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D E C I S I O N
of 14 June 2000

Case Number: T 0241/95 - 3.3.2

Application Number: 91302599.5

Publication Number: 0449562

IPC: A61K 31/135

Language of the proceedings: EN

Title of invention:
Use of R-Fluoxetine as selective serotonin IC-receptor ligands

Applicant:
ELI LILLY AND COMPANY

Opponent:
-

Headword:
Serotonin receptor/ELI LILLY

Relevant legal provisions:
EPC Art. 84, 54, 111(1)

Keyword:
"Main request: clarity of the functional definition (no)"
"First auxiliary request: novelty (no) ; therapeutic effect already described in animals"
"Second auxiliary request: specific diseases never considered by the Examining Division - remittal to the department of first instance"

Decisions cited:
T 0068/85, T 0158/96

Headnote:
I. The selective occupation of a receptor cannot be considered

in itself as a therapeutic application; the discovery that a substance selectively binds a receptor, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a **defined**, **real**

treatment of any pathological condition in order to make a technical contribution to the art and to be considered as an invention eligible for patent protection (see reasons, point 3.1.2).

II. When a claim is directed to a further therapeutic application of a medicament and the condition to be treated is defined in functional terms, e.g. any condition susceptible of being improved or prevented by selective occupation of a specific receptor, the claim can be regarded as clear only if instructions, in the form of experimental tests or any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise which conditions fall within the functional definition and accordingly within the scope of the claim (see reasons, point 3.1.1) (following T 68/85, Synergistic herbicides/ CIBA-GEIGY, OJ EPO 1987, 228).

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Case Number: T 0241/95 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 14 June 2000

Appellant: ELI LILLY AND COMPANY
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Representative: Hudson, Christopher Mark
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 27. October 1994 refusing European patent application No. 91 302 599.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: C. Germinario
R. E. Teschemacher

Summary of facts and submissions

I. European patent application No. 91 302 599.5 (publication No. 0 449 562) was refused by the examining division under Article 97(1) EPC on the grounds of lack of clarity and lack of inventive step of the subject-matter of claim 1. The decision was taken on the basis of a single claim 1 filed with a letter dated 4 August 1994 and reading as follows:

"The use of (R)-fluoxetine, that is (R)-fluoxetine substantially free of (S)-fluoxetine, or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for treating a mammal suffering from or susceptible to a condition which can be improved or prevented by selective occupation of the 5-HT_{IC} receptor"

II. The following documents were considered *inter alia* during the examination proceedings:

(1) Journal of Medical Chemistry, Vol. 31, No. 7, 1998, pages 1412-1417 (D. W. Robertson et al.);

(3) Psychopharmacology, Vol. 99, 1989, pages 196-201 (J.C. Neill et al.);

A further document, not belonging to the state of the art, was also cited in the European search report as being a document useful for understanding the invention:

(4) Neuropsychopharmacology, Vol. 5, No. 1, August 1991, pages 43-47 (D. T. Wong, P. G. Threlkeld, D. W. Robertson).

III. The examining division held that claim 1 under consideration was unclear because it characterised the matter for which protection was sought by way of a functional definition, but the application did not provide the skilled person with the necessary teaching for assessing what subject-matter was actually comprised in this definition. In fact, although the scope of the claim was not limited to the specific examples of "conditions" disclosed in the description, no test or other indication could be derived from the application in suit or the common general knowledge to recognise all other conditions improved or prevented by the selective occupation of the 5-HT_{IC} receptor and, accordingly, comprised in the scope of the claim.

For this reason the claim was not considered to meet the requirements of Article 84 EPC.

In addition, the examining division also held that the claimed subject-matter did not involve an inventive step.

In the examining division's opinion, document (1) already suggested the use of fluoxetine in racemic form in the treatment of conditions also cited in the application in suit. Therefore the use of the (R)-isomer of fluoxetine for the treatment of similar conditions was regarded as obvious. Nor could the disclosed specificity of the (R)-isomer for the 5-HT_{IC} receptor endow the claimed subject-matter with an inventive step, since, according to the examining division, this property was derivable from the teaching of document (3).

IV. The appellant lodged an appeal against this decision and filed as main request a set of 4 claims having the same claim 1 as that considered by the examining division and further auxiliary requests on 24 February 1995.

V. With a communication issued on 14 June 1999, the following new prior-art document was introduced by the Board into the proceedings:

(5) The Journal of Neuropsychiatry and Clinical Neurosciences, Vol. 1, No. 3, summer 1989, pages 253-262 (S. J. Peroutka et al.)

VI. In reply to the official communication, the appellant produced additional documents and experimental results, namely tests showing the different specificity of fluoxetine racemate, (R)-isomer and (S)-isomer on the 5-HT_{IC} receptor, and tests showing the pharmacological effect on animal models of (R)-fluoxetine in migraine, obsessive compulsive disorder (OCD) and pain.

VII. At the oral proceedings, which were held on 14 June 2000, the appellant maintained an unchanged main request, but filed new first, second, third and fourth auxiliary requests.

Claim 1 of the main request is the same as that considered in the decision under appeal. The two claims 1 according to the first and second auxiliary requests read as follows:

First auxiliary request

"The use of (R)-fluoxetine, that is (R)-fluoxetine

substantially free of (S)-fluoxetine, or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for treating a mammal suffering from or susceptible to obesity, bulimia, alcoholism, pain, sleep apnea, obsessive-compulsive disorders, substance abuse or migraine"

Second auxiliary request

"The use of (R)-fluoxetine, that is (R)-fluoxetine substantially free of (S)-fluoxetine, or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for treating a mammal suffering from or susceptible to sleep apnea, substance abuse or migraine".

Claims 1 of the third and fourth auxiliary requests related to sleep apnea and to migraine respectively.

VIII. The appellant argued in writing and during the oral proceedings that the invention was based on the discovery that the (R)-isomer of fluoxetine showed an unexpectedly high selectivity for the 5-HT_{IC} receptor. This property offered the advantage that, at a given dosage level, (R)-fluoxetine was potentially free of side effects due to unspecific binding at other receptors.

With regard to the objection raised by the examining division that there was an undue burden in identifying all the conditions embraced by claim 1 (present main request), the appellant argued that the selective binding to the 5-HT_{IC} receptor already in itself pointed to conditions in relation to CNS disorders and that many animal models were available for assessing the

development of such disorders. On the other hand, a list of such conditions was given in the description which did not need to be exhaustive but simply indicative.

Moreover, the efficacy of (R)-fluoxetine in treating migraine, pain and OCD was shown with the experimental tests produced in Annex Z. However, during the discussion of these tests, the appellant admitted that there was no conclusive evidence or demonstration showing that the observed therapeutic effects were due to the specific 5-HT_{IC} receptor occupation rather than to the concomitant inhibition of the serotonin synaptic uptake, which was indeed the predominant fluoxetine pharmacological effect.

IX. The appellant requested that the decision of the examining division be set aside and the patent be granted on the basis of the main request; alternatively on the basis of one of the four auxiliary requests, all as submitted during the oral proceedings.

Reasons for the decision

1. The appeal is admissible.

2. *Article 123(2) EPC*

Claim 1 according to all the requests includes the passage "that is (R)-fluoxetine substantially free of (S)-fluoxetine" which was not present in the text of the filed application. From a reading of the original description, it is immediately understood that the invention is directed to the use of the sole

(R)-isomer, which is cited in the third and fourth paragraphs of page 1 as the form according to the invention as opposed to the known racemic form. The description also cites several known standard methods for resolving the racemate into the (R) and (S) isomers and for preparing the pure (R)-form (see lines 12 to 24 on page 3). Therefore, the Board can conclude that the application as filed implicitly disclosed the use of the (R)-fluoxetine free of the (S)-isomer.

As regards the deletion of the passage "a condition which can be improved or prevented by selective occupation of the $5HT_{IC}$ receptor", from the text of claim 1 according to all the auxiliary requests the Board notes that this feature of the originally claimed subject-matter has been replaced by specific diseases cited in the original application as examples of such a "condition". Since the Board has no means or reason to confute the validity of the statement in the description that these specific conditions are improved or prevented by the selective occupation of the $5HT_{IC}$ receptor, the amendment is held not to extend the content of the application as filed.

Therefore, the Board considers that the amended claims according to all the requests comply with the requirements of Article 123(2) EPC.

3. *Main request*

3.1 Article 84 EPC

3.1.1 Claim 1 defines the disease or disorder to be treated with (R)-fluoxetine as a condition which is capable of being improved or prevented by selective occupation of

the 5-HT_{IC} receptor. The functional terms used to define the condition to be treated are acceptable as long as the claim still meets the requirements of Article 84 EPC. According to decision T 68/85 (OJ EPO 1987, 228), cited by the appellant, the requirement of clarity demands not only that the skilled person be able to understand the wording of the claim but also that he be able to implement it (see T 68/85, point 8.4.3). In other words, the functional feature must be accompanied by instructions which are sufficiently clear for the expert to reduce them to practice. This implementation of the invention implies that means must be available to the skilled person, either from the patent application or from the common general knowledge at the relevant date of the application, to recognise and evaluate the technical effect of the functional definition.

When the claim is directed, according to the usual wording, to a further therapeutic application of a medicament and the condition to be treated is defined in functional terms, such as those in the claim under consideration, the skilled person must be given instructions, in the form of experimental tests or any testable criteria, allowing him to recognise which conditions fall within the functional definition and accordingly whether or not the therapeutic indication representing the heart of the invention falls within the scope of the claim.

3.1.2 In the present case, the invention is based on the discovery that the (R)-isomer of fluoxetine shows a high specificity for the serotonin 5-HT_{IC} receptor. Accordingly, the claimed therapeutic indication of (R)-fluoxetine is the treatment of any condition

susceptible of being improved or prevented by selective occupation of this specific receptor. The Board wishes to stress that the "selective occupation" of a receptor, although being indisputably a pharmacological effect, cannot in itself be considered a therapeutic application. The discovery on which the invention is based, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a **defined**, **real** treatment of any pathological condition in order to make a technical contribution to the art and be considered an invention eligible for patent protection.

Specifically for this purpose, the description cites a list of examples of such conditions, namely obesity, bulimia, alcoholism, pain, sleep apnea, obsessive-compulsive disorders, substance abuse and migraine, intended to be treated according to the present invention.

Yet, due to the functional definition of the claimed subject-matter, the scope of claim 1 is not limited to the treatment of said specified conditions but, by contrast, embraces an undefined number of other conditions all allegedly capable of being improved or prevented by the selective occupation of the $5HT_{IC}$ receptor. Under these circumstances, the independent claim can only be regarded as clear if means are available to the skilled person for assessing whether or not an additional condition, not expressly cited in the application, but nevertheless affected by the administration of (R)-fluoxetine is comprised in the scope of claim 1.

3.1.3 The appellant contends that this condition is indeed

met by the invention since the skilled person is aware of the many animal models known for the different CNS disorders and useful for assessing a posteriori the improvement or prevention caused by (R)-fluoxetine. Therefore, in the applicant's opinion, the skilled person is indeed able to establish whether or not such a condition falls within the scope of the claim.

To corroborate these arguments, the appellant relied on the three experimental tests showing the effect on animal models of (R)-fluoxetine on migraine, OCD and pain (Annex Z of 14 February 2000).

3.1.4 The Board cannot concur with the appellant's opinion.

The selective occupation of the 5-HT_{IC} receptor is only one of the pharmacological activities of fluoxetine, either as (R)-isomer or racemate. In fact, as described in document (5), pages 258 and 259 and table 4, fluoxetine additionally shows a serotonin-uptake inhibiting activity in the synapses and this activity would appear to amount to its main pharmacological effect. The teaching of document (5) is even confirmed by D. W. Robertson and D. T. Wong, the inventors mentioned in the present application, who suggested in the late-published document (4) that the inhibition of 5-HT uptake accounts for most of the enhancement of 5-HT transmission and other pharmacological responses in animals treated with fluoxetine or its congeners (see page 43, abstract, and page 46, "Discussion").

Accordingly, the experimental tests produced by the appellant in Annex Z have to be considered in the light of this, at least, double activity of fluoxetine. The tests demonstrate the therapeutic efficacy of (R)-

fluoxetine in the treatment of migraine, OCD and pain, but, as is evident from the reading of their description, they fail to elucidate any mechanism leading to such an effect since they are devised simply to monitor a final, mainly behavioural, result. Therefore, these tests, while proving indeed a therapeutic activity of (R)-fluoxetine, do not solve the question of whether such therapeutic effects are caused by the occupation of the 5-HT_{IC} receptor or by the concomitant 5-HT uptake inhibition or even by any other, so far unknown, effect of fluoxetine.

The view that neither the cited tests nor any other known test normally used to study CNS disorders are effective in elucidating the mechanism of action of (R)-fluoxetine was also confirmed at the oral proceedings by the appellant himself, who admitted that it had not been conclusively demonstrated that the reported therapeutic activity resulted from the selective occupation of the 5-HT_{IC} receptor rather than from the 5-HT uptake inhibition.

Under these circumstances, the Board is of the opinion that at the filing date of the application no means involving testable criteria existed to assist the skilled person in assessing whether or not a "condition" improved or prevented by (R)-fluoxetine was comprised in the functional definition of the claimed subject-matter.

For these reasons, the Board holds that claim 1 does not meet the requirements of Article 84 EPC.

4. *First auxiliary request*

The expression "a condition which can be improved or prevented by selective occupation of the $5HT_{IC}$ receptor" has been dropped from the text of claim 1 of the first auxiliary request, which is limited to the preparation of a medicament for the treatment of defined conditions, namely obesity, bulimia, alcoholism, pain, sleep apnea, obsessive-compulsive disorders, substance abuse or migraine. The claim as presently worded is regarded as clear.

4.1 Article 54 EPC

4.1.1 The amendments introduced in the definition of the claimed subject-matter have drastically changed the essence of the invention. For this reason, the Board considers that novelty of the claimed subject-matter, although not a point at issue in the decision under appeal, is now to be evaluated in the light of the cited prior documents, specifically document (1).

This document discloses the absolute configuration and the pharmacological activities of the (R)- and (S)-isomers of fluoxetine. Three in vivo studies are reported to show the effects of the separate isomers in (a) endogenous pain control and opiate-induced antinociception, (b) inhibition of the induced mouse brain serotonin depletion and (c) depression of palatability-induced ingestion (drinking). In all animal models the two isomers proved to be active with little enantiospecific differences. More specifically, in the endogenous pain control test, both (R) and (S) fluoxetine, when injected alone or in combination with a sub-analgesic dose of morphine, antagonised acetic acid-induced abdominal constriction, blocking writhing in a dose-dependent fashion, the (R) isomer being

slightly more effective than the (S) isomer (see the heading "Pharmacology" on pages 1414 and 1415). The Board considers that the disclosure in document (1) of the ability of (R)-fluoxetine to control endogenous pain is prejudicial to the novelty of claim 1, which also envisages the treatment of a mammal suffering from or susceptible to pain.

4.1.2 During the oral proceedings, the appellant argued that document (1) does not actually disclose the preparation of a medicament within the meaning given in the present application or in claim 1. In fact, the experimentation was carried out on animals and without the intention of achieving a therapeutic effect, typically characterising a real therapeutic treatment.

The Board wishes, first of all, to stress that the (R)-fluoxetine solution injected into animals in the different test described in (1) is indeed to be considered as a "medicament", since it comprises a therapeutically active agent and it is suitable for use as a medicament, at least in animals.

Furthermore, the subject-matter of claim 1 is not a product but the use of a substance, known in itself, for the preparation of a medicament, also known in itself, for a specific therapeutic application, and that the novelty of this claim, if any, can only derive from the novelty of said therapeutic use.

It is a well-established and accepted principle that, for the purpose of patent protection of a medical application of a substance, a pharmacological effect or any other effect such as a behavioural effect observed either in vitro or on animal models is accepted as

sufficient evidence of a therapeutic application if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application. This principle was laid down in decision T 158/96 dated 28 October 1998 ((1999) E.P.O.R., page 285) relating to an alleged therapeutic application, which, unlike the present one, was not made plausible by any such preliminary effect. On the contrary, the efficacy of (R)-fluoxetine in controlling acetic acid-induced abdominal constriction (writhing) and potentiating morphine-induced antinociception in mice, as shown in document (1), directly and unambiguously reflects one of the therapeutic applications cited in claim 1, namely the treatment of pain.

For this reason, the Board holds that the subject-matter of claim 1 is not novel in relation to the teaching in document (1).

5. *Second auxiliary request*

The above reasons cannot be maintained for the second auxiliary request.

Claim 1 according to this request is limited to three specified conditions, which are sleep apnea, substance abuse or migraine.

Even more so than in the case of the first auxiliary request, the amendments introduced in the text of claim 1 do not represent a simple limitation of the scope of the claim, but rather a radical change to the heart of the invention. Whereas the invention as filed or amended during the examination proceedings related to any condition susceptible of being improved or

prevented by the selective occupation of the 5-HT_{IC} receptor, after amendment it relates to three specific diseases, which were never cited as a characterising feature of a claim submitted to the examining division.

Under these circumstances, the Board avails itself of the discretionary power conferred by Article 111(1) EPC and remits the case to the examining division for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside,

2. The case is remitted to the department of first instance for further prosecution on the basis of the second auxiliary request as submitted during the oral proceedings.

The Registrar: The Chairman:

M. Dainese P. A. M. Lançon