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Datasheet for the decision of 9 November 2015

Case Number: T 0045/12 - 3.3.02

Application Number: 01203170.4

Publication Number: 1174135

IPC: A61K31/4439, A61K31/64

Language of the proceedings: EN

Title of invention:
Pharmaceutical composition comprising pioglitazone and glimepiride for use in treatment of diabetes

Patent Proprietor:
Takeda Pharmaceutical Company Limited

Opponents:
Laboratorios CINFA, S.A.
Teva Pharmaceutical Industries Ltd.

Headword:
Combination of pioglitazone and glimepiride for treating diabetes/TAKEDA

Relevant legal provisions:
EPC Art. 100(a), 100(b), 100(c)

Keyword:
Main request - allowable (yes)

Decisions cited:
T 1329/04, T 1357/06

Catchword:

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European Patent Office
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Case Number: T 0045/12 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 9 November 2015

Appellant: (Patent Proprietor)	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku Osaka (JP)
Representative:	Dossmann, Gérard Casalonga & Partners Bayerstrasse 71-73 80335 München (DE)
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Representative:	Jané Bonet, Montserrat ZBM PATENTS Zea, Barlocci & Markvardsen Pl. Catalunya, 1 08002 Barcelona (ES)
Respondent 2: (Opponent 2)	Teva Pharmaceutical Industries Ltd. 5 Basel Street, P.O. Box 3190 Petah Tiqva 49131 (IL)
Representative:	Prins, Hendrik Willem Arnold & Siedsma Bezuidenhoutseweg 57 2594 AC The Hague (NL)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 22 December 2011 revoking European patent No. 1174135 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	U. Oswald
Members:	M. C. Ortega Plaza
	D. Prietzel-Funk

Summary of Facts and Submissions

I. European patent EP 1 174 135, based on European patent application No. 01203170.4, which was filed as a divisional application of European patent application No. 98200252.9, parent application, which itself was filed as a divisional application of European patent application 96304570.3, root application, was granted with eleven claims.

II. Claim 1 as granted reads as follows:

"1. Pharmaceutical composition which comprises an insulin sensitivity enhancer selected from pioglitazone or a pharmacologically acceptable salt thereof in combination with the insulin secretion enhancer glimepiride."

III. Oppositions were filed and revocation of the patent in its entirety was requested pursuant to Article 100(a) in conjunction with Article 56 EPC, for lack of inventive step, Article 100(b) EPC and Article 100(c) EPC.

IV. The following documents were cited *inter alia* in opposition and appeal proceedings:

O3 P.S. Gillies et al., "Pioglitazone", Drugs 2000, 60(2), 333-343

O4 R. W. Whitcomb et al., "Thiazolidinediones", Exp. Opin. Invest. Drugs, 1995, 4(12), 1299-1309

O5 T. Ishida et al., "Oral hypoglycemic agents - new oral drugs and new strategy of treatment", Clinic All-round, 1994, 43, 2615-2621 (English translation)

O6 B. C. C. Cantello et al., "[[ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents", J. Med. Chem., 1994, 37, 3977-3985

O7 EP 0 193 256

O8 T. Kuzuja et al., "A pilot clinical trial of a new oral hypoglycemic agent, CS-045, in patients with non-insulin dependent diabetes mellitus", Diabetes Research and Clinical Practice, 1991, 11, 147-153

O9 H. Ikeda et al., "Effects of pioglitazone on glucose and lipid metabolism in normal and insulin resistant animals", Arzneim.-Forsch./ Drug Res., 1990, 40(I) Nr. 2, 156-162

O10 B. T. Kinsley, "Using the oral hypoglycemic agents", The Endocrinologist, 1993, 3(5), 321-329

O13 E. Draeger, "Clinical profile of glimepiride", Diabetes Research and Clinical Practice, 1995, 28, Suppl., S139-S146

O14 G. Müller et al., "Stimulation of glucose utilization in 3T3 adipocytes and rat diaphragm *in vitro* by the sulphonylureas, glimepiride and glibenclamide, is correlated with modulations of the cAMP regulatory cascade", Biochemical Pharmacology, 1994, 48(5), 985-996

O15 H. Mlodzik, "Antidiabetics: analysis of patenting 1990-1994", Exp. Opin. Ther. Patents, 1995, 5(7), 685-688

O19a News release: "AD-4833" developed by Takeda" Takeda Chemical Industries, Ltd., February 29, 1996 (English translation)

O26 K. Kosaka et al., "Clinical evaluation of a new oral hypoglycemic drug CS-045 in patients with non-insulin dependent diabetes mellitus poorly controlled by sulfonylureas", Journal of

Clinical Therapeutics and Medicine, 1993, 9, Suppl. 3, 1-38

O27 B. M. Forman et al., "15-Deoxy-$\Delta^{12,14}$-Prostaglandin J_2 is a ligand for the adipocyte determination factor PPARγ", Cell, 1995, 83, 803-812.

V. The present appeal lies from a decision of the opposition division revoking the patent under Article 101(2) EPC.

The opposition division considered that the main request (claims as granted) did not contain added matter under Article 100(c) EPC (together with Articles 76(1) and 123(2) EPC) for analogous reasons to those given in decision T 1357/06 of 16 September 2008 (same board as in the present case but in another composition) in relation to the patent deriving from the parent application.

However, the opposition division was of the opinion that the subject-matter claimed in the main request lacked inventive step (Article 100(a) in conjunction with Article 56 EPC).

Additionally, the opposition division did not admit the late-filed document T2 into the proceedings since it was no more relevant than the documents already on file and did not specifically disclose the claimed combination therapy of antidiabetic agents.

VI. The patent proprietor (appellant) lodged an appeal against said decision and filed grounds thereto.

The appellant requested with its grounds of appeal that the decision under appeal be set aside and that the

patent be maintained as granted, or alternatively that the case be remitted to the first instance for further prosecution since the decision of the opposition division was insufficiently reasoned in the sense of Rule 111(2) EPC, which amounted to a substantial procedural violation.

VII. Respondent 1 filed a reply to the grounds of appeal.

It requested that the decision of the opposition division not to admit document T2 be overturned and that the appeal be dismissed.

VIII. With its reply to the grounds of appeal respondent 2 filed again a copy of document T2 and two other documents, which it had filed for the first time in opposition proceedings with its letter of 6 October 2011. However, respondent 2 did not request that the opposition division's decision not to admit document T2 into the proceedings be overturned. Moreover, it no longer pursued its objection of lack of novelty based on document T2.

Respondent 2 also filed an expert declaration by Mr Gerich, together with a post-published document by M. C. Riddle in support of its arguments of lack of inventive step.

Moreover, respondent 2 submitted arguments within the meaning of Article 100(c) EPC and Article 100(b) EPC.

Respondent 2 requested that the appeal be dismissed and that the request for remittal to the opposition division be refused.

IX. The board sent a communication pursuant to Article 15(1) RPBA as an annex to the summons to oral proceedings.

With this communication the board gave *inter alia* a preliminary view on added matter (Article 100(c) EPC) with regard to the main request on file (claims as granted). Moreover, the board expressed the preliminary opinion that the decision of the opposition division was reasoned within the sense of Rule 111(2) EPC since it contained sufficient reasons in support of the findings that the claimed subject-matter lacked inventive step over prior-art document O5. Furthermore, the board made some observations about inventive step and pointed to document O4 as possible closest prior art.

The board further indicated that it did not intend to overrule the opposition division's decision not to admit document T2 since the opposition division had duly exercised its discretionary power by applying the correct principles. As a consequence the board noted that novelty was not within the framework of the present appeal.

X. With its letter of 24 September 2015 the appellant filed a reply to the board's communication. It also filed a new main request and an auxiliary request.

The set of claims of the main request differs from the set of claims as granted in that granted claims 6 and 11 were deleted and the remaining claims were renumbered accordingly.

Claim 1 of the main request is identical to claim 1 as granted (see paragraph II above).

Claims 2, 3, 4, 5, 6, 8 and 9 read as follows:

"2. Pharmaceutical composition according to claim 1, wherein the insulin sensitivity enhancer and the insulin secretion enhancer are mixed all together."

"3. Pharmaceutical composition according to claim 1, wherein the insulin sensitivity enhancer and the insulin secretion enhancer are formulated independently for administration independently of each other, either concurrently or at staggered times to the same subject."

"4. Pharmaceutical composition according to anyone of claims 1 to 3, for the prophylaxis or treatment of diabetes."

"5. Pharmaceutical composition according to anyone of claims 1 to 3, for the prophylaxis or treatment of diabetic complications."

"6. Use of an insulin sensitivity enhancer selected from pioglitazone or a pharmacologically acceptable salt thereof in combination with the insulin secretion enhancer glimepiride, for the manufacture of a pharmaceutical composition for the prophylaxis and treatment of diabetes."

"8. Use of an insulin sensitivity enhancer selected from pioglitazone or a pharmacologically acceptable salt thereof in combination with the insulin secretion enhancer glimepiride for the manufacture of formulations wherein the insulin sensitivity enhancer and the insulin secretion enhancer are formulated independently, to be administered independently, either

concurrently or at staggered times to the same subject, for the prophylaxis and treatment of diabetes."

"9. Use of an insulin sensitivity enhancer selected from pioglitazone or a pharmacologically acceptable salt thereof in combination with the insulin secretion enhancer glimepiride for the manufacture of formulations wherein the insulin sensitivity enhancer and the insulin secretion enhancer are formulated independently, to be administered independently, either concurrently or at staggered times to the same subject, for the prophylaxis and treatment of diabetic complications."

XI. With a letter dated 13 October 2015 respondent 2 informed the board that it would not attend the oral proceedings.

XII. Oral proceedings took place on 9 November 2015 in the absence of respondent 2.

In the course of the oral proceedings the appellant stated that it withdrew its request for remittal to the opposition division on the grounds that the opposition division's decision was not sufficiently reasoned.

Respondent 1 declared at the oral proceedings that it did not maintain its request to admit document T2 into the appeal proceedings. It further announced that it had no objections against the admission into the appeal proceedings of the requests filed by the appellant with letter of 24 September 2015.

Moreover, none of the parties present at the oral proceedings contested the chairman's statement that the grounds pursuant to Article 100(c) EPC, Article 100(b)

EPC and Article 100(a) in conjunction with Article 56 EPC, were within the framework of the appeal.

The board notes that although the appellant submitted amended page 2 of the description (the only amendment is the deletion of paragraph [0017]), according to the printout of the B1 document the page in which deletion of paragraph [0017] should be undertaken is page 3 of document B9. Page 3 of document B9 corresponds to page 2 of document B1 with the correction of paragraph [0009] (the word "enhancer" was deleted after the word "pioglitazone" and reintroduced after the word "sensitivity").

As regards the submitted amended page 4 of the description (deletion of the text of the claims, text of the specification unamended) of document B1, the specification corresponds identically to that on page 5 of document B9.

XIII. The appellant's arguments, as far as relevant for the present decision, may be summarised as follows:

Added matter

The appellant argued that the root application disclosed on page 24, lines 24 to 28 in general terms the form of the claimed formulations as being together in admixture or being formulated independently for administration as a kit-of-parts. Thus, there was a clear basis for the features characterising claims 2, 3, 8 and 9. The appellant stressed that respondent 1 no longer objected to the combination of pioglitazone (or a pharmacologically acceptable salt thereof) with glimepiride. As regards the technical effects mentioned

in claims 4 to 9, they derived directly and unambiguously from the root application as filed.

Inventive step

The appellant submitted that the problem-solution approach should be correctly applied for assessing inventive step in order to avoid an ex-post-facto analysis.

Furthermore, the appellant stated that document O4 represented the closest prior art since it disclosed a concrete combination of troglitazone, an insulin sensitivity enhancer (insulin resistance-improving drug), with glibenclamide, a sulfonylurea compound, whereas document O5 only disclosed the general concept of combining an insulin resistance-improving drug with a sulfonylurea agent and did not disclose an actual combination. Document O5 related to an invitation to perform a research programme and glimepiride was a possible sulfonylurea agent among many others known at that time.

The combination claimed differed from the combination disclosed in document O4 in its two active agents. The objective technical problem was thus the provision of an improved composition for the treatment of diabetes or diabetic complications. This problem was plausibly solved, as shown in the experimental data submitted on 21 June 2007; the glucose-lowering effect was four to five times improved when compared to the effect for the combination known from document O4. The magnitude of the improvement was attributable to the combination of the two agents and not solely to a possible difference in potency of troglitazone and pioglitazone. The dose of 400 mg mentioned in

document O4 was administered to adult human patients. Assuming an average body weight of 75 kg, the employed dose of 3 mg/kg body weight in the animal experimental model was adequate.

Decision T 1329/04 28 June 2005 was not relevant at the present case since the function of the two active ingredients as antidiabetic agents was known to the filing date of the patent.

The appellant stressed that document O6 disclosed the class of thiazolidinediones known at the filing date of the patent and it taught that the most potent hypoglycemic thiazolidinedione was compound 37 (also known as rosiglitazone) and not pioglitazone (page 3980, Tables 1 and 2).

Moreover, none of the remaining prior-art documents provided an indication to replace both active agents of the combination in document O4.

Sufficiency of disclosure

The appellant submitted again that the invention related to the combination of two agents known in the art as antidiabetics for the treatment of diabetes or diabetic complications. The invention did not rely on a new therapeutic use for the known compounds. Therefore the disclosure provided in the patent was sufficient for a person skilled in the art in order to put the invention into practice.

XIV. Respondent's 1 arguments, as far as relevant for the present decision, may be summarised as follows:

Added matter

Respondent 1 argued that the subject-matter of claim 3 contained added matter as several selections were necessary from the root application as filed. Although it did not raise objections against claim 1, it took the view that at least the choice of the specific active ingredients represented a first selection and that the form of the formulation being a single dosage form or being administered independently as a kit-of-parts represented a further selection. Such a formulation was not individualised in the root application and thus was not allowable. Claims 2, 6, 8 and 9 contained added subject-matter for analogous reasons. Respondent 1 further argued that claims 4 and 5 contained added subject-matter since the root application provided a basis only for the prophylaxis and treatment of diabetes (page 28, line 29) but not for the prophylaxis or treatment of diabetes as claimed.

Inventive step

Respondent 1 stated that document O5 represented the closest prior art since it disclosed the combined use of an insulin resistance-improving drug and a sulfonylurea agent (page 7, line 30 to 32). Document O5 described only a very limited number of combinations possible: glimepiride was the only specifically mentioned sulfonylurea (page 6, section IV) and ciglitazone, pioglitazone and CS-045 (troglitazone) were the only three specifically mentioned insulin resistance-improving drugs (page 5, section III).

Additional experimental evidence should not be taken into account in the present case, by analogy with the situation in T 1329/04, since the patent was not the first disclosure of a combination of an insulin

sensitivity enhancer with a sulfonylurea agent, thus the effect of improvement over the individual antidiabetic ingredients mentioned in the patent was not relevant. As the patent in suit did not contain any data for the particular combination of pioglitazone with glimepiride, the objective technical problem could not be defined as the provision of an improved composition, but had to be formulated in a less ambitious way as the provision of an alternative composition for the treatment of diabetes. Such an alternative was obvious in the light of the disclosure in document O5, alone, or combined with the teaching in document O6. Document O6 described that pioglitazone was more potent than ciglitazone and troglitazone (page 3980, table 1) and thus provided a clear indication for choosing pioglitazone from the three insulin resistance-improving drugs disclosed in O5.

Respondent 1 submitted that in the experimental data provided with letter of 7 October 2011 sub-therapeutic doses for troglitazone and ciglitazone had been used in view of the results for the combinations containing them, when compared to control. Respondent 1 also said the duration of the experiments submitted by the appellant was too short to provide conclusive data. In the context of the dosage for the active agents, in particular for the insulin sensitivity enhancer, it referred to document O9 (page 160, right-hand column), document O4 (page 1305, left-hand column, third paragraph) and document O3 (page 333, abstract). Furthermore, respondent 1 argued that in the experiments of 21 June 2007 the initial plasma glucose level was not stated. Therefore, the appellant's calculations in the statement of grounds of appeal (page 7) expressed as percentages of reduction should not be used since they were relative to the unknown

initial glucose concentration. Furthermore, the measurement of the difference delta (Δ) of the plasma glucose was less appropriate than the measurement of the area under the curve (AUC).

Respondent 1 filed further arguments in account of documents O3 to O10, O13 to O15, O19, O26 and O27 supporting its view that document O5 was the closest prior art and that the skilled person would consider it obvious to choose the combination of pioglitazone with glimepiride in the light of the technical effects disclosed in the prior art for pioglitazone or glimepiride.

Sufficiency of disclosure

During the oral proceedings respondent 1 endorsed respondents 2' arguments submitted with its reply to the grounds of appeal.

XV. Respondent 2's written arguments, as far as relevant for the present decision, may be summarised as follows:

Added matter

The earlier application as filed only gave directions towards the combination of pioglitazone with either voglibose or glibenclamide. The selection of pioglitazone in combination with glimepiride had to be considered a new technical teaching for which there was no direct and unambiguous disclosure in the application as filed.

Inventive step

Respondent 2's essentially submitted the same line of arguments as respondent 1. The arguments in the expert opinion of Mr Gerich are analogous to those submitted by respondent 1 at the oral proceedings before the board.

Sufficiency of disclosure

Respondent 2 argued that claims 3 to 5 and 7 to 11 of the set of claims as granted (they correspond to claims 3 to 5 and 6 to 9 of the main request), which concerned medical uses, were not sufficiently disclosed. The patent did not provide enough disclosure to show the suitability of the claimed composition for the medical use, namely the treatment of diabetes or diabetic complications, wherein no adverse effects even in the long term and additionally efficacy for a large cohort of the diabetic population were achieved. In fact, the patent contained no experimental data for the specific combination claimed. Even though the active agents were known in the art for their anti-diabetic properties, it was not evident that the claimed combination would achieve the desired medical effects.

XVI. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request or, alternatively, on the basis of the auxiliary request, both requests filed with the letter dated 24 September 2015.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. The oral proceedings before the board took place in the absence of respondent 2 who had been duly summoned but decided not to attend, as announced with its letter of 13 October 2015. According to Rule 115(2) EPC, if a party duly summoned to oral proceedings does not attend them, the proceedings may continue without that party.

As stipulated by Article 15(3) RPBA the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case.

In the present case, respondent 2's announcement that it would not be attending the oral proceedings was made after the appellant had filed a new main request with the letter of 24 September 2015. It was respondent 2's own choice not to attend the oral proceedings and not to file in writing any comments addressing the admission of this request, or the amendments made. Since the set of claims of the main request filed with the letter of 24 September 2015 differs from the main request previously on file (set of claims as granted) merely in the deletion of two claims, respondent 2's submissions filed with its letter of 6 November 2012, as far as relevant, have been considered for the present decision.

3. Main request

3.1 The main request was filed as a direct reply to the board's communication pursuant to Article 15(1) RPBA, expressing the board's preliminary opinion.

The set of claims of the main request differs from the set of claims as granted in that claims 6 and 11 as granted have been deleted and claims 7 to 10 have been renumbered accordingly. These amendments do not open new issues for discussion.

Therefore, the main request was admitted into the proceedings.

Respondent 1 did not contest the admission of the main request and respondent 2 did not file any comments in this respect.

3.2 *Added subject-matter*

3.2.1 The claims remaining in the main request are identical to claims as granted, since the only difference between the main request and the set of claims as granted is the deletion of two claims (claims 6 and 11) which were specifically directed to the salt of pioglitazone with hydrochloric acid.

3.2.2 Article 100(c) EPC was filed as a ground for opposition during the nine-month opposition period (Article 99 EPC).

Claim 1 is a product claim which relates to the combination of pioglitazone (or a pharmacologically acceptable salt thereof) with glimepiride.

The root application as filed relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics. An analogous situation to the case of the parent application (see decision T 1357/06 of 16 September 2008) arises in the present case for the

subject-matter of claim 1 in consideration of the following: all through the description of the root application as filed (the same applies to the parent application as filed) pioglitazone is disclosed as the most preferred sensitivity enhancer to be used in combination with another antidiabetic agent. Among the antidiabetic agents to be used in combination with pioglitazone, the (most preferred) specific compounds are explicitly mentioned. Glimepiride is one specific antidiabetic agent disclosed for use as second component in the pharmaceutical composition (page 23, line 21 of the root application, and parent application as filed). Thus, even assuming that the pharmaceutical composition containing pioglitazone and glimepiride would require a selection (among the specific antidiabetic agents disclosed to be combined with pioglitazone) this one-dimensional selection does not introduce added subject-matter over the content of the root and parent applications as filed. Insulin secretion enhancers (this class of compounds includes glimepiride) are mentioned as an alternative to "an insulin preparation" (last paragraph on page 22 of the root application as filed). However, the disclosure in the paragraph bridging pages 23 and 24 makes it clear that the combination of pioglitazone (most preferred compound of formula II, see page 18 of root application as filed) with an insulin enhancer is the one preferred.

In view of the above, the specific combination of pioglitazone (or a pharmacologically acceptable salt thereof) with glimepiride is singularised in the root application as filed. Moreover, in the light of the disclosure on page 1, first paragraph of the root application, the pharmaceutical composition comprising the specific combination is also disclosed.

Additionally, the general disclosure on page 24, first full paragraph, does not exclusively relate to a combination of an insulin sensitivity enhancer and a further antidiabetic generically defined; rather, it applies directly and unambiguously to each combination of active ingredients singled out in the root application. Even if the combination of pioglitazone and glimepiride is not explicitly mentioned on page 24, it is inevitable that the general disclosure on page 24, lines 18 to 28 of the root application as filed directly applies to it since it is one of the combinations singularised in said application. Thus, it is directly and unambiguously disclosed in the root application as filed (page 24, lines 18 to 28) that this particular combination of active ingredients may be in admixture (claim 2 of the main request), or formulated independently for administration either concurrently or at staggered times to the same subject (kit-of-parts, claim 3; use claims 8 and 9 of the main request).

Additionally, the claims of the main request do not single out any dosage form from among those defined more specifically in the description (paragraph bridging pages 24 and 25 and following paragraphs on pages 25, 26 and 27, lines 1 and 2) but remain only in the general terms appearing on page 24, lines 18 to 28.

The combinations of antidiabetic agents are disclosed in the root application as filed for their antidiabetic use (page 1, first paragraph, page 2, under the heading "Summary of the invention"). The root application as filed discloses combinations of an insulin sensitivity enhancer together with another antidiabetic agent with a different mode of action for prophylaxis or treatment

of diabetes (page 2, lines 34, 35, page 4, line 10). The combinations containing the most preferred insulin sensitivity enhancer, pioglitazone, are also disclosed for the prophylaxis or treatment of diabetes (page 5, line 14, page 5, line 23). Therefore, this general disclosure concerning treatment and prophylaxis of diabetes directly and unambiguously applies to the combination of pioglitazone with glimepiride, glimepiride being explicitly disclosed as insulin secretion enhancer (page 23). Moreover, the root application as filed discloses that the pharmaceutical compositions lower blood glucose in diabetics and that they can be used for the prophylaxis and treatment of diabetic complications (page 28, second paragraph). Thus, the purposive product claims and the use claims of the main request which are directed to the treatment or prophylaxis of diabetes, and of diabetic complications (claims 4 to 9 of the main request), also find an allowable basis in the description of the root application as filed.

Correspondingly, the subject-matter of the main request is directly and unambiguously disclosed in the root application as filed (these findings also apply to the parent application as filed, which contains analogous passages to those mentioned for the specification in the root application).

3.2.3 Respondent 1's argument that claim 5 of the main request contained subject-matter because it stated "for the **prophylaxis or treatment** of diabetic complications" instead of "for the prophylaxis **and** treatment of diabetic complications" cannot succeed for the following reasons. This objection is purely linguistic and asks for a literal support for the claim's wording in the root application as filed. However, it is not a

prerequisite that the claim's wording should find *verbatim* support for claimed subject-matter not extending beyond the content of the earlier (root) application as filed. The skilled person in the medical field reading the sentence "can be advantageously used for the prophylaxis and treatment of diabetic complications" on page 28, lines 29 and 30, readily understands that the usefulness of the pharmaceutical compositions covers both options, namely prophylaxis and treatment of diabetic complications. These options are translated into purposive product claim 5.

3.2.4 Consequently, the claims of the main request do not contain added subject-matter within the meaning of Article 100(c) EPC.

3.2.5 Owing to the fact that the claims directed to the salt of pioglitazone with hydrochloric acid were deleted as a direct reply to the board's communication pursuant to Article 15(1) RPBA expressing the board's opinion that the specific salt pioglitazone hydrochloride was not singled out in the root application as filed, paragraph [0017] of the specification was also deleted.

3.2.6 Additionally, there is no legal basis for respondent 1's request that the "working example" in paragraphs [0032] and [0033] of the patent be renamed "reference example", if not deleted. Paragraph [0032] clearly expresses that "The following working example is merely intended to illustrate as a reference the present invention in further detail but it is not within the scope of the invention".

Consequently, this request by respondent 1 is not admissible.

3.3 As expressed in the board's communication sent under Article 15(1) RPBA, the ground for opposition concerning lack of novelty pursuant to Article 100(a) EPC in conjunction with Articles 52(1) and 54 EPC for lack of novelty was not filed in accordance with Article 99 EPC within the nine-month period. During opposition proceedings, opponent 2 raised an objection of lack of novelty for the first time with its letter of 6 October 2011 on the basis of document T2 which had been filed as an annex to said letter.

The decision of the opposition division (making use of its discretionary power) not to admit document T2 into the proceedings because it was no more relevant than other documents already on file implies that the late-filed ground for opposition was not admitted into the proceedings.

Respondent 2 did not pursue its objections of lack of novelty vis-à-vis document T2 during the appeal proceedings. Respondent 1, which had raised an objection of lack of novelty vis-à-vis document T2 with its reply to the statement of grounds of appeal, withdrew at the oral proceedings before the board its request to admit T2. Moreover, respondent 2 did not contest the board's findings that novelty (Article 100(a) in conjunction with Articles 52(1) and 54 EPC) was not within the framework of the present appeal proceedings.

3.4 Inventive step

3.4.1 Preliminary remark

The relevant date for Article 54(2) EPC is the filing date of the application (20 June 1996) since the

priority date is not valid as effective filing date for the specific combination of pioglitazone with **glimepiride**. This has not been contested by the appellant.

3.4.2 Document O5 is a paper published in 1994 concerning new developments in the treatment of Diabetes Mellitus and its complications, which is entitled "Oral hypoglycemic agents - new oral drugs and new strategy of treatment". Section III which is entitled "Insulin resistance-improving drugs" recalls the prevalence of non-insulin-dependent Diabetes Mellitus (NIDDM) in Japan and the meaning of insulin resistance (insufficient insulin activity) as a promoting factor. Document O5 describes Takeda's pioglitazone and Sankyo's troglitazone as insulin resistance-improving drugs which "are currently evaluated in clinical studies". Document O5 then goes on to describe the pharmacological actions of these two drugs which lead to a decrease in plasma glucose.

Insulin resistance-improving drugs have also been called insulin sensitivity enhancers (see paragraph [0003] of the patent in suit) owing to their mode of action. In fact, the expression "insulin sensitivity enhancers" is also used in the paragraph below Figure 4 on page 6 of document O5.

Additionally, Figure 3 on page 5 depicts the structural formulae of ciglitazone, pioglitazone and troglitazone (all of them being thiazolidinedione derivatives) and Figure 4 on page 6 depicts a schematic drawing on the mechanism of action of insulin resistance-improving drugs. Document O5 explains that "insulin resistance-improving drugs are useful in improving insulin resistance, one of the etiologic factors for NIDDM. Although this class of drugs is slightly less effective

in reducing plasma glucose than sulfonylureas, they are effective for the treatment of obesity-related diabetes mellitus without inducing hypoglycemia" (page 6, first paragraph).

Section IV of document O5 is entitled "New insulin secretion stimulators" and states: "Interest has been centered on new antidiabetic drugs such as glucose absorption inhibitors and insulin resistance-improving drugs. Because of their mild nature in activity, however, these drugs are considered to be used in combination with sulfonylureas or insulin preparations rather than used alone". Section IV goes on to give a generic description of a generation of sulfonylureas (with rapid onset of action) and new insulin secretion stimulators with additional actions which "are currently evaluated in clinical studies". Hoechst's glimepiride (a sulfonylurea) is explicitly mentioned on the paragraph bridging pages 6 and 7, which states that "glimepiride is potent in reducing plasma glucose" and explains that "The fact that this drug has an ability to improve insulin resistance, one of the etiologic factors for NIDDM, further supports the usefulness of glimepiride as an antidiabetic drug".

On page 7 document O5 mentions a further drug, newly developed by Novo Nordisk, which is "a compound completely different from sulfonylureas".

Section V of document O5, which is entitled "Development of NIDDM and new therapeutic strategy at each disease stage" reads as follows: "At present, diabetes mellitus is primarily treated by preservative or symptomatic therapy. Either of these is not a radical therapy aimed to eliminate etiologic factors and to achieve complete cure" (page 7, first paragraph

under section V). Further on in the second paragraph, the following is stated: "In diabetic state, combined use of drugs shown below is attempted depending on the severity of pathologic conditions, impaired insulin secretion, and insulin resistance (Fig. 6)". In fact, Figure 6 on page 9 shows schematically the following therapeutic strategies for NIDDM (in case of values 140-199 mg/dl for fasting plasma glucose): "sulfonylurea alone; combined use of sulfonylurea agent and insulin resistance-improving drug; three-drug combination (sulfonylurea agent + insulin resistance-improving drug + α-glucosidase inhibitor)". Thus, this disclosure of a combined use of drugs with different mode of action is of a general nature and invites the reader to perform a research programme for choosing the adequate active ingredients. Moreover, document O5 does not explicitly disclose which are the specific insulin resistance-improving drug and the specific sulfonylurea agent actually used in combination in the new therapeutic strategy, since it merely states that "If fasting plasma glucose is in a range from 140 to 199 mg/dl, a sulfonylurea agent is used alone, or combined use of sulfonylurea and insulin resistance-improving agent is attempted. Also in this case, it is preferable to use an α-glucosidase inhibitor in combination with these drugs (three-drug combination)" (on page 7, lines 30 to 33).

An objective reading of the content of document O5 does not permit the conclusion that glimiperide is inevitably the sulfonylurea used in the 'attempted' combined use mentioned on page 7 of document O5. The skilled person knew that sulfonylureas was a class of antidiabetic agents encompassing several compounds developed throughout the years (sulfonylureas have been used as oral hypoglycemic agents, OHAs, since the

1950s; see document O13, abstract). Moreover, the skilled person also knew that thiazolidinediones was a class encompassing several compounds (document O6 confirms this aspect). The teaching in section V of document O5 is generic and addresses the combined use of a sulfonylurea agent (not necessarily the product developed by Hoechst) and an insulin resistance-improving drug (not necessarily one of the three drugs depicted in Figure 3 on page 5) as a new therapeutic strategy. Therefore, document O5 does not concretise any particular combination of glimepiride with one of the insulin resistance-improving drugs in Figure 3, namely ciglitiazone, pioglitazone and troglitazone. Since document O5 does not concretise which is the two-drug combination for use as a new therapeutic strategy, it is necessary to look for a specific and thus more promising starting point where a particular combination therapy of a sulfonylurea and an insulin sensitivity enhancer is specifically disclosed.

Document O4 is a review article published in the year 1995 entitled "Thiazolidinediones" and disclosing their pharmacological action as insulin sensitivity enhancers. Document O4, which specifically discloses the combination therapy of the insulin sensitivity enhancer troglitazone with glibenclamide (sulfonylurea agent) (page 1304, right-hand column, last paragraph) represents the closest prior art. In particular, document O4 discloses that the specific use of troglitazone in combination with glibenclamide led to a decreased glucose level in NIDDM subjects (same paragraph).

3.4.3 In the light of the closest prior art the problem to be solved lies in the provision of an improved combination of antidiabetic agents for lowering plasma glucose.

The proposed solution is the combination of pioglitazone with glimepiride.

The experimental data submitted on 21 June 2007 relate to experimental tests performed on male Wistar fatty rats, which genetically showed obesity and type 2 diabetes (corresponds to NIDDM). These experiments tested a control group (A) with no antidiabetic drug, and four groups with the combinations of antidiabetic drugs pioglitazone with glimepiride (B), ciglitazone with glimepiride (C), troglitazone with glimepiride (D) and troglitazone with glibenclamide (E). The delta (Δ) plasma glucose (mg/dL) at 240 minutes, i.e. differences of plasma glucose from 0 minutes, were measured and the results shown in Table 1 and Figure 1, where values are expressed as mean with the standard deviation (SD) for each group. The results show that the combination of pioglitazone with glimepiride (group B) lowered the Δ plasma glucose (mg/dL) more markedly than any other combination. Thus, the combination pioglitazone with glimepiride shows an improvement in lowering plasma glucose when compared to the specific combination of the closest prior art (troglitazone with glibenclamide). Moreover, this improvement is attributable to the particular combination claimed, since the combination troglitazone with glimepiride gives similar results to the combination troglitazone with glimenclamide.

The absolute figures of the experimental results submitted on 21 June 2007 (and their statistical significance) have not been contested. However, the following has been disputed by the respondents: the experimental dose for the active ingredient, in particular troglitazone, the duration of the

experiments, and the non-stated initial glucose concentration values.

Document O4 states a daily dose for the treatment of human patients with troglitazone as 400 mg/d (page 1305, right-hand column, line 2). NIDDM patients are treated with 200, 400, 600 or 800 mg/d in clinical trials (page 1304, bridging paragraph left- and right-hand columns). Daily dosages of troglitazone (CS-405) (400 mg is preferred over 200 mg) are also administered in a pilot clinical trial to human patients with NIDDM reported in document O8. Assuming an average body weight of 75 kg in clinical trials with human patients, the daily dose of 3 mg/kg body weight for the experimental tests on obese rats, submitted on 21 June 2007, is of an acceptable order of magnitude. Moreover, administering each of the individual antidiabetic agents in the submitted experimental animal model at a different dose would have introduced an additional variable interfering with the results obtained for the combinations, which would have not allowed a straight comparison between the combinations. The skilled person comparing results for different combinations can calculate which combinations are better in relation to the control when all active ingredients are administered at the same dose. The experiments in document O9 do not test combinations of active agents. Document O9 discusses, for instance, the effect of different dosages depending on the type of animals employed, normal rats or obese rats. Additionally, document O9 teaches that the "effective dose" of the thiazolidinedione (when taken alone as hypoglycemic agent) for a 25% reduction of blood glucose level was 31 mg/kg/d for ciglitazone and 6 mg/kg/d for pioglitazone ("Discussion", page 160, right-hand column).

However, document O6 shows that the order of magnitude for the percentage of reduction in area under the tolerance curve (AUC) at 3000 µmol/kg of diet is similar for ciglitazone and pioglitazone.

Document O3 is a monograph about pioglitazone disclosing that the daily dose for human patients is 15 to 45 mg/day.

Additionally, it is only natural that different active compounds achieve comparable levels of efficacy at different dosages, but this knowledge does not invalidate the experimental design in the data submitted on 21 June 2007 for comparative purposes with the closest prior art. Moreover, arithmetic calculations do not render predictable, with a certain degree of certainty, the pharmacological effect of a new combination of two active ingredients. Only after the new combination is actually tested does the skilled person know whether it results in cumulative or contradictory effects.

As regards the duration of the experiments it has to be said that the experimental data submitted on 21 June 2007 relate to a valid animal model for measuring the effect on lowering glucose, which is the technical effect disclosed in the patent for the combination of antidiabetic agents. In the experimental animal model of NIDDM disclosed in document O6, the thiazolidine-dione compound is administered for eight days to genetically obese mice (in the experimental tests submitted on 21 June 2007, the thiazolidinedione compound is administered for seven days). Additionally, clinical trials on human patients are not a

prerequisite for obtaining patents in the medical field.

The experimental design measures Δ plasma glucose (mg/dL) in a control group to which no antidiabetic drug was administered. Thus, the results for Δ plasma glucose (mg/dL) of groups B to E can be compared with the control group. Since in the experimental data submitted on 21 June 2007 the initial plasma glucose concentration values of the obese rats are not explicitly stated, a relative value (and not the absolute value) can be calculated for the attained decrease in plasma glucose. However, there is no evidence proving that the combination pioglitazone with glimepiride would not lead to a greater reduction in plasma glucose, when expressed as a reduction in AUC, than the known combination of the prior art. As a matter of fact the appellant submitted on 7 October 2011 experimental data showing a significant reduction in plasma glucose AUC_{0-240} expressed as mg.h/mL for the combination pioglitazone with glimepiride (group B). Neither of the respondents has submitted experimental data disproving these findings. The experimental data submitted on 7 October 2011 not only show that there is a significant reduction in plasma glucose when compared to control but also show that the reduction for the claimed combination is greater than that attained with the combinations ciglitazone with glimepiride (group C), or troglitazone with glimepiride (group D). The fact that the results for groups C and D are poor shows that these two combinations are far less potent than the combination pioglitazone and glimepiride. These results are not contradictory with the results in the experimental report submitted on 21 June 2007.

Finally, the respondents have not discharged their onus of proof by filing their own experimental reports to disprove the appellant's experimental data.

In view of the above, the respondents' objections have not thrown serious doubts on the finding that an improvement in the lowering of plasma glucose has been achieved by the claimed combination.

Additionally, having regard to the fact that the combination of two antidiabetic agents, namely an insulin sensitivity enhancer with a sulfonyl urea, was generically and specifically known in the prior art for lowering plasma glucose, the problem initially defined in the patent (paragraph [0030], improvement in lowering plasma glucose over the individual active ingredients) had to be reformulated. Thus, the submission of an experimental report taking into account the prior-art knowledge is admissible, since the prior art and the subject-matter claimed are so close that the tests are necessary as an indication of inventive step. Moreover, the present situation differs from the situation in appeal case T 1329/04 of 28 June 2005 because both active ingredients were known at the filing date as antidiabetic agents. Since the pharmacological function of the individual active ingredients was already known at the filing date and the combination is claimed for its antidiabetic effects, it is not necessary that the patent contains actual data in this respect.

3.4.4 It has now to be assessed whether the proposed solution is obvious in the light of the cited prior art.

As already mentioned above, document O5 does not concretise which combination of an insulin sensitivity

enhancer and a sulfonyl urea is tested. Thus, the skilled person does not have any hint in document O5 to choose a specific combination which would bring an improvement over the combination troglitazone with glibenclamide known from document O4.

Document O6 is a scientific paper published in the year 1994 about the compound class thiazolidinediones as "potent antihyperglycemic agents". Document O6 mentions pioglitazone, troglitazone and englitazone as being progressed clinically (page 3977, sentence bridging left and right-hand column). However, the teaching in document O6 is not reduced to these three derivatives. Tables 1 and 2 show the pharmacological activity (expressed as % reduction in area under glucose tolerance curve at µmol kg^{-1} of diet) for many thiazolidinedione derivatives. Whereas it is correct to say that pioglitazone shows better results than ciglitazone or troglitazone (CS-045) at 3000 µmol kg^{-1}, the thiazolidinedione compound showing the best results is compound 37 (even at a lower dose, namely at 300 µmol kg^{-1}). Document O6 teaches that the thiazolidiedione derivatives 31, 32, 37 and 49 (none of them being pioglitazone) are far more potent analogues than troglitazone (page 3980, paragraph bridging left- and right-hand columns under Table 2).

Document O7 is a patent application published in the year 1986 which discloses the thiazolidinedione derivative pioglitazone (compound of formula I in Table 1 on page 9). Pioglitazone shows better results in relation to blood glucose values than ciglitazone (ciglitazone is a thiazolidinedione developed earlier than pioglitazone). Thus, the older document O7 does not add anything to the teaching in document O6.

Document O9, which is a scientific publication from 1990 relating to the effects of pioglitazone on glucose and lipid metabolism in normal and insulin-resistant animals, confirms the findings in document O7 that pioglitazone, when used alone, shows better results than ciglitazone (page 157, left-hand column, page 160, left- and right-hand columns). Thus, document O9 does not add any further teaching to the teaching in document O6 in relation to the thiazolidinedione derivatives available as insulin sensitivity enhancers at the filing date of the patent in suit.

Document O8 teaches the skilled person that the rate of efficacy of troglitazone (CS-045) when given in combination with another oral hypoglycemic agent, OHA (the compound 'other OHA' is not specified in Table 2, page 151 of document O8) is the same as when troglitazone is given alone (abstract). Thus, document O8 does not contain any pointer when looking for a particular improved combination of an insulin sensitivity enhancer with a sulfonylurea.

Document O10 reports in the year 1993 about the "Future trends in treatment of NIDDM" on page 326. Under that heading, document O10 teaches that insulin sensitisers such as the thiazolidinediones are currently undergoing human trials in patients with NIDDM and further states that "The most extensively studied members in this group are ciglitazone, pioglitazone, and englitazone, all of which have similar pharmacological effects". Further on document O10 reports on a 'new' thiazolidinedione derivative CS-405 (troglitazone) and its pharmacological profile as insulin sensitiser. Document O10 explains that one future use for thiazolidinediones is "a combination therapy as insulin sensitizers in patients already on sulfonylureas or

metformin" (a biguanide derivative). Thus, document O10 does not teach the skilled person how to provide an improved combination of antidiabetic agents over the combination troglitazone with glibenclamide of document O4.

Document O3, published in the year 2000 and relating to a monograph about pioglitazone, does not form part of the state of the art (Article 54(2) EPC). Moreover, even if its content were taken as a kind of post-published evidence, it remains silent about which are the sulfonylureas used in the combined therapy mentioned on page 340, and the test results in Figure 4 about cholesterol levels do not add anything to the problem-solution approach.

Document O13 concerns a scientific paper relating to the clinical profile of glimepiride, a "new" sulfonylurea. Document O13 states that "Glimepiride was well tolerated and fewer episodes of hypoglycemia were observed in the glimepiride than in the glibenclamide group" (abstract). Document O13 further teaches that the "results of phase II and III clinical trials showed that glimepiride achieves blood glucose lowering effects with the lowest dose of any sulfonylurea compounds" and a "more rapid onset of action" (page S145, left-hand column). Apart from the fact that document O13 does not give any hint about the behaviour of these sulfonylureas in a combination therapy, the experimental tests filed on 21 June 2007 show that the improvement attained by the combination pioglitazone with glimepiride cannot be explained by the properties of glimepiride when compared to glibenclamide, since the results obtained by the combinations troglitazone with glimepiride (D) and troglitazone with glibenclamide (E) are similar.

An analogous reasoning to that given above in relation to document O13 applies to document O14, which relates to the 'novel' sulfonylurea glimepiride, and document O15 (Antidiabetics, analysis of patenting 1990-1994). Document O14 does not add anything more relevant than document O13 to the knowledge of the skilled person looking for a solution to the technical problem. Document O15 confirms that Hoechst-Roussel was introducing glimepiride, "a once-daily active sulfonylurea derivative for the treatment of type II diabetes", before the filing date of the patent in suit, and that the compound was found to lower blood sugar levels more than glibenclamide. However, as shown by the comparison between groups (D) and (E) in the experimental data of 21 June 2007, the difference in the profiles glimepiride and glibenclamide does not reflect an improvement in the decrease of (Δ) plasma glucose (mg/dL). Thus, the knowledge about a sulfonylurea monotherapy cannot be directly transposed to a combination therapy with an insulin sensitivity enhancer. Moreover, even if the skilled person contemplated the possibility of replacing the sulfonylurea glibenclamide with glimepiride, he would not necessarily contemplate simultaneously changing the insulin sensitivity enhancer.

Document O26, published in the year 1993 and relating to the clinical evaluation of a 'new' oral hypoglycemic drug CS-405 (troglitazone) in patients with non-insulin dependent diabetes mellitus poorly controlled by sulfonylureas, merely confirms that the choice of the specific combination therapy disclosed in document O4 as the most promising starting point is correct.

The fact that phase III test was completed for AD-4833, developed by Takeda (this compound is pioglitazone), shortly before the filing date of the patent in suit (document O19 and its English translation O19a) does not influence the choice of the closest prior art, since the skilled person starts from a concrete combination of an insulin sensitivity enhancer and a sulfonyl urea. Moreover, the fact that phase III test was completed for pioglitazone does not diminish the technical teaching in document O6, which goes in the direction of rosiglitazone and its analogues as most potent thiazolidinediones. Additionally, the information about pioglitazone in document O19 does not demonstrate which are the actual compounds tested in the combination with a sulfonylurea generally mentioned in document O5, which remain unidentified in the prior-art document.

The board notes that document O27, which investigates a possible correlation between the adipocyte determination factor PPARγ (potential regulator of adipogenesis) binding affinity and the antidiabetic potency for six different thiazolidinediones (page 809, right-hand column), neither indicates nor contra-indicates the use of pioglitazone together with glimepiride as a solution to the stated problem.

Finally, document O5 does not only teach a combination of two antidiabetic agents but also addresses a three-drug combination therapy with an α-glucosidase inhibitor (page 7, lines 32-33).

Further documents cited by respondent 2 in writing are no more relevant than the documents already discussed above. As regards the post-published document filed with respondent 2's reply to the grounds of appeal as

an annex to the expert opinion, its content does not reflect the knowledge of the skilled person at the time of the invention, namely the filing date.

3.4.5 Correspondingly, the cited prior art does not render obvious the solution proposed in the claims of the main request, where both active ingredients have been exchanged in the combination. As a consequence, the subject-matter claimed in the main request involves an inventive step (Article 56 EPC).

3.5 Sufficiency of disclosure

The objections in relation to lack of sufficiency of disclosure put forward by respondent 2 with its reply to the grounds of appeal, and endorsed by respondent 1 during the oral proceedings before the board, do not hold because both active ingredients of the specific combination in the claims of the main request are known in the prior art as antidiabetic agents, in particular as oral hypoglycemic agents. The technical effects for which the combination is claimed are plausible in the light of the description and the general knowledge of the skilled person at the filing date of the patent.

Moreover, it is the sufficiency of the invention claimed which has to be investigated. The claims directed to the medical use do not define an absence of possible adverse effects for the long-term therapy. Moreover, clinical trials showing efficacy for a large cohort of a (diabetic) population is not a prerequisite for sufficiency of disclosure of inventions in the medical field.

The skilled person knows how to carry out the invention by performing the combination therapy: administration

of the known compounds either in admixture or separately, since he knows from his general knowledge how to put into practice the mode of administration.

The claims of the main request correspond to claims as granted (only the claims directed to pioglitazone hydrochloride were deleted). Thus, in the light of the evidence on file the ground for opposition pursuant to Article 100(b) EPC does not prejudice the maintenance of the patent on the basis of those claims.

3.6 Since the main request is allowable, there is no need to discuss the auxiliary request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the claims of the main request filed with the letter of 24 September 2015 together with the description as amended during the oral proceedings before the board.

The Registrar: The Chairman:

N. Maslin U. Oswald

Decision electronically authenticated