BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [ ] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 14 May 2008

Case Number: T 1648/06 - 3.3.04

Application Number: 01952310.9

Publication Number: 1311293

IPC: A61K 45/06

Language of the proceedings: EN

Title of invention:
Combinations of SSRI and estrogenic agents

Applicant:
Wyeth

Headword:
Combinations of SSRI and estrogenic agents/WYETH

Relevant legal provisions:
-

Relevant legal provisions (EPC 1973):
EPC Art. 56

Keyword:
"Main request - inventive step (no)"
"Auxiliary request - inventive step (no)"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1648/06 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 14 May 2008

Appellant: Wyeth
Five Giralda Farms
Madison, NJ 07940-0874 (US)

Representative: Eder, Michael Dr.
df-mp
Fünf Höfe
Theatinerstr. 16
D-80333 Munich (DE)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 6 April 2006 refusing European patent application No. 01952310.9 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

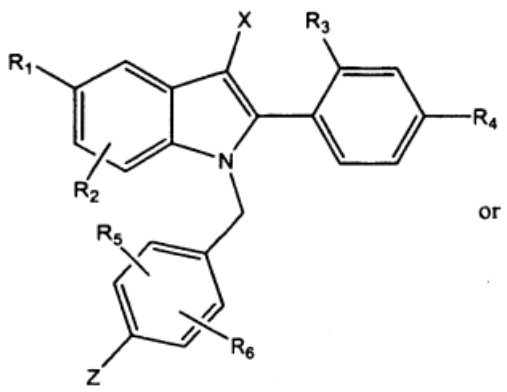
Chair: U. Kinkeldey
Members: R. Gramaglia
G. Weiss

Summary of Facts and Submissions

I. European patent application No. EP 01 952 310.9 published as WO 02/03975 with the title "Combinations of SSRI and estrogenic agents" was refused by the examining division pursuant to Article 97(1) EPC.

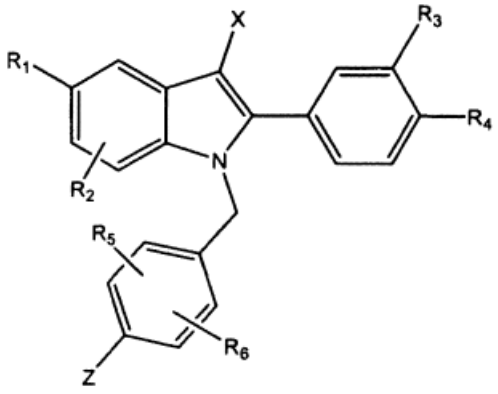
II. Claims 1 and 12 of the main request then on file which is also the main request in appeal proceedings read as follows:

"1. Use of venlafaxine, or a pharmaceutically acceptable salt thereof, and a compound of formulae I or II:



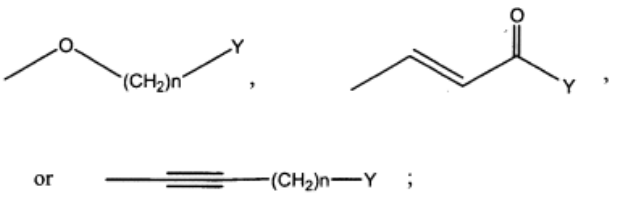
I

or



II

wherein Z is a moiety selected from the group of:



wherein:

R_1 is selected from H, OH or the C_1-C_{12} esters or C_1-C_{12} alkyl ethers thereof, benzyloxy, or halogen; or C_1-C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether;

R_2, R_3, R_5 and R_6 are independently selected from H, OH or the C_1-C_{12} esters or C_1-C_{12} alkyl ethers thereof, halogens, or C_l-C_4 halogenated ethers, cyano, C_1-C_6 alkyl, or trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH;

R_4 is selected from H, OH or the C_1-C_{12} esters or C_1-C_{12} alkyl ethers thereof, halogens, or C_1-C_4 halogenated ethers, benzyloxy, cyano,C_1-C_6 alkyl, or trifluoromethyl;

X is selected from H,C1-C6 alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 1, 2 or 3;

Y is selected from:

a) the moiety:

wherein R_7 and R_8 are independently selected from the group of H, C_1-C_6alkyl, or phenyl optionally substituted by CN, C_1-C_6 alkyl, C_1-C_6alkoxy, halogen, -OH, $-CF_3$, or $-OCF_3$; or R_7 and R_8 are combined by $-(CH_2)_p-$, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydroxyl, halo, C_1-C_4alkyl, trihalomethyl, C_1-C_4alkoxy, trihalomethoxy, C_1-C_4alkylthio, C_1-C_4alkylsulfinyl, C_1-C_4alkylsulfonyl, hydroxy(C_1-C_4)alkyl, $-CO_2H$, -CN, -CONH(C_1-C_4)alkyl, $-NH_2$, C_1-C_4alkylamino, di-(C_1-C_4)-alkylamino, $-NHSO_2$(C_1-C_4)alkyl, -NHCO(C_1-C_4) alkyl and $-NO_2$;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4alkyl)-, -N=, and -S(O)$_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C_1-C_4alkyl, trihalomethyl, C_1-C_4alkoxy, trihalomethoxy, C_2-C_4acyloxy, C_1-C_4alkylthio, C_1-C_4alkylsulfinyl, C_1-C_4alkylsulfonyl, hydroxy(C_1-C_4)alkyl, -CO_2H-, -CN, -CONHR_1, -NH_2, C_1-C_4alkylamino, di-(C_1-C_4)alkylamino, -NHSO_2R_1, -NHCOR_1, -CONH(C_1-C4)alkyl, -NHSO_2(C_1-C_4)alkyl, -NHCO(C_1-C_4)alkyl; -NO_2 and phenyl optionally substituted with 1-3(C_1-C_4)alkyl;

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4alkyl)-, -N=, and -S(O)$_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C_1-C_4alkyl, trihalomethyl, C_1-C_4alkoxy, trihalomethoxy, C_2-C_4acyloxy, C_1-C_4alkylthio, C_1-C_4alkylsulfinyl, C_1-C_4alkylsulfonyl, hydroxy(C_1-C_4)alkyl, -CO_2H-, -CN, -CONHR_1, -NH_2, C_1-C_4alkylamino, di-(C_1-0C_4)alkylamino, -NHSO_2R_1, -NHCOR_1, -CONH(C_1-C4)alkyl, -NHSO_2(C_1-C_4)alkyl, -NHCO(C_1-C_4)alkyl; -NO_2 and phenyl optionally substituted with 1-3(C_1-C_4)alkyl;

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -

O-, -NH-, -N(C_1-C_4alkyl)-, -N=, and -S(O)$_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C_1-C_4alkyl, trihalomethyl, C_1-C_4alkoxy, trihalomethoxy, C_2-C_4acyloxy, C_1-C_4alkylthio, C_1-C_4alkylsulfinyl, C_1-C_4alkylsulfonyl, hydroxy(C_1-C_4)alkyl, -CO_2H, -CN, -CONHR_1, -NH_2, C_1-C_4alkylamino, di-(C_1-C_4)alkylamino, -NHSO_2R_1, -NHCOR_1, -CONH(C_1-C4)alkyl, -NHSO_2(C_1-C_4)alkyl, -NHCO(C_1-C_4)alkyl; -NO_2 and phenyl optionally substituted with 1-3(C_1-C_4)alkyl; or

e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4alkyl)-, -N=, and -S(O)$_m$-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C_1-C_4alkyl, trihalomethyl, C_1-C_4alkoxy, trihalomethoxy, C_2-C_4acyloxy, C_1-C_4alkylthio, C_1-C_4alkylsulfinyl, C_1-C_4alkylsulfonyl, hydroxy(C_1-C_4)alkyl, -CO_2H, -CN, -CONHR_1, -NH_2, C_1-C_4alkylamino, di-(C_1-C_4)alkylamino, -NHSO_2R_1, -NHCOR_1, -CONH(C_1-C4)alkyl, -NHSO_2(C_1-C_4)alkyl, -NHCO(C_1-C_4)alkyl; -NO_2 and phenyl optionally substituted with 1-3(C_1-C_4)alkyl;

or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of hot flush."

"12. A product comprising a compound of formula I or II as defined in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, and

venlaxaxine [sic] or a pharmaceutically acceptable salt thereof, for administration as a combined preparation for simultaneous, separate or sequential use in treating hot flush in a mammal."

Dependent claims 2 to 10 related to further features of the use of claim 1, whereas claim 11 addressed a pharmaceutical composition.

In claims 1 and 12 of the first auxiliary request then on file, which is also the first auxiliary request in appeal proceedings, the wordings in the corresponding claims of the main request "for the treatment of hot flush" (end of the claim 1) and "for the treatment of hot flush in a mammal" (end of the claim 12) have been amended to read "for the treatment of hot flush in a mammal susceptible to estrogen deficiency bone loss".

III. The examining division refused the application for lack of inventive step in view of the combined teachings of documents D1 and D3 (infra).

IV. The appellant (applicant) filed an appeal against the decision of the examining division, paid the appeal fee and submitted a statement of grounds of appeal.

V. Oral proceedings took place on 14 May 2008.

VI. The following documents are mentioned in this decision:

D1 WO-A-99/59969;

D3 Loprinzi C.L. et al., Journal of Clinical Oncology, Vol. 16, No. 7, pages 2377-2381 (July 1998);

D5 Darniche M. et al., Atlantic Psychosomatology (April 1999), available online;

D6 Merchenthaler I. et al., Maturitas, Vol.30, pages 307-316 (1998);

D7 The Merck Manual, Section 18, Chapter 236, Menopause, available online.

VII. The submissions by the appellant can be summarized as follows:

– Document D1 was to be considered as the closest prior art because it described the estrogenic indole derivatives of formula I or II referred to in claim 1 for treating conditions associated with estrogen deficiency and preventing bone loss.

– The problem to be solved vis-à-vis this reference was the provision of a treatment for hot flushes in patients who were at the same time susceptible to bone loss due to estrogen deficiency.

– Document D1 taught that estrogens regulated via the central nervous system a number of physiological processes, including hot flush. Therefore, this document D1 suggested to combine indoles of formula

I or II with another estrogen, not with venlafaxine, in order to alleviate hot flush.

– The invention lay with the unexpected discovery that the estrogens of formula I or II did not interfere with the efficacy of the other agent, namely venlafaxine. The experiments made in the appellant's laboratories using the morphine-dependent rat flush model indeed showed that the estrogenic indole derivative of formula I TSE-424 did not antagonize the effect of the antidepressant.

– Documents D3 and D5 to D7 illustrated a prejudice by the skilled person to combine the two ingredients.

– Document D3 showed that two different drugs used together often interfered.

– Document D5 showed that estrogens had antidepressant activity in respect of neurotransmitter, receptor function and the level of monoamine oxidase activity. Hence, the skilled person would be concerned that using an estrogen agonist/antagonist of formula I or II together with a SSRI drug acting via serotonin reuptake inhibition (venlafaxine) would render the latter ineffective.

– The prejudice by the skilled person to combine the two ingredients was strengthened by documents D6 and D7, teaching that raloxifene could worsen the hot flushes.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis

of the claims according to the main request submitted with letter dated 10 May 2004 or, alternatively, on the basis of the claims according to the auxiliary request submitted with letter dated 20 December 2005.

Reasons for the Decision

1. The only issue which the board is required to assess is that of inventive step.

Main request

2. Claim 1 of this request relates to the combined use of venlafaxine with an estrogenic indole derivative of formula I or II for the treatment of hot flushes (also called hot flashes), which is a significant clinical problem in menopausal women. From the context of the application (see pages 1 and 2, "Background of the invention") and from claim 1 ("a compound of formula I or II"), it is implicit that the treatment is directed to patients in need for concomitant estrogenic therapy.

3. The closest prior art is represented by document D1, which discloses indole derivatives of formula (I) or (II) (see pages 4 and 5) for use in treating or preventing conditions associated with oestrogen deficiency (page 7, 2nd paragraph) or for use in hormone replacement therapy (page 8, first full paragraph). These compounds behave as estrogen agonists or antagonists according to the tissue selectivity (see page 6, lines 18-26).

4. The problem to be solved is the provision of a medicament for the treatment for hot flushes in patients in need for concomitant estrogenic therapy.

5. As to the question whether or not the above problem has been solved, the present application does not provide any clinical data. However, in a letter dated 10 May 2004 (see paragraph 3), the applicant submitted an account of how the hot flush utility described in the present application has been demonstrated using the morphine-dependent rat model, which measures the abatement of a naloxone-induced hot flush in a pre-clinical rat model. According to these experiments, when a representative estrogenic compound of formula (I), namely TSE-424 (see page 8, lines 15-16 of the present application) was tested alone or in combination with an antidepressant that had pharmacological properties in common with venlafaxine, TSE-424 in combination with the antidepressant was effective in reducing a naloxone induced hot flush in the above pre-clinical rat model, whereas TSE-424 alone failed. In view of this evidence, the board is satisfied that the problem emphasised in point 4 supra has indeed been solved.

6. The decisive question to be answered is thus whether or not the prior art contains information or pointers that would guide in an obvious way a skilled person embarking on solving this problem.

7. According to the appellant, document D1 taught that estrogens regulated via the central nervous system a number of physiological processes, including hot flush (see page 8, line 26). Therefore, in the appellant's

view, document D1 suggested to combine indoles of formula I or II with another estrogen, rather than with venlafaxine, in order to alleviate hot flush. The board agrees that document D1 taken alone suggested to focus on compounds of formula I or II and estrogens (see page 1, lines 4-8) for treating hot flush.

8. However, the skilled person would also come across document D3, disclosing the use of venlafaxine for treating hot flashes. Venlafaxine is an antidepressant belonging to the "SSRI family", which acts by inhibiting the re-uptake of serotonin and norepinefrin in the brain's synapses (hence the acronym). Therefore, in the board's view, the skilled person, looking for a treatment for hot flashes in patients in need for concomitant estrogenic therapy, would prima facie combine the teachings of documents D1 and D3.

9. The appellant maintains that the invention lay with the unexpected discovery that the estrogens of formula I or II did not interfere with the efficacy of the other agent, namely venlafaxine. The experiments described in point 5 supra indeed showed that the estrogenic indole derivative of formula I TSE-424 did not antagonize the effect of the antidepressant.

10. To buttress the above view, the appellant cites several passages from documents D3, and D5 to D7, which illustrate a prejudice by the skilled person to combine the two ingredients, as shown in more detail below.

11. Document D3 has been cited to show that two different drugs used together often interfere (see page 2377, l-h column, last paragraph: "low dose progesterone

theoretically might ...interfere with tamoxifen"). However, in the board's judgement, this particular situation involving progesterone and tamoxifen cannot be generalised to any couple of drugs, let alone to a very specific combination of estrogen compounds of formula I or II and venlafaxine, which are structurally and pharmacologically different from progesterone and tamoxifen.

12. In a different line of argument, the appellant maintains that estrogen compounds have antidepressant activity in respect of neurotransmitter, receptor function and the level of monoamine oxidase activity (see document D5, third paragraph). Hence, the skilled person would be concerned that using an estrogen agonist/antagonist of formula I or II together with a SSRI drug acting via serotonin reuptake inhibition (venlafaxine) would render the latter ineffective.

13. Document D5 relates indeed to the antidepressant activity of estrogen. It is stated in the third paragraph of this document that this antidepressant activity is linked to an enhancement of the serotonergic function or to changes in the level of monoamine oxidase. Starting from this information, in the board's view, no extrapolation can reasonably be made by the skilled person about a possible interference between the two ingredients referred to in present claim 1. This is because the estrogen agonist/antagonist of formula I or II and the pathology to be treated, namely hot flashes, differ significantly from estrogen (see document D1, page 6, lines 28-32) and depression, respectively.

14. A further appellant's argument for illustrating a prejudice by the skilled person to combine the two ingredients is that the skilled person was aware that raloxifene could worsen the hot flushes (see document D7, page 3, fourth paragraph). This adverse effect was confirmed by document D6, according to which raloxifene behaved as an anti-estrogen in the central nervous system and hence it increased the incidence of hot flushes (see page 314, r-h column, end of first paragraph).

15. However, this argument is not convincing because firstly raloxifene does not belong to the indoles of formula I or II since it is a benzothiophene (see document D1, page 1, line 29). Moreover, the raloxifene's property of behaving as an anti-estrogen in the central nervous system (see document D6, supra) and hence of worsening hot flushes, cannot be generalised to any non steroidal estrogen. In fact tamoxifen exhibited in the same rat model for hot flush described in document D6 significant estrogen agonist activity (see Abstract), and hence this non steroidal estrogen did not worsen the hot flushes (see ibidem, page 314, r-h column, lines 8-10: "tamoxifen may have limited utility in treating hot flushes").

16. In conclusion, claim 1 of this request is not valid for lack of inventive step.

First auxiliary request

17. In claim 1 of this request, the wording in the corresponding claim of the main request "for the treatment of hot flush" (end of the claim 1) has been

amended to read "for the treatment of hot flush in a mammal susceptible to estrogen deficiency bone loss".

18. When dealing with the main request, the board has already come to the conclusion that the skilled person, looking for a treatment for hot flashes in patients in need for concomitant estrogenic therapy, would combine the teachings of documents D1 and D3 and by doing so, arrive in an obvious way at the claimed subject-matter.

19. This negative conclusion also extends to claim 1 of the auxiliary request since document D1 explicitly teaches that the patients in need for concomitant estrogenic therapy are those suffering from bone loss (page 7, line 22), from osteoporosis (line 23) and from bone loss resulting from secondary osteoporosis (line 28).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: Chair:

P. Cremona U. M. Kinkeldey