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Application Number: 98957382.9
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Language of the proceedings: EN
Title of invention: Treatment of schizophrenia with ampakines and neuroleptics
Patent Proprietors: CORTEX PHARMACEUTICALS, INC. The Regents of The University of California
Opponent: ELI LILLY AND COMPANY GLAXO GROUP LIMITED
Headword: Ampakine combinations with atypical antipsychotics/CORTEX
Relevant legal provisions: EPC Art. 56 RPBA Art. 15(3)
Keyword: "Oral proceedings - non attendance of appellants and respondents"
"Main and auxiliary requests: inventive step (no) - improvement not credible, obvious modification"
Decisions cited: 

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Catchword:
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Case Number: T 0044/09 - 3.3.01

DECISION
of the Technical Board of Appeal 3.3.01
of 30 April 2013

Appellant 1: ELI LILLY AND COMPANY
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Composition of the Board:

Chairman: C. M. Radke
Members: G. Seufert
L. Bühler
Summary of Facts and Submissions

I. Appellants 1 and 2 (opponents 1 and 2) lodged an appeal against the interlocutory decision of the opposition division dispatched on 13 November 2008 on the amended form in which European patent No. 1 026 950 could be maintained.

II. In this decision the following numbering will be used to refer to the documents:

(11) P. Riederer et al., Arzneimittel-Forschung, vol. 42, no. 2a, 1992, 265-268
(22) Declaration of S. A. Johnson with annexed Exhibit SAJ1 (curriculum vitae) and SAJ2
III. Notices of opposition were filed by appellants 1 and 2 requesting revocation of the patent in suit in its entirety on the grounds of lack of novelty and inventive step and insufficiency of disclosure (Articles 100(a) and (b) EPC).

IV. The decision under appeal was based on the main request filed with letter of 2 July 2007, first auxiliary request filed with letter of 30 September 2008 and second auxiliary request filed originally as first auxiliary request with letter of 6 August 2008.

The opposition division held that the feature "in a synergistically effective amount" was clear and supported by the application as filed. Accordingly, the main request was considered to comply with Article 123(2) and (3) and Article 84 EPC. However, since synergy was apparently dependent on the dose of the drugs as well as the antipsychotic drug used and the patent in suit did not contain clear guidance on the selection of the drugs that provided a synergistic effect or the determination of their respective amounts, the opposition division held that the skilled person was not able to perform the invention over the whole scope of the claims without undue burden, contrary to the requirement of Article 83 EPC. The same applied to the first auxiliary request.

The second auxiliary request was considered to comply with Articles 123(2) and (3), 84 and 83 EPC, since it no longer referred to "synergistically effective amounts". Its subject-matter was novel and involved an inventive step over document (8), which the opposition division considered to be the closest prior art, since
neither this document nor documents (1), (5) or (6) suggested the claimed combinations or provided any hint as to their synergistic effect.

V. Auxiliary request 2, which according to the decision under appeal met the requirements of the EPC, consists of 22 claims. Independent claims 1, 4, 21 and 22 read as follows:

"1. Use of a composition that comprises a first compound that enhances the stimulation of α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid ("AMPA") receptors in a subject and a second atypical antipsychotic compound for the manufacture of a medicament for the treatment of schizophrenia."

"4. A kit comprising a container containing a composition that comprises a first compound that enhances the stimulation of α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid ("AMPA") receptors in a subject and a second atypical antipsychotic compound and instructions for using the composition for treating schizophrenia in a subject."

"21. A composition that comprises a first compound that enhances the stimulation of α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid ("AMPA") receptors in a subject and a second atypical antipsychotic compound."

"22. A composition that comprises a first compound that enhances the stimulation of α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid ("AMPA") receptors in a subject and a second atypical antipsychotic compound for use as a medicament."
VI. With letter dated 4 August 2009 the respondents (patent proprietors) defended the request, which according to the decision under appeal met the requirements of the EPC, and filed an auxiliary request.

The auxiliary request differs from the main request in that in dependent claim 18 the compound "zotepine" was deleted.

VII. In a communication accompanying the summons to oral proceedings the board expressed its preliminary opinion. Concerning inventive step, the board indicated that one of the issues for discussion would be whether or not the claimed technical effect was sufficiently demonstrated by the data provided and, if so, whether or not it could support an inventive step, in view of the teaching of documents (1), (9) and (11), which seemed to indicate that treatment with a combination of an ampakine and an antipsychotic would be therapeutically beneficial.

VIII. With letters of 15 January 2013, 6 March 2013 and 3 April 2013, respectively, both the appellants and the respondents informed the board that they would not attend the oral proceedings. No further comments or observations in substance were submitted on the issues indicated in the Board's communication.

IX. The arguments provided by appellant 1, to the extent that they are relevant for the present decision, can be summarised as follows:
The respondents' definition of synergy, namely the arithmetic sum of the values obtained in rat rearing and crossing tests, was extremely simplistic and assumed a linear relationship between the measured parameter and the amount of the administered drugs. Even if this flawed definition was adopted, the anomalous and inconsistent experimental data provided in the patent in suit did not allow a proper conclusion as to the presence of a synergistic effect. Crossing as well as rearing test data for CX516 alone were highly inconsistent and consequently unreliable. Apparently, effects described as being dramatic in the patent in suit turned out not to be statistically significant. Furthermore, rearing and crossing tests led to contradictory results.

In the absence of a surprising effect, the problem to be solved starting from document (8) could only be seen in the provision of a pharmaceutical composition expected to be useful for the treatment of schizophrenia.

The combination of antipsychotics with ampakines was expected to be beneficial in the treatment of schizophrenia. This was recognised not only in document (1), but also in documents (11) and (12). The selection of atypical antipsychotics was obvious in view of the fact that they showed lower incidence of side effects and increased therapeutic efficacy.

X. The arguments provided by appellant 2, to the extent that they are relevant for the present decision, can be summarised as follows:
The introduction of the word "atypical" into claim 1 rendered the claim unclear. The characterisation of the second drug as atypical implied that the first drug, i.e. the ampakine, must also be atypical. Ampakines, however, were not necessarily atypical.

Document (8), disclosing the use of combinations of an ampakine with the typical antipsychotics haloperidol and fluphenazine in a model for schizophrenia, was the closest prior art. No improvement of the claimed combinations over those of document (8) had been shown. This was apparent by comparing row 1 in table 1 of the patent in suit referring to a prior art combination, namely ampakine plus haloperidol, with rows 4 and 5 referring to claimed combinations, namely ampakine plus an atypical antipsychotic. Thus, the problem to be solved could only be seen in the provision of an alternative combination for the treatment of schizophrenia. The use of atypical antipsychotics was obvious, because there were only two types of antipsychotic drugs, typical and atypical, and it was well known that atypical antipsychotics had fewer side effects. They were therefore the more logical choice. Furthermore, it was obvious to replace an antipsychotic known to have dopamine receptor activity, with other antipsychotics having the same activity. Both typical as well as atypical antipsychotics were known to exhibit dopamine receptor activity.

XI. The arguments provided by the respondents, to the extent that they are relevant for the present decision, can be summarised as follows:
Clarity was not open for debate, because the feature "atypical" in claim 1 of the main request was already present in claim 18 of the patent as granted.

The respondents' definition of synergy was consistent with the generally accepted view as expressed in professional textbooks. The synergistic effect was properly demonstrated over the whole scope of the claims by the data presented in the patent in suit and in document (22). The opposition division had therefore correctly defined the problem to be solved as the provision of a combination therapy for the treatment of schizophrenia providing an effect which is higher than the sum of the effects provided by each single drug alone. Appellant 1's criticism concerning the experimental data presented in the patent in suit, which being based on animal behaviour was inherently noisy and variable, merely showed that it did not understand the experimental paradigm or the substance of the data. Appellant 2 in defining the technical problem as a mere alternative did not properly consider the effect of the difference between the disclosure of document (8) and the claimed subject-matter.

The claimed subject-matter was inventive, because the synergistic effect of the claimed combinations was neither obvious from document (8), which disclosed an additive effect for a combination of an ampakine with a typical antipsychotic, nor from any other documents.

XII. The appellants requested in writing that the decision under appeal be set aside and the patent be revoked.
XIII. The respondents requested in writing that the appeal be dismissed or, alternatively, that the patent be maintained on the basis of the auxiliary request filed with letter of 4 August 2009.

XIV. At the end of the oral proceedings, which took place as scheduled on 30 April 2013 in the absence of the parties, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Non-appearance at oral proceedings before the Board.

2.1 As announced (see point VIII above) neither the appellants nor the respondents were present at the oral proceedings to which they had been duly summoned.

2.2 According to Rule 115(2) EPC, oral proceedings may continue in the absence of a duly summoned party that does not appear. According to Article 15(3) RPBA, the Board is not obliged to delay any step in the proceedings, including its decision, by reasons only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case. In deciding not to attend oral proceedings the appellants and the respondents chose not to avail themselves of the opportunity to orally present their observations and comments but instead to rely solely on their written case.
2.3 The respondents were informed of the objections raised against the patent in suit and the issues that had to be discussed at the oral proceedings with the board's communication annexed to the summons to oral proceedings. Therefore, they were well aware that during the oral proceedings the board would consider these objections and issues, to which they had chosen not to reply in substance during the written proceedings. Hence, the board concludes that the respondents had an opportunity to present their observations and comments on the grounds and evidence on which the board's decision, arrived at during oral proceedings, is based. The board was, therefore, in a position to take a final decision at the oral proceedings despite the absence of the duly summoned respondents.

Main request (second auxiliary request which according to the contested decision meets the requirements of the EPC)

3. Clarity

3.1 Appellant 2 raised an objection under Article 84 EPC against claim 1 of the respondents' main request arguing that the introduction of the term "atypical" rendered it unclear. The board has doubts as to whether appellant 2's interpretation of claim 1 reflects the skilled person's understanding of that claim. However, in view of the negative outcome with respect to inventive step (see point 4 below), the board can limit itself to the consideration of this requirement.
4. Inventive step

4.1 Claim 1 of the main request is directed to the use of a combination of an ampakine and an atypical antipsychotic in the manufacture of a medicament for the treatment of schizophrenia.

4.2 In the contested decision, the opposition division considered document (8) as the closest prior art. This was not disputed by the parties and the board sees no reason to deviate from the opposition division's finding. Accordingly, the board takes document (8) as the starting point for the assessment of inventive step.

This document describes a combination of compound CX516 (10 mg/kg) with either haloperidol (0.12 mg/kg) or fluphenazine (0.2 mg/kg). CX516 is an ampakine according to claim 19 of the present main request (see also paragraph [0058] of the patent in suit). Haloperidol and fluphenazine belong to the class of typical antipsychotics. According to document (8) the combinations were shown to antagonise in an additive manner methamphetamine (hereinafter METH)-induced behavioural hyperactivity (locomotion and rearing) in rats - an animal model of schizophrenia.

4.3 Starting from document (8), the opposition division defined the technical problem to be solved by the present invention as "the provision of a combination therapy for the treatment of schizophrenia providing an effect which is higher than the sum of the effects provided by the single drugs alone", i.e. a synergistic effect. The respondents agreed with the opposition division's formulation of the technical problem and
referred to the data present in the patent in suit and in document (22) in support of the asserted synergistic effect.

4.4 In examples 2 and 3 of the patent in suit the influence of combinations of ampakines and antipsychotics on the enhanced locomotor and stereotype rearing behaviour (hereinafter crossing and rearing tests) induced by amphetamines was measured in groups of rats, which had received either METH alone, METH + CX516, METH + clozapine, risperidone, haloperidol or fluphenazine or METH + CX516 + clozapine, risperidone, haloperidol or fluphenazine. The percent reduction in rearing and crossing was measured and the results are summarised in table 1 of the patent in suit:

<table>
<thead>
<tr>
<th>Antipsychotic dose in mg/kg</th>
<th>Activity</th>
<th>Antipsychotic alone</th>
<th>CX516 alone</th>
<th>CX516 plus Antipsychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (0.05)</td>
<td>Crossing</td>
<td>16</td>
<td>22</td>
<td>71</td>
</tr>
<tr>
<td>Haloperidol (0.12)</td>
<td>Crossing</td>
<td>89</td>
<td>90</td>
<td>84</td>
</tr>
<tr>
<td>Fluphenazine (0.2)</td>
<td>Crossing</td>
<td>57</td>
<td>47</td>
<td>70</td>
</tr>
<tr>
<td>Clozapine (1)</td>
<td>Crossing</td>
<td>-5</td>
<td>34</td>
<td>80</td>
</tr>
<tr>
<td>Risperidone (0.1)</td>
<td>Crossing</td>
<td>81</td>
<td>28</td>
<td>122</td>
</tr>
</tbody>
</table>

1 The dose of CX516 was 10 mg/kg in all experiments except 50 mg/kg in this case.

Haloperidol or fluphenazine are typical antipsychotics, clozapine and risperidone fall within the definition of atypical antipsychotics. According to the patent in suit clozapine alone had allegedly no effect on METH-induced rearing (-5%), whereas CX516 caused a modest, but statistically insignificant (34%) antagonism of METH-induced rearing. The combination of clozapine and CX516 allegedly acted synergistically and greatly reduced METH-induced rearing (90%) (table 1, row 4 and
paragraph [0096]). Similar effects on METH-induced rearing were allegedly observed for risperidone (table 1, row 5 and paragraph [0097]).

4.5 Appellant 1 and the respondents were divided as to the correct definition of synergy. According to the respondents, the additive effect was simply the arithmetic sum of the effects for each of the individual compounds alone and synergy was present, if the combined effect was greater than this sum:

\[
\text{The effect of } (X \text{ mg of } A + Y \text{ mg of } B) > \text{The effect of } X \text{ mg of } A + \text{The effect of } Y \text{ mg of } B
\]

Appellant 1 considered this to be an overly simplistic approach. In its opinion, synergy occurs when the effect of combining two drugs is greater than the expected effect:

\[
\text{The effect of } (X \text{ mg of } A + Y \text{ mg of } B) > \text{The effect of } \left( X \text{ mg of } A + \text{an amount of } A \text{ which is equivalent to } Y \text{ mg of } B \right)
\]

4.6 In the present case it is, however, not necessary to decide on this issue, because even adopting the respondents' definition, the results in table 1 of the patent in suit are such that they cannot be relied on as adequate support for the alleged synergistic effect.

4.6.1 Firstly, the board notes that the data observed when CX516 (10mg/kg) is administered alone are highly variable. In the crossing test, the results range from a 47% reduction to no reduction to a 32% increase
Similar effects can be observed in the data for the rearing test ranging from a 28% to a 43% reduction (table 1, column 4, rows 2-5). Furthermore, a three times higher amount of CX516 alone causes the lowest effect, i.e. only a 23% reduction in the rearing and a 10% reduction in the crossing test. In view of these variations in the results for CX516 alone, no proper conclusion as to the presence of a synergistic effect can be drawn purely from table 1 of the patent in suit without some statistical considerations taking this variability into account. This can be illustrated by the following considerations: the rearing test data for risperidone (table 1, row 5) show a 51% reduction for risperidone alone, an (unusually low) 28% reduction for CX516 alone and a 102% (sic) reduction for the combination of risperidone and CX516. According to the respondents this example demonstrates a synergistic effect for the combination of risperidone and CX516, since the observed effect (102%) is higher than the sum of the effect of each of the compounds (78%). However, in view of the fact that the value for CX516 alone varies considerably (between 28% and 43% reduction in the rearing test in table 1), a proper conclusion as to whether the observed effect is in fact the result of synergy and not merely an accidental result due to the variability of the results of CX516 alone cannot be drawn. Similar considerations apply to the crossing test data for risperidone. Applying the respondents' concept that synergy is present if the combined effect of the two compounds is greater than the sum of the effects of each compound given alone, the results in table 1 allegedly show synergy (a 43% reduction for risperidone alone plus an (unusual) 0% reduction for
CX516 alone compared to 54% for risperidone + CX516). However, in view of the fact that the result for the same amount of CX516 can vary considerable (from 47% reduction to 32% increase), no conclusion as to the presence of a synergistic effect can be drawn without duly taking this variability into account. No explanation is offered in the patent in suit with respect to the variability of the data for CX516 alone, let alone an explanation as to how this variability has been taken into account in establishing the presence of synergy. Nor is such an explanation available from document (7), the corresponding post-published scientific article by the present inventors, which describes the same experiments (document (7), page 393, right column, last paragraph - page 394, right column, line 19, fig. 2).

4.6.2 The respondents argued in their written observations that animal behaviour data are inherently noisy and variable, and cannot be viewed in the same context as enzyme reactions used to produce rate constants which can usually be given a fairly narrow confidence. In their opinion synergy was clearly demonstrated, when viewed as a simple graph of average results.

4.6.3 However, in these circumstances, it is of the utmost importance to eliminate, as much as possible, the influence of noise and variability before any conclusion as to an effect can be drawn. In general, this requires a detailed statistical analysis in order to avoid conclusions being based on mere accidentally observed results. The patent in suit makes some statements with respect to statistical significance of the rearing results for clozapine and risperidone in
paragraphs [0096] and [0097] of the patent in suit. However, these statistical considerations are based on the data summarised in row 4 and 5 of table 1 (a -5\% and 34\% reduction vs. a 90\% reduction and a 51\% and 28\% reduction vs. a 102\% reduction). The variability in the results of CX516 alone (28\% to 43\% reduction) is not taken into account. The same applies to figure 1 and 2 of the patent in suit, which are graphical representations of the rearing results for clozapine as described in table 1 (paragraph [0096] of the patent in suit).

4.6.4 Secondly, the board notes that according to table 1 of the patent in suit clozapine and CX516 on their own allegedly produce an increase in crossing of -6\% for clozapine and -32\% for CX516. For the combination of both drugs a 35\% reduction in crossing is observed. Applying the respondents' definition of synergy, this clearly demonstrates a synergistic effect. However, according to document (7), this rather dramatic result is considered not to be statistically significant (document (7), table 1, footnote g). As pointed out by appellant 1, the statistical analysis in document (7) is confined to the comparison of the combination of CX516 and an antipsychotic with either the antipsychotic alone or CX516 alone. The statement "not significant" in footnote g) therefore means that the effect observed for the combination is not significantly greater than the effect of either drug alone. In other words no effect, let alone a synergistic effect has been demonstrated. The same applies to the data for risperidone which, applying the respondents' definition, show a synergistic effect in the crossing test, i.e. the combined effect (a 54\%
reduction) is higher than the arithmetic sum of the effects of each of the compounds alone (a 43% plus 0% reduction), while according to document (7) the results are not statistically relevant. No explanations were provided by the respondents with respect to this issue.

4.6.5 In this context, it should also be noted that according to the patent in suit the crossing and rearing test are both considered to be reliable indicators of the effect of a drug on schizophrenia (see page 21, lines 39-48). According to the respondents, the rearing test data show synergy for a combination of CX516 with either clozapine or risperidone. As already mentioned in point 4.6.4 above, the crossing test data for the same combinations are statistically not significant. Thus, taken on their own, the rearing test points to synergy, while the crossing test, in contrast, does not support even an additive effect. The respondents did not provide any evidence, from which it can be deduced that the results observed in the rearing test are more reliable than those in the crossing test in predicting the effects of a drug or drug combination in the treatment of schizophrenia. Thus, no conclusion as to whether or not the claimed combinations provide a synergistic effect in the treatment of schizophrenia can be properly drawn from the observed contradictory results.

4.7 In support of the alleged effect, the respondents also relied on experimental data provided in document (22) and in particular on exhibit SAJ2.
Document (22) is a declaration by Mr. Johnson, one of the inventors of the patent, stating that the combination of CX516 with clozapine as well as the combinations of CX691, CX717 or CX731 with clozapine or olanzapine show synergy in the METH-induced rearing test. Exhibit SAJ2 consists of a single table describing the results of the METH-induced rearing test for the latter combinations. For details of the methodology used in obtaining the above results SAJ2 merely refers to document (7).

However, document (22) offers no explanation with respect to the observed variability for CX516 alone as observed in table 1 of the patent in suit and its significance with respect to a reliable conclusion of synergy in the treatment of schizophrenia. Nor are the results of the crossing test addressed therein. Furthermore, the table in SAJ2 does not contain any information as to whether or not the observed results are even statistically significant. As can be seen from point 4.6.4 above, an effect which appears to be significant may turn out not to be so. Finally, no crossing test results are provided.

Document (22) therefore does not constitute appropriate evidence for the presence of a synergistic effect.

In view of the above and contrary to the opposition division's and the respondents' opinion, the board concludes that the alleged synergistic effect has not been demonstrated.

It is established jurisprudence of the boards of appeal that alleged advantageous effects, in the present case
the synergistic effect, can only be taken into account in the assessment of inventive step, if there is conclusive evidence to support them. Since in the present case the alleged effect lacks the required experimental evidence, the technical problem as defined in point 4.3 above needs to be redefined in a less ambitious way and may only be considered as the provision of a further medicament for a combination therapy in the treatment of schizophrenia.

The board has no reason to doubt that this problem was successfully solved. This was also undisputed by the appellants.

4.10 It then remains to be decided whether or not the proposed solution, namely the claimed combination of ampakines and atypical antipsychotics, is obvious in view of the prior art.

4.10.1 Schizophrenia is a mental disorder which is conventionally treated with antipsychotic drugs having dopamine D<sub>2</sub>-receptor antagonistic activity. This treatment is based on the hypothesis that excessive dopaminergic activity contributes at least to some of aspects of schizophrenia (document (1), page 127, left column, line 1 - right column, line 4). Findings prior to the priority date of the patent in suit suggested that decreased glutamatergic neurotransmission may also play a role in psychosis. This lead to the development of ampakines, which are positive modulators of AMPA-type glutamate receptors, as potentially useful drugs in the treatment of schizophrenia (document (1), page 127, right column, line 4 - 17; page 128, left column, line 10 - line 25). In view of the available evidence
it was postulated that schizophrenia reflects an imbalance in the activities of functionally antagonistic dopaminergic/glutamatergic systems (document (1), page 128, left column lines 1-6, including the references [9] and [38] corresponding to present documents (9) and (11)). This implies that antagonists of the dopamine system and positive modulators of the glutamatergic system should complement each other, which has lead to the suggestion that ampakines are useful adjuncts to more conventional pharmacological therapies for schizophrenia (document (1), page 128, left column, lines 7-10).

4.10.2 It follows from the above that document (1) provides the skilled person faced with the problem of providing further combinations useful in the treatment of schizophrenia with a clear incentive on how to solve this problem, namely by replacing the conventional antipsychotic drugs haloperidol or fluphenazine by other conventionally used antipsychotic drugs. It is undisputed that atypical antipsychotics, like clozapine or risperidone, have been used in the treatment of schizophrenia over many years. Furthermore, atypical antipsychotics, like clozapine, are also known to antagonise the dopamine D₂-receptors. This fact was not disputed by the respondents and is even acknowledged in the patent in suit (paragraph [0099]). It is also confirmed by document (25) (table 1; page 1, left column, lines 13-18). Finally, the use of atypical antipsychotics is often preferred, since these drugs are less likely to cause extrapyramidal symptoms, a well-known and severe side-effect of typical antipsychotic drugs (see also document (25), page 239, left column, lines 33-38). The skilled person would
therefore be motivated to at least try out replacing haloperidol or fluphenazine by atypical antipsychotic drugs, like clozapine or risperidone, in the combinations according to document (8).

4.10.3 The respondents argued that the step from additive combinations of an ampakine with typical antipsychotics as disclosed in document (8) to synergistic combinations with atypical antipsychotics was just too big a step to be taken by the skilled person without inventive contribution. However, since the objective technical problem to be solved is just the provision of a further medicament for a combination therapy in the treatment of schizophrenia, the presence or absence of synergy is not part of the technical problem and therefore irrelevant for the assessment of inventive step.

4.10.4 The respondents also indicated that the disclosure in document (8) was not considered to be enabling. However, they did not provide any reasons for this opinion. Furthermore, according to the decision under appeal, the respondents themselves considered document (8) as the closest prior art and they did not provide any other document as the closest prior art during the appeal proceedings. On the contrary, the respondents agreed with the definition of the technical problem as formulated by the opposition division, which is based on document (8) as starting point for the assessment of an inventive step.

4.10.5 Finally, the respondents argued that the combination treatment with ampakines was apparently not so obvious to have occurred to others in the pharmaceutical sector
since the discovery of ampakines. The respondents were the first to report such combinations. This argument cannot succeed in view of the disclosure in document (8), which was published before the priority date of the patent in suit and which describes such combinations. Furthermore, the potential benefit of ampakines, or more generally a drug targeting the glutamatergic system, to which the ampakines belong, and antipsychotic drugs was already recognised in the prior art, as can be seen from documents (1), (9) or (11) all published before the priority date (see point 4.10.1 above).

4.11 For these reasons, the board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

Auxiliary request

5. Inventive step

Since the claims of the auxiliary request are identical to the claims of the main request, except for the deletion of "zotepine" in dependent claim 18 (see point VI above), the same considerations and conclusion with respect to inventive step as set out in points 4.6 - 4.11 above also apply to the auxiliary request. Hence, the respondents' auxiliary request is also refused for lack of inventive step (Article 56 EPC).
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 C. M. Radke