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**Datasheet for the decision
of 7 May 2012**

Case Number: T 0184/10 - 3.3.02

Application Number: 98200252.9

Publication Number: 861666

IPC: A61K 31/4439, A61K 31/155,
A61P 3/10

Language of the proceedings: EN

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

Patentee:
Takeda Pharmaceutical Company Limited

Opponent:
Teva Pharmaceutical Industries Ltd.

Headword:
Treatment of diabetes/TAKEDA PHARMACEUTICAL COMPANY LIMITED

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - (no): insufficient comparative tests"

Decisions cited:
T 1357/06

Catchword:
-



Case Number: T 0184/10 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 7 May 2012

Appellant: Teva Pharmaceutical Industries Ltd.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
27 November 2009 concerning maintenance of
European patent No. 861666 in amended form.

Composition of the Board:

Chairman: H. Kellner
Members: A. Lindner
L. Bühler

Summary of Facts and Submissions

- I. European patent No. 0 861 666 based on application No. 98 200 252.9 was granted on the basis of a set of 23 claims.

Independent claim 1 reads as follows:

"1. Pharmaceutical composition which comprises an insulin sensitivity enhancer selected from pioglitazone, 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2, 4-thiazolidinedione or a pharmacologically acceptable salt thereof in combination with metformin."

- II. The patent was opposed under Article 100(a) EPC for lack of inventive step and under Article 100(c) EPC for amendments that contain subject-matter extending beyond the content of the earlier application as filed.

- III. The documents cited during the opposition and appeal proceedings included the following:

- (7) T. Kuzuya, et al., Diabetes Research and Clinical Practice, 11 (1991), 147-153
- (8) B.C.C. Cantello, et al., J.Med. Chem., 37 (1994), 3977-3985
- (8a) H.E. Lebovitz, Drugs, 44 (Suppl. 3), (1992), 21-28
- (13) A.J. Sheen, et al., Diabète & Métabolisme, 19 (1993), 547-559
- (14) B.T. Kinsley, et al., The Endocrinologist, 3 (1993), 321-327

- IV. In the decision pronounced on 1 June 2006 and posted on 3 July 2006, the patent in suit was revoked by the opposition division, as the ground of opposition mentioned in Article 100(c) EPC prejudiced the maintenance of the European patent in its unamended and amended form.
- V. In decision T 1357/06 of 16 September 2008, the board decided that the subject-matter of claim 1 of the main request, relating to the combination of pioglitazone and metformin, met the requirements of Articles 76 and 123(2) EPC and remitted the case to the department of first instance for further prosecution.
- VI. In the interlocutory decision of the opposition division pronounced on 16 November 2009 and posted on 27 November 2009, the main request was found to meet the requirements of the EPC. The wording of its claim 1 is unchanged with respect to claim 1 of decision T 1357/06.

The opposition division decided that the subject-matter of the main request was novel over document (14), as the skilled person would have to select from two lists of some length in order to arrive at the subject-matter of claim 1.

Regarding inventive step, the opposition division defined the provision of a combination treatment for non-insulin-dependent diabetes mellitus (NIDDM) with improved efficacy and decreased side effects as the technical problem, which had been convincingly solved in the light of the tests submitted by the patentee (then applicant) with letter dated 7 March 2002. The

solution in the form of the specific combination comprising pioglitazone and metformin involved an inventive step, as document (14) did not make any particular suggestions in connection with combinations of active agents to be used. Neither was the specific combination of pioglitazone and metformin rendered obvious by document (7) or (8).

VII. The opponent (appellant) lodged an appeal against that decision.

VIII. With a letter dated 5 April 2012, the appellant submitted new evidence in the form of a declaration and five documents.

IX. Oral proceedings before the board took place on 7 May 2012. Claim 1 of the main and sole request reads as follows:

"1. Pharmaceutical composition which comprises the insulin sensitivity enhancer, pioglitazone, or a pharmacologically acceptable salt thereof, in combination with metformin."

X. The appellant's arguments can be summarised as follows:

The combination of pioglitazone with metformin for the treatment of NIDDM was specifically disclosed in document (14), so that the subject-matter of claim 1 lacked novelty.

Regarding inventive step, document (14), which disclosed the combination of a thiazolidinedione (TZD), selected from ciglitazone, pioglitazone, englitazone

and troglitazone, with a second active agent, selected from a sulfonylurea and metformin, for the treatment of NIDDM, was defined as closest prior art. The specific combination of pioglitazone with metformin constituted one of several possibilities for carrying out the teaching of document (14), each of them being obvious in the absence of any unexpected effect. Both sets of comparative tests submitted by the respondent in the course of the proceedings were insufficient.

XI. The respondent's arguments can be summarised as follows:

Document (14) was not relevant to novelty, as the combination of pioglitazone with metformin involved a selection from two lists.

Regarding inventive step, it was emphasised that document (14) was speculative and therefore not suitable as closest prior art. Moreover, the beneficial effects obtained by combining pioglitazone with metformin were clearly demonstrated in the comparative tests submitted with the letters dated 7 March 2002 and 21 October 2010, while the appellant had not filed any evidence disproving the existence of said effects. As a consequence, the claimed subject-matter involved an inventive step.

XII. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 861 666 be revoked.

The respondent (patentee) requested that the appeal be dismissed. It requested further not to admit the declaration and documents filed by the appellant with

letter dated 5 April 2012 into the appeal proceedings. In case these documents were admitted into the proceedings, the respondent requested remittal of the case to the department of first instance and apportionment of costs according to Article 104 EPC.

Reasons for the Decision

1. The appeal is admissible.
2. Novelty

Document (14) mentions in the paragraph headed "Future Trends in Treatment of NIDDM" (see first complete paragraph of the right-hand column on page 326) that thiazolidinediones (TZDs) were currently undergoing human trials in patients with NIDDM. Four TZDs, namely ciglitazone, pioglitazone, englitazone and CS-045 (= troglitazone) are specifically disclosed. Further down in the same paragraph comes the statement that TZDs might turn out to be "first-line agents", but that it was more likely that they could play a role in combination therapy as insulin sensitizers in patients already on sulfonurea or metformin and that they could act as "insulin sparers" by reducing the insulin dose in NIDDM patients treated with insulin. This means that, in order to arrive at the subject-matter of present claim 1, the skilled person would have to select pioglitazone from a list of four TZDs and metformin from a second list consisting of sulfonylurea, metformin and insulin.

In this context, it is noted that the board cannot agree with the appellant's statement that metformin is the most preferred active agent of the second list. Reference is made to the paragraph headed "Side effects of Metformin" on page 325 of document (14), according to which lactic acidosis constitutes the classical side effect associated with biguanide therapy, which requires careful patient selection. The board concludes therefrom that both sulfonylureas and metformin have their advantages and disadvantages and that neither of them is suitable for every type of patient. Furthermore, the second list is not restricted to sulfonylureas and metformin, but additionally comprises insulin, which means that metformin has to be selected from a list of three active agents of about equal ranking.

As a consequence, document (14) does not specifically disclose the subject-matter according to present claim 1, so that the requirements of Article 54 EPC are met.

3. Inventive step

3.1 The subject-matter of present claim 1 concerns a pharmaceutical composition comprising the insulin sensitivity enhancer pioglitazone or a pharmaceutically acceptable salt thereof in combination with metformin.

3.2 Document (14), which like the contested patent relates to the treatment of NIDDM (see first sentence of the summary on page 321), constitutes the closest prior art.

The respondent argued that document (14) did not qualify as closest prior art because of its speculative character. Indeed, there are some phrases to be found in the first paragraph of the section "Future Trends in Treatment of NIDDM" on page 326 (e.g. "compounds that act as insulin sensitizers **might be expected** to have an important role in treatment", "[a] group of drugs which **may act in this manner**, the thiazolidinediones...", "[it] is **interesting to speculate** on the possible future role of the thiazolidinediones...", "[it] is even **more likely** that they could play a role in combination therapy..." [emphasis by the board]) which, at first sight, might lead to such a conclusion. However, the above-mentioned paragraph of document (14) also reveals that at the time when document (14) was published, the TZDs, and in particular ciglitazone, pioglitazone and englitazone, were undergoing human trials in patients with NIDDM and that further data concerning, among others, the mechanism of action, were available from animal models. Taking into consideration these data as well as common general knowledge, the author of document (14) then gave an outlook into future trends, which were of course not yet verified by experimental evidence. In view of the fact that this outlook was based on the data available at the time, the skilled person would not dismiss it as pure speculation. Instead, he would regard it as a serious attempt to interpret the existing state of the art. As a consequence, the content of document (14) qualifies as closest prior art.

Document (14) recommends, in the first paragraph of the section "Future Trends in the Treatment of NIDDM" (see right-hand column on page 326), a combination therapy

for the treatment of NIDDM, comprising a TZD such as ciglitazone, pioglitazone, englitazone or troglitazone and a second active agent selected from the group consisting of a sulfonylurea, metformin and insulin. As can be derived from point 2 above, the combination pioglitazone + metformin is not specifically disclosed therein. To define the technical problem solved by the invention according to present claim 1 with regard to document (14), it is necessary to evaluate the experimental evidence submitted by the respondent in the course of the proceedings.

3.2.1 Comparative tests submitted by the respondent (then applicant) with the letter dated 7 March 2002

These tests involve genetically obese and diabetic male Wistar rats, which were divided into groups A to D, each consisting of six rats. Group A served as control group, in group B 1 mg/kg body weight per day of pioglitazone HCl, in group C 300 mg/kg body weight per day of metformin and in group D 1 mg/kg body weight of pioglitazone HCl and 300 mg/kg body weight of metformin per day were orally administered for 15 days. At day 14, blood was collected from the tail vein and analysed. The following results were obtained:

Table 1:

Group	Plasma glucose (mg/dl)
A (control)	391.43 ± 25.79
B (pioglitazone HCl)	224.05 ± 48.75
C (metformin)	305.43 ± 52.11
D (pioglitazone HCl + metformin)	149.88 ± 29.98

Table 2:

Group	Body weight increase (g/15 days)
A (control)	8.0 ± 7.6
B (pioglitazone HCl)	72.5 ± 11.3
C (metformin)	20.6 ± 4.7
D (pioglitazone HCl + metformin)	58.1 ± 7.8

Regarding the decrease in plasma glucose, it is noted that table 1 shows a less than additive effect for group D (391.43 mg/dl - 149.88 mg/dl = 241.55 mg/dl) as compared to the sum obtained from the decrease in plasma glucose according to groups B and C ((391.43 mg/dl - 224.05 mg/dl) + (391.43 mg/dl - 305.43 mg/dl) = 253.38 mg/dl). The obtained effect was therefore entirely predictable and cannot serve to demonstrate an improvement over the prior art.

The data according to table 2 are supposed to demonstrate an unexpected decrease in weight gain for the combination pioglitazone + metformin. Weight gain is an undesirable side effect of many active agents used in the treatment of NIDDM including pioglitazone. Table 2 shows a weight gain for group C, i.e. the group treated only with metformin, as compared to the control group A. This finding is contradictory to the established teaching of the prior art, according to which metformin does not lead to weight gain. This established teaching can be found, among others, in the following documents: document (8a) discloses that the

administration of metformin is usually associated with a modest weight loss (see the last complete sentence on the right-hand column of page 24). Document (14) mentions a 1-3% weight loss caused by the administration of metformin (see penultimate sentence of the chapter "Effects of Metformin" in the right-hand column of page 324). Document (13) notes that "Metformin does not cause weight gain in diabetic patients ... and often promotes weight loss, notably in patients who follow an energy-restricted diet... During one year of metformin therapy, there was an average weight loss of 1.2 kg in obese diabetic patients compared with an average weight gain of 5.2 kg in patients receiving chlorpropamide..." (see second paragraph of the chapter "1) Metformin" in the left-hand column of page 552).

This established teaching of the prior art is now challenged by an animal model. Animal models are useful means for demonstrating a pharmacological effect, in particular in the early stages of development, in which clinical data are frequently not yet available. Usually, the results thus obtained are then extrapolated to clinical conditions involving human patients. However, despite being accepted as a valuable source of information, animal models constitute only an approximation to the real conditions, so that their data are less meaningful than those obtained from treatment of human patients. As a consequence, results obtained from animal models are useful pointers but cannot overturn a technical teaching based on treatment of human patients as is the case with the documents cited in the preceding paragraph. Therefore, the tests submitted with the letter dated 7 March 2002, which

include a comparison between the weight gain of rats treated with pioglitazone HCl (table 2, group B) with rats treated with pioglitazone HCl plus metformin (table 2, group D), raise doubts as to whether this specific animal model constitutes at all suitable evidence for demonstrating whether or not the administration of metformin, alone or in combination with other active agents, leads to weight gain in human patients. As a consequence, the tests did not persuade the board on the balance of probabilities that the administration of metformin results in weight gain in human patients.

In view of this finding, evaluation of whether the experimental conditions were correctly chosen is not necessary.

3.2.2 Comparative tests submitted by the respondent with the letter dated 21 October 2010

These tests, which are again based on an animal model using Wistar rats, are supposed to show that the combination pioglitazone + metformin significantly lowers the glucose concentration in the blood as compared to the combinations ciglitazone + metformin and troglitazone + metformin. The results, expressed as Δ -glycosylated hemoglobin (Δ GHb), are summarised in table 3.

Table 3:

Group	ΔGHb (%)
A (control)	-0.17 ± 0.08
B (pioglitazone + metformin)	-1.87 ± 0.19
C (ciglitazone + metformin)	-1.22 ± 0.20
D (troglitazone + metformin)	-1.33 ± 0.15
E (metformin)	-1.22 ± 0.25

Table 3 shows that group B effects a statistically significant reduction of ΔGHb as compared to groups C and D. However, in view of the fact that there are no data relating to the administration of pioglitazone, ciglitazone and troglitazone alone, i.e. without metformin, it is not possible to attribute the enhanced ΔGHb to the specific combination of pioglitazone + metformin as claimed. It may just as well be caused by a higher potency of pioglitazone as compared to ciglitazone or troglitazone alone, in which case the enhanced ΔGHb observed in group B is foreseeable for the skilled person. As a consequence, these tests do not constitute suitable evidence, in that the attained beneficial effect cannot unambiguously be related to the distinguishing features of claim 1.

3.3 In view of the fact that none of the comparative tests is suitable for showing an unexpected effect for the combination pioglitazone + metformin, the underlying problem may be defined as simply putting into practice the teaching of document (14). The solution proposed by the subject-matter defined in claim 1 of the main and sole request consists in the selection of the combination of pioglitazone and metformin. In view of the overall disclosure of the original application, in

particular as far as the passages on page 1, lines 4-8, page 2, lines 25-36, page 18, lines 2-3, and page 20, line 32 to page 21, line 2, are concerned, the board is satisfied that the problem defined above has been plausibly solved.

As was already mentioned above, document (14) recommends a combination therapy for the treatment of NIDDM in which a TZD, preferably a TZD selected from ciglitazone, pioglitazone, englitazone and troglitazone, is combined with a sulfonylurea, metformin or insulin. In order to carry out the teaching of document (14), the skilled person must make a choice: he must select one of the four TZDs mentioned above and combine it with any one agent of the second list. In the absence of any unexpected effect, each of the possible combinations suggested by document (14) is an arbitrary choice and therefore devoid of an inventive activity. As a consequence, the requirements of Article 56 EPC are not met.

4. In view of this finding, a decision on the admissibility of the evidence filed by the appellant with the letter dated 5 April 2012 as well as on the apportionment of costs according to Article 104 EPC is not necessary.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:

N. Maslin

H. Kellner