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D E C I S I O N
of 16 January 2006

Case Number: T 0715/03 - 3.3.02

Application Number: 98307170.5

Publication Number: 0901789

IPC: A61K 31/495

Language of the proceedings: EN

Title of invention:

Method of treating Tourette's syndrome

Applicant:

Pfizer Products Inc.

Opponent:

-

Headword:

Use of ziprasidone for treating Tourette's syndrome/PFIZER

Relevant legal provisions:

EPC Art. 56

Keyword:

"Article 56 (yes): it would be speculative for the skilled person to pretend that the prior art teaches that ziprasidone possesses an activity useful for TS"

Decisions cited:

T 0158/96

Catchword:

-



Case Number: T 0715/03 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 16 January 2006

Appellant: Pfizer Products Inc.
(Opponent) Eastern Point Road
Groton
CT 06340-5146 (US)

Representative: Hayles, James Richard
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 31 January 2003
refusing European application No. 98307170.5
pursuant to Article 97(1) EPC.

Composition of the Board:

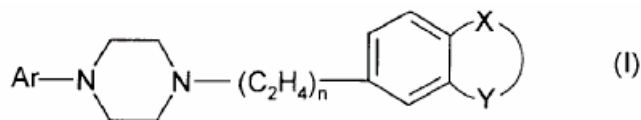
Chairman: U. Oswald
Members: M. C. Ortega Plaza
P. Mühlens

Summary of Facts and Submissions

I. European patent application EP-A-0 901 789 based on application No. 98 307 170.5 was filed with 9 claims.

Claim 1 read as follows:

"1. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating Tourette's syndrome, obsessive compulsive disorder, chronic motor or vocal tic disorder in a mammal, including a human



wherein Ar is benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by one fluoro, chloro, trifluoromethyl, methoxy, cyano, nitro or naphthyl optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; quinolyl; 6-hydroxy-8-quinolyl; isoquinolyl; quinazolyl; benzothiazolyl; benzothiadiazolyl; benzotriazolyl; benzoxazolyl; benzoxazolonyl; indolyl; indanyl optionally substituted by one or two fluoro, 3-indazolyl optionally substituted by one or two fluoro, 3-indazolyl optionally substituted by 1-trifluoromethylphenyl; or phthalazinyl;

n is 1 or 2; and

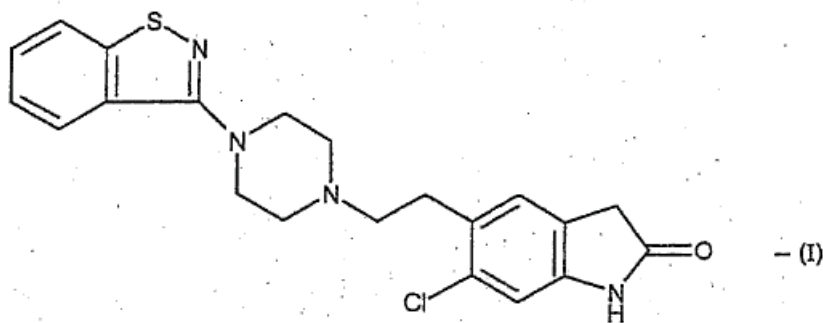
X and Y together with the phenyl to which they are attached form quinolyl; 2-hydroxyquinolyl;

benzothiazolyl; 2-aminobenzothiazolyl;
benzothiazolyl; indazolyl; 2-hydroxyindazolyl;
indoyl; spiro; oxindol optionally substituted by one to
three of (C₁-C₃)alkyl or one chloro, fluoro or phenyl,
said phenyl optionally substituted by one chloro or
fluoro; benzoxazolyl; 2-aminobenzoxazolyl;
benzoxazolonyl; 2-aminobenzoxazolonyl; benzothiazolonyl;
benzoimidazolonyl; or benzotriazolyl."

During the examining procedure the claims were amended
to a set of five claims (set of claims filed with the
letter of 7 March 2002).

Claim 1 of the set of claims filed with the letter of
7 March 2002 read as follows:

"1. The use of a compound of the formula (I) or of a
pharmaceutically acceptable salt thereof in the
manufacture of a medicament for treating Tourette's
syndrome, obsessive-compulsive disorder, chronic motor
or vocal tic disorder in a mammal



II. The following documents were cited inter alia during the proceedings:

- (1) P. B. Chappell, MD, et al, Neurologic Clinics of North America, vol. 15(2), pages 429-450, May 1997
- (4) P. B. Chappell, MD, et al, J. Am. Acad. Child Adolesc. Psychiatry, vol. 39(3), pages 292-299, 2000.
- (5) A.K. Shapiro et al, "Treatment of tic disorders with haloperidol", Chapter 18 of "Tourette's syndrome and tic disorders" published by New York Wiley & Sons, pages 268-280, 1988.

III. The appeal lies from a decision of the examining division refusing the patent application under Article 97(1) EPC.

IV. The examining division considered the subject-matter claimed (set of claims filed with the letter of 7 March 2002) to be novel vis-à-vis the contents of document (1) since the said document did "not disclose any final conclusion as to whether ziprasidone is indeed effective for the treatment of TS (Tourette's syndrome)".

The examining division considered that the claimed subject-matter lacked an inventive step (Article 56 EPC). In the examining division's opinion, document (1) represented the closest prior art. According to the examining division's findings, document (1) disclosed that ziprasidone was currently being tested in a placebo-controlled pilot study in children and

adolescents with TS and that the study was nearing completion. In the examining division's view, this meant that the efficacy of the compound was being tested in patients in a controlled manner. The examining division defined the problem to be solved as to answer the question whether or not the treatment suggested in document (1) had indeed a beneficial effect. The examining division considered that the fact that the conclusion of the study had not been published did not mean that the skilled person would not be able to assume that some beneficial effects were present and that the drug did not have any serious adverse effects which would have caused the interruption of the study. Therefore, the examining division considered that the skilled person would have had some expectation of success.

- V. The applicant (appellant) lodged an appeal against the above decision and filed grounds of appeal. With its grounds of appeal the appellant filed a main set of claims with only one claim as sole request.

Claim 1 of the main request reads as follows:

"1. The use of a compound of the formula (I) or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating Tourette's syndrome in a mammal.

the priority date of the application in suit were well known in the treatment of schizophrenia.

In the appellant's view the examining division correctly determined that the disclosure of document (1) was not prejudicial to the novelty of the subject-matter claimed. In this context it cited decision T 158/96 dated 28 October 1998, not published in the OJ EPO.

The appellant contested, however, the assumptions made by the examining division when assessing inventive step as factually incorrect.

In particular, the appellant referred to the sworn declaration by Dr Chappell, MD, dated 26 February 2002 and filed during the examination proceedings with the letter of 7 March 2002. Basically, the appellant pointed out that the nature of a double-blind randomised placebo controlled trial such as the one referred to in document (1) was that all patients, investigators and the sponsoring study monitor were kept blind as to the assigned treatment conditions (i.e. as to whether a given patient is receiving a placebo or drug) until after the end of the trial. Furthermore, the "pilot study" referred to was a Phase II study which is the first type of study designed to establish safety and efficacy in patients. The appellant also stressed that Phase I studies had as their primary object the goal of investigating the safety (non-toxicity) of the substance, and understanding its metabolic and pharmacokinetic profile, usually in healthy human volunteers. However, there was no information at the priority date of the application in

suit that ziprasidone was safe and effective in patients suffering from TS. Moreover, the appellant filed with its grounds of appeal two further declarations from Dr S. Rasmussen and Dr M. Brumfield where it was explained that in the case of ziprasidone, all the Phase I studies were done in the context of its initial development as a medicine for the treatment of schizophrenia. In this context the appellant also cited document (4) for showing that there was no previous clinical experience of use of ziprasidone in children and this also applied to adults. Therefore, in the appellant's view there was no basis for assuming that "some beneficial effects are present", as stated by the examining division.

The appellant defined the problem to be solved as to provide a new treatment for TS which is more effective in treating associated symptoms and/or has an improved side effect profile relative to prior art treatments. The problem was solved by use of the medicament ziprasidone. That the problem was indeed solved was proven according to the appellant's submissions by the data contained in document (4).

According to the appellant, the proposed solution to the problem was not obvious in the light of document (1) since this document did not provide the skilled person with a reason to investigate the activity of ziprasidone with any reasonable expectation of success.

The appellant stressed that the only valid assumption was that the mere fact that ziprasidone had "survived" a Phase I study meant that the drug had been shown to be non-toxic in healthy human volunteers, or perhaps in

patients suffering from schizophrenia. The appellant also stated that many, if not most, compounds that survive Phase I and progress to Phase II studies do not subsequently go on to Phase III studies where efficacy can definitively be investigated.

The appellant drew attention to the extreme complexity of TS and of the necessity of performing clinical trials to assess the effect of a medicine in such field. In this context the appellant cited document (5). The appellant also submitted that at the priority date no mechanistic link existed between D2 and 5-HT2 antagonists and treatment of TS.

Moreover, in clinical data involving children and adolescents with TS reported in document (4) it was demonstrated that ziprasidone simultaneously reduces the frequency of tic symptoms and severity of OCD (obsessive-compulsive disorder). This meant that both symptoms could be treated with one medicine instead of several; that ziprasidone unlike clozapine and risperidone does not cause weight gain; that ziprasidone appeared to be free of serious side effects such as extrapyramidal symptoms, akathisia or tardive dyskinesia.

With the declaration of the inventor Dr P. B. Chappell, MD, dated 8 September 2005, it was made clear that Mr Chappell was co-author of documents (1) and (4). It confirmed that the 56-day double-blind placebo controlled, randomized, pilot study, reported in document (4) was the same study as that referred to at page 436 of document (1). Dr Chappell also stated that the unblinded results of the aforementioned study had

been made available to him for review on or before the priority date of 5 September 1997.

- IX. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main and sole request filed with the grounds of appeal.

Reasons for the Decision

1. *Admissibility*

The appeal is admissible.

2. *Main request and sole request*

- 2.1 Claim 1 is a Swiss-type claim and relates to the use of a compound of formula (I) (ziprasidone) or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating Tourette's syndrome in a mammal.

The basis for this claim is given in originally filed claims 1 and 2, page 2, lines 13-14, of the originally filed application and specific compound on page 14, line 30, of the originally filed application.

Therefore the requirements of Article 123(2) have been met.

- 2.2 It is essential for the ruling in this case to investigate which is the actual teaching disclosed in document (1). Document (1) relates to "future therapies

of Tourette syndrome" (TS). The inventor of the application in suit is one of the authors of document (1). Document (1) was published in May 1997, i.e. only some months before the priority date of the application in suit (5 September 1997).

Document (1) discloses that "For the past three decades, conventional therapy for TS has consisted chiefly of the traditional neuroleptic medications haloperidol and pimozide - still today the only drugs approved by the FDA for TS - and the α_2 -adrenergic agonist, clonidine." (page 429)

"Haloperidol remains the most frequently prescribed medication for TS... Most patients begun on haloperidol discontinue treatment because of intolerable side effects, however." (page 430, first paragraph)

"Perhaps the most serious potential side effect of both haloperidol and pimozide, as well as other traditional neuroleptic medications, is the risk of tardive dyskinesia." (page 430, third paragraph)

Document (1) further discloses that "current pharmacotherapy for TS is characterized by both limited effectiveness (no medication can completely suppress tics) and a side effect profile that is often dose limiting and unacceptable to patients...Clearly there remains a great need for new and improved treatments for tics and the behavioural problems associated with them. Fortunately, a variety of new leads - both pharmacologic and nonpharmacologic - recently have emerged. Within the foreseeable future, these novel approaches may result in more effective and better

tolerated therapies for TS and related disorders."
(last paragraph on page 430).

Document (1) discloses that ziprasidone is a new atypical neuroleptic agent which is "currently in late phase III development. Thus, a wide range of new-generation atypical neuroleptic medications is becoming available, all of which have been demonstrated in clinical trials with adult schizophrenics to have a reduced risk of EPS (extra pyramidal symptoms) and all of which possess unique pharmacologic profiles. **Whether these newer atypical neuroleptic agents will also provide improved clinical efficacy and toleration in children and adults with TS and related disorders must await the results of future open and controlled clinical studies.**" (*emphasis added*) (last paragraph on page 431, first paragraph on page 432).

Further, in document (1), under the heading "The New Wave of 5-HT₂: D₂ Blockers" (pages 435-436) the pharmacological profiles of four antipsychotic agents, inter alia ziprasidone, are discussed. There are substantial variations among the receptor affinity profile of these four compounds.

Further, on page 436 it can be read: "The **potential clinical efficacy and tolerability** of these new atypical neuroleptics in patients with TS will have to be systematically assessed in future open and controlled clinical studies. **Currently, an industry-sponsored, placebo-controlled pilot study of ziprasidone in children and adolescents with TS is nearing completion** (*emphasis added*)... As with the traditional neuroleptic medications, TS patients may

have a lower threshold for side effects, including extrapyramidal symptoms, even with the newer atypical antipsychotics. Conversely, the diverse potent effects of the new atypical antipsychotics on dopaminergic, serotonergic, and adrenergic systems that have been implicated in the pathophysiology of TS suggest that these new medications are very likely to have significant effects on both tics and associated behavioral problems such as OCSs (obsessive compulsive symptoms). It will be of great interest to determine if variations among the receptor-binding profiles of the new atypical agents are correlated with differences in clinical effect within subgroups of TS patients (i.e. patients with TS alone vs. patients with TS and OCD)."

Accordingly, document (1) teaches that the known antipsychotic ziprasidone undergoes a phase II (clinical trial on efficacy and tolerability in TS patients) double blind (since it is placebo controlled) study which is unfinished and whose results are unknown.

This is confirmed by the declaration of Dr P. B. Chappell, MD, dated 26 February 2002 (filed during the examination proceedings).

The fact that phase II studies are running also means that phase I studies are concluded. However, from this information the skilled person can only conclude that the results on safety and tolerability in humans, as well as the pharmacokinetics studies, were positive. However, there is no information about a possible beneficial effect on TS patients. Indeed, the phase I studies may be those made within the framework for the

investigation of the neuroleptic and antipsychotic activity.

Additionally, contrary to the examining division's opinion, it cannot be seen that the skilled person would conclude that "**some beneficial effects** are present" (cf. point 6 of the decision) just because the clinical trials are "nearing completion". Indeed, since they are double blind trials the skilled person only knows after the completion of the trials and evaluation of the results whether this is the case. Moreover, in order that the skilled person can have access to the results, these have to be made available to the public at the priority date of the application in suit, which is not here the case.

Finally, it can be accepted that, as further explained in the declaration of Dr P. B. Chappell, MD, dated 26 February 2002, the complexity of the psychiatric disorder named TS and the non-existence of animal models for preclinical studies in this field do not allow the skilled person to extract any further teaching from the contents of document (1).

2.3 Correspondingly, the contents of document (1) cannot be considered to anticipate the subject-matter claimed, i.e. the second medical indication of the known compound ziprasidone relating to the treatment of Tourette's syndrome in a mammal (Article 54 EPC).

2.4 As regards the requirements of inventive step (Article 56 EPC) the following has to be said.

2.4.1 The teaching in document (1) referring to the known therapies for TS can be considered to represent the closest prior art (see pages 429 and 430, in particular passages quoted in point 2.2), since, as it becomes evident from the analysis of document (1) made in point 2.2 above, it would be speculative for the skilled person to pretend that document (1) teaches that ziprasidone possesses an activity useful for the treatment of TS.

Therefore in the light of the teaching of the closest prior art the definition of the problem to be solved can be seen as to provide an alternative treatment for TS.

2.4.2 The solution relates to the use of ziprasidone.

It has to be investigated whether the proposed solution actually solves the technical problem.

As stated in the decision of the examining division, the present application does not contain any pharmacological or clinical data.

Although the board in principle agrees with the appellant that it is not a prerequisite for the acknowledgment of inventive step that the application as filed includes actual pharmacological or clinical data, it is a condition sine qua non that it is credible that the problem was plausibly solved at the priority date.

The appellant has cited document (4) as additional technical support for demonstrating that ziprasidone actually solves the problem mentioned above.

An investigation of document (4) shows that the **56-day**, double-blind, placebo-controlled, randomized, pilot study disclosed therein may be the same as that mentioned in document (1). The appellant has confirmed this fact by means of the declaration of Dr Chappell, MD, dated 8 September 2005.

Dr Chapell, MD, (the inventor of the application in suit), has also confirmed in the above-mentioned declaration that on the priority date (September 1997) it was already aware of the positive results of the studies for ziprasidone announced by himself in document (1) of May 1997 as nearing completion. Therefore it is an indication for the plausibility of the statements made in the application in suit with respect to the suitability of the compounds disclosed therein, in particular ziprasidone, for the treatment of TS. Hence, the above-stated problem has been plausibly solved.

- 2.4.3 It remains to be assessed whether the proposed solution appears obvious in the light of the cited prior art.

None of the cited documents give any hint to the skilled person when looking for compounds suitable for the treatment of TS with respect to ziprasidone, neither in the sense of the required chemical structure (since all the compounds active for the treatment of TS are structurally remote from the chemical structure of ziprasidone) nor with respect to the activity class to

which ziprasidone belongs (atypical antipsychotic with affinity for 5-HT₂ receptors and reduced affinity for D₂ receptors).

Therefore, the subject-matter claimed involves an inventive step in the light of the cited prior art (Article 56 EPC).

- 2.4.4 Although the appellant defined the problem as to provide a new treatment for TS which is an improvement in respect of the side effects of the known medicaments against TS, such an improvement could not be taken in the definition of the problem underlying the application since there is no indication whatsoever in respect of such a clinical profile in the application as originally filed.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of the set of claims filed with the grounds of appeal and a description to be adapted.

The Registrar:

The Chairman:

A. Townend

U. Oswald