of 6 June 2014 with a new auxiliary request. The newly filed claim 1 differs from claim 1 of the request maintained by the opposition division (cf. above point I) with respect to feature (a), which reads as follows:

"(a) 1-2 typical antipsychotic drugs selected from chlorpromazine and haloperidol".

Additionally, the respondent submitted document (40).

- IX. The appellants' arguments, insofar as they are relevant to the present decision, may be summarised as follows:



It was submitted that the respondent's auxiliary request filed during oral proceedings before the board should not be admitted into the proceedings, since this amounted to an attempt at overcoming an objection that had been raised by appellant II in its statement of grounds of appeal. Therefore, this request could and should have been submitted earlier.

The appellants further argued that documents (28) to (39) should not be admitted, since they were predominantly post-published, and lacked pertinence. Moreover, no good reason had been given for their late filing. The same was true for document (40). Additional questions arose with respect to the latter as to whether the information provided therein had been publically available before the priority date of the patent in suit.

In contrast, document (1) should be admitted since it was acknowledged in paragraph [0002] of the patent in suit, as being the basic patent disclosing aripiprazole and its use in the treatment of schizophrenia.

Concerning the issue of sufficiency of disclosure, the appellants pointed to the fact that the claimed invention related to a use claim whereby attaining the claimed therapeutic effect in the defined patient group was a functional technical feature of the claim. Therefore, in accordance with the case law such as decision T 433/05, the patent in suit must disclose the suitability of the product for said treatment. The only experimental data provided in the patent in suit related to *in vitro* binding data for aripiprazole at 5-HT<sub>1A</sub> receptors. However, the relationship between this activity and the claimed treatment of the defined group

of cognitively impaired schizophrenic patients, not responding to both specific TADs and AADs, had not been established. The scientific literature available at the priority date of the patent in suit, as reflected in documents (2), (7) and (36), and discussed in document (8), also did not support such a link. In accordance with decision T 609/02, this fundamental defect could not be repaired by later post-published evidence disclosed in document (23). Moreover, even were document (23) to be taken into account, it could not be considered to provide a proof of the claimed effect, in particular, since there was no disclosure therein in relation to an improvement to cognition. Accordingly, the subject-matter claimed lacked sufficiency of disclosure.

- X. The respondent's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The auxiliary request filed during oral proceedings before the board should be admitted into the proceedings, since it was based on a request that had first been filed one month previously, in response to the board's communication sent as annex to the summons, and the further amendments introduced were a straightforward attempt to overcome additional formal objections raised for the first time at oral proceedings.

Concerning the admissibility of documents (28) to (39), the respondent confirmed that these were not being relied upon as post-published evidence. They had been filed in response to the statements of grounds of appeal, and as a result of a general impression arising from the written proceedings that more explanatory

information would be useful in order to provide a full picture concerning the complex mechanistic properties of aripiprazole, underlying the technical effect relied upon in the discussions on sufficiency and inventive step. In addition, it was submitted that document (35) merely provided confirmation with respect to arguments previously put forward and was to be seen as forming part of the respondent's own submissions.

Document (40) should also be admitted since it provided additional information with respect to the study explicitly referred to in document (9) and was therefore to be seen as an implicit part of the content thereof.

Finally, the respondent argued against the admission of document (1) since it had not been introduced or discussed in substance during the opposition proceedings.

In its analysis of the features claimed in claim 1 of the main request, the respondent emphasised that the disorder defined related to cognitive impairment in a group of treatment-resistant, inveterate or chronic schizophrenic patients having a treatment history of twofold resistance, characterised by the failure to respond to two types of medication selected from established groups of TADs and AADs. In other words, a third-line therapy was defined of patients suffering from a particularly severe form of schizophrenia. This was to be distinguished from the second-line therapy addressed in document (2).

As regards the issue of sufficiency of disclosure, the respondent disputed the analysis put forward by the appellants:

According to decision T 609/02, *in vitro* data could be used for establishing suitability of a compound for treating a disease, provided that a definite link had been established between the ingredient and the mechanism allegedly involved in the disease state. Similarly, decisions T 801/06 and T 433/05 respectively referred to proof of suitability by means of "any kind of data as long as they clearly and unambiguously reflect the therapeutic effect" and "some information to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease".

In the present case, the required standard of proof had been provided in the patent in suit. Thus, in paragraphs [0006] and [0007], the known binding affinities of aripiprazole with various receptors was disclosed, including its antagonistic activity at postsynaptic D<sub>2</sub> receptors. Moreover, the patent in suit provided the first disclosure that aripiprazole displayed 5-HT<sub>1A</sub> receptor partial agonistic action. A link had thus been established to the antipsychotic drug clozapine, since this was known to exhibit a similar pattern of combined D<sub>2</sub> receptor antagonism and 5-HT<sub>1A</sub> receptor agonism, and to be effective against cognitive impairment in treatment-resistant schizophrenics. Ample citations to this effect had been provided in the patent in suit. Moreover, additional prior art, such as document (6), confirmed the expectation that further ligands having dual affinity as 5-HT<sub>1A</sub> and D<sub>2</sub> receptor ligands would exhibit a similar therapeutic profile to clozapine. Therefore, the additional *in vitro* data provided in the patent in suit rendered it plausible, for the first time, that

aripiprazole would, analogously to clozapine, be useful in the treatment of cognitive impairment in patients that were non-responsive to certain other medication as claimed.

It could therefore be concluded, based on the information disclosed in the patent in suit, in combination with common general knowledge, that sufficient information had been provided to allow a well-founded conclusion as to the suitability of aripiprazole in the treatment of the claimed disorder. This was confirmed in the affidavit of Bryan L. Roth (document (35)). The requirements of sufficiency of disclosure were therefore fulfilled.

The effect relied upon had furthermore been proven by means of post-published document (23), which reported the beneficial effects of aripiprazole as a third-line therapy, as evaluated using the quality of life scale. From document (24), it could be seen that this 21-item scale summed up a multitude of aspects of schizophrenia, including in the dimensions of cognition as a core element, as particularly reflected by items 20 and 21 (empathy and emotional interaction).

The respondent also referred to post-published document (25) in this context as confirming the suitability of aripiprazole in improving cognitive functions.

The respondent did not advance any additional arguments with respect to the auxiliary request.

- XI. Appellants I and II (opponents 1 and 2) requested that the decision under appeal be set aside and that the patent be revoked.

The respondent (patent proprietor) requested that the appeals be dismissed or, alternatively, that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the first auxiliary request filed during the oral proceedings of 8 July 2014.

XII. At the end of the oral proceedings, the decision of the board was announced.

### **Reasons for the Decision**

1. The appeals are admissible.
2. *Admission of the respondent's auxiliary request*

The auxiliary request submitted during oral proceedings before the board was based on an auxiliary request filed with letter of 6 June 2014 (see above point VII), that is, one month prior to oral proceedings. The amendments undertaken with respect to the request maintained by the opposition division were straightforward. They did not result in a change in the nature of the debate and could be readily dealt with within the time available. The additional amendments introduced at oral proceedings before the board merely consisted in minor amendments in the wording of claim 1 and the deletion of a dependent claim, in direct response to formal objections raised for the first time during the oral proceedings.

Under these circumstances, the board, exercising its discretion under Article 13(1) of the Rules of

Procedure of the Boards of Appeal (RPBA), decided to admit this request into the proceedings.

3. *Admission of documents (1), and (28) to (40)*

3.1 *Documents (1) and (40)*

Document (1) was cited by appellant II as part of its submissions on novelty (see statement of grounds of appeal, point 1). Document (40) was submitted by the respondent during the course of discussions on novelty at oral proceedings before the board. The board decided to admit document (1), but not document (40). However, since the issue of novelty turned out not to be relevant for the outcome of the present appeal, the reasons for these decisions need not be discussed further (see below points 4 to 6).

3.2 *Documents (28) to (39)*

These documents were filed by the respondent with its reply of 18 February 2011 to the statements of grounds of appeal (documents (28) to (34)), with its letter of 27 May 2011 (document (35)), and with its letter of 16 January 2014 (documents (36) to (39)).

3.2.1 With respect to the affidavit of Bryan L. Roth (document (35)), the respondent argued that the content thereof was to be seen as forming part of its own submissions, and it merely reiterated arguments put forward previously. Having ascertained that this was the case, the board saw no reason not to admit said document.

3.2.2 Prior art document (36) provides an overview of the receptor binding profile of aripiprazole, and had

already been cited and discussed in the affidavit numbered as document (8) (see point 13), submitted by appellant I with its notice of opposition. As conceded by appellant I, the content of this document had therefore effectively already been introduced into the proceedings. Consequently, the board had no objections to admitting this document into the proceedings.

3.2.3 With respect to the documents (28) to (30), (32) to (34), and (37) to (39), which are all published after the effective priority date of the patent in suit, the respondent confirmed that these were not being relied upon as post-published evidence. According to the respondent, their relevance lay in providing a full picture concerning complex mechanistic properties of aripiprazole, underlying the technical effect relied upon in the discussions on sufficiency and inventive step. However, this argument is not considered to be convincing, in view of the fact that, for the purposes of assessing sufficiency and inventive step, the relevant knowledge of the skilled person is that available at the effective date of the patent in suit (priority date of 29 January 2001). Mechanistic hypotheses based on knowledge obtained after the effective date of the patent in suit cannot be used to establish whether an effect was plausible at or before that date.

Moreover, although arguing that the filing of these documents was to be seen as a direct response to the statements of grounds of appeal, the respondent could not point to any new arguments or aspects raised therein. Therefore, the board concludes that, if considered necessary, said documents could and should have been submitted at an earlier stage of the proceedings.



Finally, document (31) is a general review article, which does not specifically relate to aripiprazole. Although published prior to the effective date of the patent in suit, the information contained therein was discussed in the context of the analysis of the remaining post-published documents considered above. Therefore, the same objections apply with respect to the relevance of this document and the timing of its filing.

Consequently, the board decided not to admit documents (28) to (34) and (37) to (39) into the proceedings (Articles 12(4) and 13(1) RPBA).

4. *Main request - Sufficiency of disclosure  
(Article 100(b) EPC 1973)*

4.1 It is well-established case law with regard to medical use claims, such as the present, wherein attaining the claimed therapeutic effect is a functional technical feature of the claim, that, in order to meet the requirements of sufficiency of disclosure, the patent in suit as a whole, in the light of common general knowledge, must disclose the suitability of the product to be manufactured for the claimed therapeutic application. In this respect, *in vitro* data may be useful for establishing suitability provided that the observed effect directly and unambiguously reflects such a therapeutic application (see e.g. decisions T 609/02, point 9 of Reasons; T 433/05, point 28 of Reasons; T 801/06, points 25 and 28 of Reasons).

4.2 Present claim 1 relates to a second (further) medical use of carbostyryl compounds of formula (1) (cf. above point I).

The medical use concerns the treatment of cognitive impairment caused by treatment-resistant, inveterate or chronic schizophrenia, in a particular patient group that fails to respond to

- (a) 1-3 typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and
- (b) one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

4.3 The terminology used in this claim, as understood at the priority date of the patent in suit, may be elucidated as follows, with reference to the patent specification, and in addition to the cited documents (2), (6), (7), and (36):

4.3.1 Formula (1) encompasses two known compounds.

The compound wherein the dotted line represents a single bond is known as aripiprazole or OPC-14597 (see patent in suit, paragraphs [0002], [0036] and [0043]; document (36), title).

4.3.2 Schizophrenia was known to be characterised by a diversity of symptoms, including positive symptoms (e.g. hallucinations, delusions), negative symptoms (e.g. amotivation, apathy, alogia, flattened affect, social withdrawal), and cognitive impairment (e.g. in attention, learning and memory, visuospatial analysis, verbal fluency, fine motor function, intelligence) (see patent in suit, page 4, lines 13, 30 to 33, 45 to 49; document (2), Table 4; document (6), page 853, first sentence of main text; document (7), page 201, first two sentences of main text, and page 210,

Table 4; document (36), page 612, first sentence of main text).

It is noted that any potential differences between the terms "treatment-resistant schizophrenia", "inveterate schizophrenia" and "chronic schizophrenia" did not play a role during the present appeal proceedings, in view of the fact that a twofold resistance was specifically defined in item (ii) of claim 1.

4.3.3 The first type of resistance, defined in item (ii)(a) of claim 1, is characterised by the failure to respond to specific typical antipsychotics (TADs). This class of drugs, also referred to as first-generation or conventional antipsychotics in documents (2) and (7), respectively, was first developed in the 1950s, and known to function primarily as dopamine D<sub>2</sub> receptor antagonists, and to be effective in the treatment of positive symptoms of schizophrenia. However, these compounds produced extrapyramidal side effects (EPS), and negative and cognitive symptoms were little improved. Moreover, a significant population of resistant patients remained refractory to treatment (see patent in suit, page 4, lines 11 to 14; document (2), paragraph bridging pages 68 and 69, and page 69, first complete paragraph; document (6), page 853, right-hand column, first two sentences below abstract; document (7), page 201, right-hand column, first sentence; document (36), page 613, left-hand column, first complete paragraph).

4.3.4 The second type of resistance, defined in item (ii)(b) of claim 1, is characterised by the failure to respond to specific atypical antipsychotics (AADs). This term is used to designate the next generation of drugs developed in order to address the disadvantages of

TADs, starting with the introduction of clozapine in 1990, and followed, for example, by risperidone, olanzapine, quetiapine, and aripiprazole (see e.g. document (2), page 69).

Concerning their mechanism of action, AADs were characterised by having a diverse range of further receptor activities in addition to the D<sub>2</sub>-receptor blocking activities observed in TADs (see document (2), page 69, Table 3 and last paragraph; and also patent in suit, page 4, lines 14 to 19; document (6), page 854, right-hand column, first sentence; document (7), page 216, right-hand column, first three sentences; document (36), page 613, left-hand column, first complete paragraph, last two sentences, and following two sentences of the next paragraph).

The properties attributed to AADs are listed in Table 2 of document (2) and summarised on page 69, in the paragraph bridging the left- and right-hand columns as follows: "atypical antipsychotic drugs are regarded as having some measure of superior antipsychotic efficacy (i.e., **they are effective in some patients refractory to conventional antipsychotic drugs**, and against negative symptoms and/or neurocognitive deficits) while producing lower levels of EPS without producing sustained elevations in prolactin" (emphasis added).

- 4.4 Prior to the assessment of sufficiency of disclosure with respect to the suitability of aripiprazole for the medical indication as claimed, it must first be established what properties were attributed to aripiprazole before the priority date of the patent in suit.

Aripiprazole was known to have an atypical pharmacological profile, in that it was known to act not only as a postsynaptic dopamine D<sub>2</sub> antagonist, but also to have agonistic effect at presynaptic dopamine receptors, and to interact with a number of further receptors, such as, D<sub>3</sub> and 5-HT<sub>7</sub> (see patent in suit, paragraphs [0006] and [0007]; document (2), Table 3; document (9), second sentence; document (36), page 612, abstract).

Aripiprazole was also known to have an atypical therapeutic profile (see document (9), left-hand column; document (36), page 614, lines 14 to 17). In particular, in the study involving acutely relapsing hospitalised schizophrenic patients reported in document (9), the 30-mg dose group showed statistically significant improvement in cognition over placebo.

Finally, document (2) clearly identifies the class of AADs, including aripiprazole as listed in Table 3, as being effective in some patients refractory to TADs (see above point 4.3.4, last paragraph, excerpt emphasised in bold).

Therefore, the board, contrary to the statement in the the affidavit submitted by the respondent as document (35) (point 37, last sentence), concludes that the prior art discloses the suitability of aripiprazole in treating cognitive impairment in schizophrenic patients, and in treating patients not responding to TADs.

- 4.5 In view of the above, it remains to be decided whether, as argued by the respondent, the additional data provided for aripiprazole in the patent in suit establishes a plausible link between aripiprazole and

the medical indication as claimed, namely, the treatment of cognitive impairment in a group of schizophrenic patients that had failed to respond to two types of medication selected from established groups of TADs and AADs, designated by the respondent as being a third-line treatment.

- 4.5.1 The additional results provided in the patent in suit relate to *in vitro* data demonstrating that aripiprazole binds with high affinity and displays a potent, partial agonist activity at the 5-HT<sub>1A</sub> receptor (see patent in suit, paragraphs [0029], and [0043] to [0052]). It was not disputed by the appellants that this receptor activity had not been known before the effective date of the patent in suit, that is, before the priority date of 29 January 2001.

The respondent argued in this context that the disclosure of the 5-HT<sub>1A</sub> partial agonist activity of aripiprazole allowed parallels to be drawn, for the first time, between aripiprazole and clozapine, owing to the fact that both compounds shared this characteristic, in addition to D<sub>2</sub> receptor antagonism. This common receptor binding profile would allow the skilled person to recognise that aripiprazole, like clozapine, would potentially be suitable for treating cognitive impairment in treatment-resistant schizophrenic patients (cf. patent in suit, e.g. paragraphs [0023] to [0027]).

- 4.5.2 The board does not find this line of argumentation to be convincing for the following reasons:

It is firstly noted that there must be some doubts as to whether parallels can be drawn between aripiprazole and clozapine, since their global receptor binding

profiles, although exhibiting common aspects, also differ in others (see e.g. document (2), Table 3). According to documents (6) and (7), it is the balance in clozapine's interactions with a broad array of receptors that may account for its clinical efficacy, and not only the specific receptor binding activities highlighted by the respondent (see document (6), page 854, sentence bridging left- and right hand columns; document (7), page 216, 217, "Conclusions").

However, even were it to be accepted that, based on shared aspects of their receptor binding profile, parallels could indeed be drawn between aripiprazole and clozapine, the fact remains that there is a flaw in the respondent's chain of argumentation, since no evidence has been provided regarding the efficacy of clozapine in the medical indication as claimed, namely, in a third-line therapy of cognitive impairment in schizophrenic patients failing to respond to TADs and AADs. All the references cited in the patent in suit and by the respondent in this respect refer to treatment resistance in general (see also document (35), point 40, last sentence). As emphasised by the respondent, in particular with reference to document (2), at the priority date of the patent in suit, the term "treatment-resistance" was used to designate resistance to TADs. Therefore, the known efficacy of clozapine in treating cognitive impairment in treatment-resistant schizophrenic patients (cf. also document (7), Table 1) must also be regarded as referring to a second-line treatment of patients that had failed to respond to TADs. The respondent did not provide any evidence to the contrary, despite being challenged on this point by the appellants.

The board notes in this context that the compounds listed in item (ii) (b), namely, risperidone, olanzapine, quetiapine, and amisulpride, are themselves classed as AADs, and are generally or specifically disclosed to improve cognitive function in patients with schizophrenia (see document (7), page 216, right-hand column, first sentence; page 217, left-hand column, first paragraph; Table 1; see also document (2), Table 2). As emphasised by the respondent, the patients as defined in claim 1 as not responding to these drugs must be regarded as suffering from a particularly severe form of schizophrenia. Efficacy in a second-line treatment of cognitive impairment cannot therefore provide a sound basis for inferring the same for a third-line treatment.

Consequently, it is concluded that the disclosure in the patent in suit that aripiprazole displays 5-HT<sub>1A</sub> partial agonist activity can only be seen as providing additional knowledge with respect to its known cognitive efficacy, but does not allow a plausible link to be established between aripiprazole and the medical indication as claimed.

- 4.6 The post-published data referred to by the respondent is not considered to be pertinent:
  - 4.6.1 With respect to document (23), the respondent submitted that the patient group treated with aripiprazole corresponded to that claimed, since the patients had previously shown resistance to treatment with at least one TAD, and one AAD, namely, olanzapine or risperidone (see section entitled "Method" bridging pages 214 and 215, and Figure 1). Although the respondent acknowledged that the impact of aripiprazole on cognition had not been directly assessed, it argued,



with reference to document (24), that this had been evaluated as a core element of the quality of life scale (QLS), for which a clinically relevant improvement of 36% had been observed.

It is firstly noted with respect to the methods used to evaluate the efficacy of aripiprazole in document (23), cognition was certainly not examined as a separate aspect (see section bridging pages 215 and 216). The respondent's argument that an improvement in overall scores would necessarily entail an improvement with respect to cognition is not considered to be convincing, since it is inconsistent with its position maintained throughout the procedure, namely, that cognitive impairment in schizophrenia is a discrete disorder, separate from further symptoms (see patent in suit, paragraph [0021] and document (35), item 30). This is also reflected in the formulation of the claims, and confirmed by many of the citations in the procedure (see citations in the first paragraph of above point 4.3.2).

Regarding the QLS method referred to by the respondent, it is noted that this contains twenty-one items, grouped into four categories (see document (24), Table 1). None of these items correspond to the accepted criteria used to measure cognition (cf. above point 4.3.2). The respondent pointed to the following passage in document (24) to support its position that cognitive improvements had been evaluated as part of the QLS (page 390, middle column, second paragraph): "The Intrapsychic Foundations items (13, 14, 15, 16, 17, 20, 21) elicit clinical judgments about intrapsychic elements in the dimensions of cognition, conation, and affectivity often seen as near the core of the schizophrenic deficit. Hence, the patient's

sense of purpose, motivation, curiosity, empathy, ability to experience pleasure, and emotional interaction are assessed." It becomes clear, in particular from the second sentence cited, that cognitive aspects are not directly evaluated in the category "Intrapsychic Foundations", but at best indirectly, in so far as they influence the intrapsychic items listed. It is therefore not considered to be convincing that changes in cognitive impairment were measured as part of the QLS.

Therefore, in view of the fact that changes in cognitive impairment, if measured at all, were not evaluated as a separate aspect, it is concluded that document (23) cannot serve to confirm the efficacy of aripiprazole in the claimed treatment.

4.6.2 Document (25) reports the findings from an open-label study suggesting that the neurocognitive effects of aripiprazole are at least as good as those of olanzapine. Therefore, this document merely serves to confirm the known activity disclosed in document (9).

4.7 Having regard to the above considerations, the board concludes that the invention as defined in claim 1 of the main request fails for lack of sufficiency of disclosure.

5. *Auxiliary request - Sufficiency of disclosure*  
(Article 100(b) EPC 1973)

The auxiliary request mainly differs from the main request in the deletion in claim 1 of perphenazine from item (ii)(a) (cf. above point VIII). The respondent did not advance any additional arguments in favour of sufficiency of disclosure with regard to this request.

Indeed, the assessment presented above under point 4 applies to this request *mutatis mutandis*.

Consequently, it is concluded that sufficiency of disclosure also fails with regard to the invention as defined in claim 1 of the auxiliary request.

6. Given the lack of sufficiency with regard to both of the respondent's requests, other issues, namely, novelty and inventive step, which had been addressed at the oral proceedings before the board, are not material to the outcome of the appeal, and are thus not considered further in this decision.

## Order

### For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated