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Datasheet for the decision of 26 October 2006

Case Number: T 0512/02 - 3.3.02

Application Number: 96304570.3

Publication Number: 0749751

IPC: A61K 31/41

Language of the proceedings: EN

Title of invention:
Pharmaceutical composition for use in treatment of diabetes

Applicant:
Takeda Pharmaceutical Company Limited

Opponent:
-

Headword:
Pharmaceutical composition/TAKEDA PHARMACEUTICAL COMPANY Ltd.

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no): arbitrary choice; comparative tests were not based on closest prior art"

Decisions cited:
T 0197/86

Catchword:
-

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Case Number: T 0512/02 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 26 October 2006

Appellant: Takeda Pharmaceutical Company Limited
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 22 May 2001 refusing European application No. 96304570.3 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: J. Riolo
Members: A. Lindner
J. Willems

Summary of Facts and Submissions

I. European patent application No. 96 304 570.3 (publication No. EP-A-0 749 751) was refused by a decision of the examining division dated 9 May 2001 on the basis of Article 97(1) EPC on the grounds of lack of inventive step under Article 56 EPC.

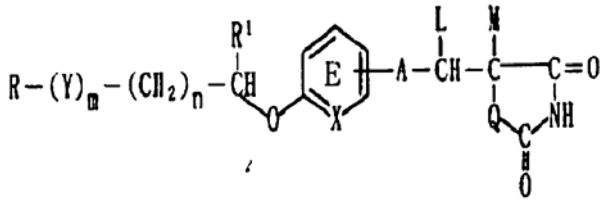
II. The following document, cited during the proceedings before the examining division and the board of appeal, remains relevant for the present decision:

(1) Clinic All-round, 43, 2615-2621 (1994) (English translation)

III. The decision was based on claims 1-36 of the main request filed with the letter of 4 August 1999 and claims 1-15 of the auxiliary request filed on 9 May 2001 during the oral proceedings before the examining division.

Independent claim 1 of the main request before the examining division reads as follows:

1. Pharmaceutical composition which comprises an insulin sensitivity enhancer selected from the group consisting of a compound represented by the formula:



(I)

wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by
-CO-, -CH(OH)- or -NR^3- (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have further 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof in combination with an α-glucosidase inhibitor selected from the group consisting of acarbose, voglibose and miglitol.

Independent claim 1 of the auxiliary request reads as follows:

1. Pharmaceutical composition which comprises the insulin sensitivity enhancer pioglitazone or a pharmacologically acceptable salt thereof in combination with an α-glucosidase inhibitor selected from the group consisting of acarbose, voglibose and miglitol.

IV. The arguments in the decision may be summarised as follows:

In connection with the main request it was held that (1), which was identified as closest prior art, clearly contained the technical teaching that an α-glucosidase

inhibitor, preferably in combination with an insulin sensitivity enhancer, is useful for treating NIDDM. The α-glucosidase inhibitors specifically disclosed in (1) comprised acarbose, voglibose and miglitol, i.e. exactly those compounds which were also claimed in claim 1 of the main request. As for the insulin sensitivity enhancer, the list of compounds specifically disclosed in (1) consisted of ciglitazone, pioglitazone and troglitazone which were all encompassed by formula (I) of the main request. Although the appellant had shown a synergistic effect for some drug combinations, this effect did not give rise to an inventive step, because:

(a) the tests in support of said effect were not representative for the subject-matter as claimed in its entirety

(b) the synergistic effect shown in said tests was not based on the closest prior art as defined by (1).

With regard to the auxiliary request it was held that the selection of three possible combinations (pioglitazone + acarbose; pioglitazone + voglibose and pioglitazone + miglitol) out of the nine possible combinations of (1) was not accompanied by any non-obvious effect. The above-mentioned synergistic effect was inherent in any of the nine possible combinations of (1). Thus, the subject-matter of claim 1 of the auxiliary request was the result of an arbitrary choice within the disclosure of document (1).

V. The appellant (applicant) lodged an appeal against said decision.

VI. The appellant filed a new main request as well as additional tests together with the statement of the grounds of appeal dated 21 September 2001.

Independent claim 1 of the new main request reads as follows:

1. A pharmaceutical composition which comprises pioglitazone or a pharmacologically acceptable salt thereof in combination with acarbose or voglibose.

VII. Oral proceedings were held before the board on 26 October 2006.

VIII. The appellant's submissions, both in the written procedure and at the oral proceedings can essentially be summarised as follows: the limitations introduced into claim 1 of the present main request should not be interpreted as a purposive selection over the disclosure of document (1), but merely as a restriction of the scope of the claimed subject-matter compared to the subject-matter of claim 1 as filed. Document (1) was not pertinent for inventive step because of its highly speculative character which would immediately be recognised by the person skilled in the art. In particular, (1) disclosed active agents which were new on the market at the time when this document was published. None of these compounds had undergone any serious clinical tests so that their suitability for antidiabetic treatment was far from being proven, in particular as far as the combination of different classes of active agents was concerned. Moreover, the language of the document, due to its translation from Japanese into English, was not always clear. The

appellant pointed out that (1) was completely silent about the synergistic effects of the specific combination of active agents as shown in the tests submitted with the statement of the grounds of appeal.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims filed with the written statement of the grounds of appeal dated 21 September 2001.

Reasons for the decision

1. The appeal is admissible.

2. In the present case, the only point at issue is inventive step.

2.1 The subject-matter of the main request concerns a pharmaceutical composition comprising the insulin sensitivity enhancer pioglitazone or a pharmacologically acceptable salt thereof in combination with an α-glucosidase inhibitor selected from acarbose and voglibose (cf. claim 1; page 1, lines 4-8; page 3, lines 2-9; page 3, line 33 - page 4, line 8 and page 20, lines 3-9).

2.2 Document (1) - like the present application - is concerned with the treatment of *diabetes mellitus* and in particular with the treatment of *non-insulin dependent diabetes mellitus (NIDDM)*. In the first part (pp. 3-7) several classes of active agents are disclosed including α-glucosidase inhibitors (named glucose absorption inhibitors in paragraph II on p. 3

of (1)), insulin sensitivity enhancers (named insulin resistance-improving drugs in paragraph III on p. 5 of (1)) and some additional active agents in paragraph IV of (1).

In the second part of (1) therapeutic schemes in the treatment of NIDDM are discussed (cf. paragraph V of (1)). Several treatment schemes are proposed depending on the level of glucose concentration in the plasma. Thus, for a certain type of NIDDM (fasting plasma glucose level = 110 mg/dl and postprandial plasma glucose is 200 mg/dl or above) the use of a sulfonylurea compound or, alternatively, of an insulin resistance-improving agent (= insulin sensitivity enhancer) or a biguanide agent is suggested. Preferably, each of the three compounds is combined with an α-glucosidase inhibitor (cf. p. 6, lines 15 to 9 from the bottom of (1); see also paragraphs 3-5 of the Declaration of Etsuko Nakao dated 22 April 1998). It follows therefrom that document (1) contains a clear teaching to use an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor for the treatment of certain forms of *NIDDM*. As a consequence, this document represents the closest state of the art.

2.3 In the absence of any comparative tests with respect to the closest state of the art as defined by (1), the technical problem underlying the application in suit can only be seen in the provision of further pharmaceutical compositions for the treatment of *NIDDM*.

2.4 The solution to this problem is the provision of pharmaceutical compositions as defined in claim 1 of the present main request.

The board is convinced that the above-mentioned problem was solved in the light of "Experimental Example 1" (cf. pages 30-31 of the application as originally filed) and of the "Experiments" filed with the statement of the grounds of appeal.

2.5 However, the provision of further pharmaceutical compositions for the treatment of *NIDDM* does not involve an inventive step over document (1) for the following reasons: as was mentioned in paragraph 2.2 above, document (1) teaches to use an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor for the treatment of certain forms of *NIDDM*. As far as specific active agents are concerned, it is noted that (1) describes three α-glucosidase inhibitors, namely acarbose, miglitol and voglibose and three insulin sensitivity enhancers: pioglitazone, troglitazone and ciglitazone which yields nine possible combinations altogether. From this very limited number of options, the applicant chose two combinations: pioglitazone plus acarbose and pioglitazone plus voglibose. In this context, it is worthwhile to analyse the expermental data submitted by the appellant as annex to the statement of the grounds of appeal. In said tests the performance of a combination of active agents of the invention is compared with each of the individual compounds but not with combinations outside the present invention but encompassed by document (1). Thus, table 1 of experiment 1 shows an enhanced plasma glucose lowering effect of the combination pioglitazone•HCl + voglibose (144 $\pm$ 23 mg/dl) as compared to pioglitazone•HCL (215 $\pm$ 50 mg/dl) or voglibose (320 $\pm$ 46 mg/dl) alone or the

control (354 ± 29 mg/dl). Similar results were obtained for the combination pioglitazone•HCl + acarbose as compared to the individual compounds (cf. Table 1 of experiment 2). The second set of tests (cf. Table 1 of experiment 1 and Table 2 of experiment 2) shows the reduction in the weight gain of the combinations of the invention as compared to the application of pioglitazone•HCl alone.

To summarise the results of the tests: said tests show effects which are not mentioned in the closest prior art as defined by document (1), **but the effects are not related to the selection of the two combinations as claimed out of the nine possible combinations of document (1)**. Therefore, they are considered to be inherent in said combinations of (1). There is no evidence at all that the two alternatives of the present invention are in any way advantageous over, e.g., the combination ciglitazone + voglibose or pioglitazone + miglitol.

It follows therefrom that the subject-matter as claimed in claim 1 merely constitutes an arbitrary selection out of the nine possible combinations of document (1) which cannot give rise to an inventive step.

3. Arguments of the appellant:

3.1 Speculative character of document (1):

3.1.1 Pharmacological data of the active agents:
The appellant pointed out that at the time document (1) was published the active agents mentioned above were new on the market and, as a consequence, no reliable

data on the pharmacological activity in the form of clinical tests existed. To support his line of reasoning, the appellant cited the passage on p. 5, lines 12-13, of (1) which reads:

> "Both of these drugs are currently evaluated in clinical studies (Fig. 3). Approval application for CS-045 has already been filed to the Ministry of Health and Welfare"

and emphasised that there did not even exist generic names for some of the active agents such as AG-EE 623 ZW (p. 7, line 3 of (1)). As a consequence, the person skilled in the art would not take document (1) into consideration.

The board cannot agree. In this context, it is noted that there is evidence that pharmacological data existed at the time (1) was published. Reference is made to (1), p. 5, lines 13-14, wherein it is stated:

> "Pharmacology and clinical efficacy of AD-4833 and CS-045 have been reviewed in detail elsewhere[7)8)]".

Having regard to the fact that references 7 and 8 of the passage cited above refer to two scientific articles published in 1991 and 1990 respectively, and taking into consideration that AD-4833 stands for pioglitazone, i.e. the insulin sensitivity enhancer selected in claim 1 of the present main request, the board can only conclude that (1) is not speculative as far as the pharmacological properties of the active agents disclosed in (1) are concerned.

3.1.2 Pharmacological data of the treatment strategies:
Again, the appellant held that the treatment strategies of (1) were highly speculative and would not, as a consequence, be followed by the person skilled in the art.

It is certainly true that (1) does not contain any experimental evidence which would prove the efficacy of the combination of active agents and in particular of the combination insulin sensitivity enhancer + α-reductase inhibitor. However, this is not unusual for a review article and certainly does not allow the conclusion that the person skilled in the art would disregard this teaching. On the contrary: as was mentioned above, there is no doubt about the pharmacological activity of the active agents described in (1) so that the skilled person would most certainly be interested in a combination of active agents which is classified as a preferred treatment scheme in (1). After all, the combination of active agents with different mechanisms of action for treating the same disease is quite common in pharmacy. Furthermore, it is again emphasised that the number of possible combinations in (1) is very limited: with only nine possible choices, the person skilled in the art is certainly more inclined to combine active agents than if he were confronted with a vast number of possible combinations where he could not reasonably expect all of them to give the desired effect.

3.2 Clarity of the translated text of document (1):
As far as the clarity of the language of (1) is concerned, it is noted that the text shows that it was

translated from a language that is very remote from English. However, it can be clearly understood, in particular in the light of the Declaration of Etsuko Nakao dated 22 April 1998. In the absence of any evidence to the contrary, the board has no reason to doubt that the translation of the original Japanese text is accurate.

3.3 Alleged synergistic effect

The appellant, making reference to the tests discussed in paragraph 2.5 above, argued that two non-obvious effects were shown for the compositions as claimed: surprisingly low plasma glucose levels and a reduction of the body weight increase caused by long-term application of pioglitazone.

The board does not contest that these effects were indeed shown by said tests. It is also correct that these effects are not mentioned in (1). However, the effects in question cannot establish an inventive step for the following reasons: it has been established case law at the EPO that, if comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect, the nature of the comparison with the closest state of the art must be such that the said effect is convincingly shown to have its origin in the distinguishing feature of the invention (T 0197/86, OJ 1989, 371). This is clearly not the case here, as the comparison was made with individual active agents rather than with combinations of an insulin sensitivity enhancer plus an α-reductase inhibitor encompassed by (1) but outside the scope of present claim 1.

3.4 As for appellant's argument that the limitations introduced into claim 1 are merely a restriction of the scope of the claimed subject-matter compared to claim 1 as originally filed and should not be interpreted as a purposive selection over document (1), the board wants to emphasize that this point is irrelevant, as the assessment of inventive step is based on an objective comparison between the subject-matter as defined by the claims and the closest state of the art.

As a consequence, the arguments of the appellant cannot succeed. Under these circumstances, there is no need to consider the remaining claims.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman

A. Townend J. Riolo