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D E C I S I O N
of 30 September 2003

Case Number: W 0020/02 - 3.3.4

Application Number: PCT/US 01/43847

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Title of invention:
Combination Therapy for Estrogen-Dependent Disorders

Applicant:
Pharmacia & Upjohn Company

Opponent:
-

Headword:
Therapy for estrogen-dependent disorders/PHARMACIA

Relevant legal provisions:
PCT Art. 17(3)(a)
PCT R. 40.1, 40.2, 40.3

Keyword:
"Unity of invention - (yes)"
"Additional search fees - refund - (yes)"
"Protest fee - refund - (yes)"

Decisions cited:
G 0001/89

Catchword:
-

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Case Number: W 0020/02 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 30 September 2003

Applicant: Pharmacia & Upjohn Company

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Decision under appeal: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 5 June 2002 .**

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: A. L. Marie
B. Günzel

Summary of Facts and Submissions

I. International patent application PCT/US 01/43847 was filed on 6 November 2001 with twenty-nine claims, claims 26, 28 and 29 read as follows:

"26. Use of an aromatase inhibitor in the manufacture of a medicament for treating a sex steroid dependent cancer in a mammal undergoing a simultaneous, separate or sequential treatment with LHRH agonist or antagonist, and wherein, when the cancer is breast cancer, and a) the LHRH agonist is triptorelin, then the aromatase inhibitor is other than formestane, b) the LHRH agonist is goserelin, then the aromatase inhibitor is other than vorozole or formestane, or c) the LHRH agonist is leuprorelin, then the aromatase inhibitor is other than fadrozole."

"28. Use according to claim 26, wherein the aromatase inhibitor is exemestane, the LHRH agonist is triptorelin and the sex steroid dependent cancers are ovarian and breast cancers."

"29. Product containing an aromatase inhibitor and a LHRH agonist or antagonist as a combined preparation for simultaneous, separate or sequential use in treating sex-dependent cancers, and wherein when the cancer is breast cancer, and a) the LHRH agonist is triptorelin, then the aromatase inhibitor is other than formestane, b) the LHRH agonist is goserelin, then the aromatase inhibitor is other than vorozole or formestane, or

c) the LHRH agonist is leuprorelin, then the aromatase inhibitor is other than fadrozole."

II. On 5 June 2002 the European Patent Office, acting as an International Searching Authority (ISA), invited the applicant to pay within a time limit of 45 days eighteen additional search fees pursuant to Article 17(3)(a) PCT, Rule 40.1 and 40.3 PCT and issued a partial search report on claims 26 to 29. The invitation mentioned 19 groups of inventions, of which groups 1 to 4 read as follows:

(1) Claims 26 to 29 (partial): a product comprising the aromatase inhibitor exemestane in combination with an LHRH agonist, (in particular triptorelin or goserelin) and the use of that product in relation to the treatment of ovarian, breast, uterin, fallopian tube, celomic epithelial and germ cell ovarian cancers.

(2) Claims 26 to 29 (partial): a product comprising the aromatase inhibitor exemestane in combination with an LHRH antagonist, and the use of that product in relation to the treatment of ovarian, breast, uterin, fallopian tube, celomic epithelial and germ cell ovarian cancers.

(3) Claims 26 to 29 (partial): a product comprising the aromatase inhibitor exemestane in combination with an LHRH agonist or antagonist, (in particular triptorelin or gonerelin [sic]) and the use of that product in relation to the treatment of testicular and prostate cancers.

(4) Claims 26 to 29 (partial): a product comprising the aromatase inhibitor exemestane in combination with an LHRH agonist or antagonist, (in particular triptorelin or goserelin) and the use of that product in relation to the treatment of pancreatic, and lung cancers.

III. The invitation stated that there was no single inventive concept underlying the plurality of claimed inventions and reference was made to the following documents:

(1) L. Celio et al., Anticancer Research, 1999, Vol. 19, pages 2261 to 2268

(2) N. Tsuchiya et al., Int. J. Clin. Oncol., 2000, Vol. 5, pages 183 to 187

(3) M. Dowsett et al, Breast Cancer Research and Treatment, 1999, Vol. 56, pages 25 to 34

(4) R.C. Stein et al., Br. J. Cancer, 1990, Vol. 62, pages 679 to 683

It was found that the general idea to use aromatase inhibitors in combination with LHRH agonists or antagonists for the treatment of sex steroid dependent cancers was already disclosed in the prior art and exemplified in documents (1) to (4) for the treatment of breast cancer, which disclosed the use of several of such combinations, such as vorozole and goserelin, fadrozole and leuprorelin, formestane and triptorelin or formestane and goserelin. Although these specific combinations were excluded from the claimed subject-

matter by way of disclaimer, the general idea was no longer novel and inventive. No further technical feature was seen in the application which was susceptible to be regarded as a special technical feature linking the different inventions.

IV. On 9 July 2002, the applicant paid three additional fees for the groups of inventions 2, 3 and 4 under protest pursuant to Rule 40.2(c) PCT. The applicant disagreed with the separation into four groups of inventions on the basis of the specific types of cancers, because they were all sex steroid dependent cancers or on the basis of the distinction agonist/antagonist, because both inhibited the pituitary-gonadal axis. Finally, nothing was said or suggested in the prior art about the use of exemestane, which was unique among the aromatase inhibitors because of its mode of action (suicide inhibition). Exemestane was a special technical feature linking the different inventions together.

V. On 16 October 2002, the ISA issued the international search report for the four groups of inventions mentioned above (cf *supra* section II) with the indication that, although claims 1 to 29 were directed to a method of treatment of the human or animal body, the search had been carried out and based on the alleged effects of the compound/composition.

VI. On the same day, the ISA communicated to the applicant the result of its review under Rule 40.2(e) PCT. The finding of lack of unity was confirmed for the following reasons:

– the idea of using aromatase inhibitors together with LHRH agonists or antagonists was disclosed in documents (1) to (4),

- exemestane and formestane were known from document (5)(P.E. Lonning et al., Journal of Clinical Oncology, 2000, Vol. 18, No. 11, pages 2234 to 2244) as "suicide inhibitors", so that the mode of action of the aromatase inhibitor was not the linking feature,

- the substitution of formestane by exemestane did not provide a special technical feature in the sense of Rule 13 PCT,

- the use of LHRH agonists and antagonists were alternative selections as well as the distinction made by the ISA between the treatment of female reproductive cancers, male reproductive cancers and cancers common to both females and males.

The applicant was invited to pay a protest fee.

VII. The protest fee was paid on 13 November 2002.

Reasons for the Decision

1. The protest is admissible.

2. According to Rule 13.1 PCT, the international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. If the ISA considers that the claims

lack this unity, it is empowered, under Article 17(3)(a) PCT, to invite the applicant to pay additional fees.

3. Lack of unity may by directly evident *a priori*, ie before the examination of the merits of the claims in comparison with the state of the art revealed by the search. Alternatively, having regard to decision G 1/89 (EPO OJ 1991, 155), the ISA is also empowered to raise an objection *a posteriori*, ie after having taken the prior art revealed by the search into consideration. This practice is laid down in the PCT Search Guidelines, Chapter VII-9. (PCT Gazette, special issue of October 1998, page 26) which are the basis for a uniform practice of all ISAs. Decision G 1/89 indicated that such consideration only represents a provisional opinion on novelty and inventive step which is in no way binding upon the authorities subsequently responsible for the substantive examination of the application (point 8.1 of the Reasons for the Decision). Further, decision G 1/89 mentioned (point 8.2) that a invitation to pay additional search fees should always be made "*with a view to giving the applicant fair treatment*" and should only be made in clear cases.

4. According to Rule 13.3 PCT, the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

5. The question to be answered is whether the subject-matter of the claims of groups 1 to 4 (cf *supra* section II) can be considered to be part of the same general inventive concept.

6. In the applicant's view, the unitary link is provided by the fact that all the cancers are sex steroid dependent ones, the LHRH agonists and antagonists work similarly on the pituitary-gonadal axis and the exemestane is unique as an aromatase inhibitor because of its special mode of action.

7. Documents (1) to (4) describe the combined use of LHRH agonist/antagonist and aromatase inhibitor in the treatment of breast cancer. Document (1) concerns the use of triptorelin, as a LHRH agonist/antagonist, and formestane, as an aromatase inhibitor. Document (2) describes the combination treptorelin (LHRH agonist) and fadrozole (aromatase inhibitor). Document (3) uses goserelin (LHRH agonist) and vorozole (inhibitor), whereas document (4) discloses the use of goserelin and formestane. However, the combined use of exemestane with a LHRH agonist/antagonist, as in the four groups of inventions defined by the ISA, is not disclosed in any of documents (1) to (4) or in the other cited prior art documents and is hence novel.

8. If any one of documents (1) to (4) is considered as the closest prior art, then the problem to be solved can be defined as the provision of another combination of a LHRH agonist/antagonist with an aromatase inhibitor.

9. The solution proposed by the claims of the four groups of inventions defined by ISA lies in the use of exemestane as an aromatase inhibitor in said combination.

10. The question to be answered in the context of unity of invention is whether the skilled person would have deduced this solution in an obvious manner from the closest prior art mentioned above, considered alone or in combination with the common general knowledge or other cited prior art documents and thus, whether the claimed use of exemestane in otherwise known combinations provides the roof linking any of the claimed combinations together which all solve the stated problem, this being the decisive yardstick when examining unity of invention if, as in this case, an *a posteriori* inventive step consideration is at issue.

11. Document (5) describes the use of exemestane, as an inhibitor of aromatase, in the treatment of breast cancer. Its mode of action is described on page 2234 (right column, first full paragraph), is identical to that of formestane (page 2234, right column, second full paragraph) and corresponds to that of the so-called type I aromatase inhibitors acting by "suicide inhibition". The advantages of exemestane over formestane are described as providing a more potent inhibitor efficacy and the possibility to be given orally.

12. However, exemestane was not the only steroidal, type I aromatase inhibitor known at the filing date of the present application:

- document (6)(L.J. Scott and L.R. Wiseman, Drugs, 1999, Vol. 58, No. 4, pages 675 to 682), besides formestane and exemestane, also mentions on page 681 (right column) atamestane.

– document (7)(A.M.H. Brodie and V.C.O. Njar, Steroids, 2000, Vol. 65, pages 171 to 179) indicates on page 174 (right column, first paragraph) that in addition to formestane a number of other steroidal inhibitors have been identified and cites, besides exemestane and atamestane, 10-propagylandrostenedione. Atamestane and 10-propagylandrostenedione are defined as potent aromatase inhibitors and highly effective in lowering estrogen levels in breast cancer.

– document (8)(A.M.H. Brodie and V.C.O. Njar, J. Steroid Biochem. Molec. Biol., 1998, Vol. 66, No. 1-2, pages 1 to 10) describes in Figure 3 the steroidal aromatase inhibitors MLD 18962 and FCE 24304.

– document (9)(G.J. Kelloff et al., Cancer Epidemiology, Biomarkers and Prevention, 1998, Vol. 7, pages 65 to 78) describes in Figure 4 plomestane, besides atamestane, formestane and exemestane.

13. Therefore, the skilled person had at the filing date of the present application the choice between several potential substitutions to formestane in any of the combinations of documents (1) to (4). In the Board's opinion, the question of whether or not the selection of exemestane could be deduced in an obvious manner from the cited prior art, specially in view of the positive judgement given in document (7) on atamestane and 10-propagylandrostenedione, thus drawing the attention of the skilled person to these aromatase inhibitors and not to exemestane, which was also

mentioned in document (7), should not be answered in a proceedings like the present one where a dialog with the applicant is not provided for. The Board thus considers this case as one envisaged by the Enlarged Board of Appeal in decision G 1/89 (cf *supra* point 3). This decision demands fair treatment to the applicant and in this sense the Board accepts that *prima facie* the replacement of formestane by exemestane in every of the combinations disclosed in documents (1) to (4) provides the technical link to the four groups of invention defined by the ISA (cf *supra* section II), so that an objection of lack of unity pursuant to Article 17(3)(a) and Rule 40.1 and 40.3 PCT is in the Board's view not founded.

Order

For these reasons it is decided that:

1. Refund of the three additional search fees paid by the applicant is ordered.

2. The protest fee shall be refunded.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey