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**Datasheet for the decision  
of 11 December 2008**

**Case Number:** T 1287/05 - 3.3.04

**Application Number:** 96304924.2

**Publication Number:** 0753298

**IPC:** A61K 45/06

**Language of the proceedings:** EN

**Title of invention:**

Synergistic combination comprising an insulin sensitizer and a HMG-CoA reductase inhibitor for treating arteriosclerosis

**Patentee:**

Sankyo Company Limited

**Opponent:**

Novo Nordisk A/S

**Headword:**

Synergistic combination/SANKYO

**Relevant legal provisions:**

EPC Art. 56, 83, 111(1)

**Relevant legal provisions (EPC 1973):**

-

**Keyword:**

"Main request - sufficiency of disclosure (yes)"

"Inventive step - partially (yes)"

"Remittal (yes)"

**Decisions cited:**

G 0005/83, G 0006/88, T 0192/82, T 0019/90, T 1319/04

**Catchword:**

-



Case Number: T 1287/05 - 3.3.04

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.04  
of 11 December 2008

**Appellant:** Novo Nordisk A/S  
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**Respondent:** Sankyo Company Limited  
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**Representative:** Andrews, Tim and Wallace, Sheila  
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**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
26 July 2005 concerning maintenance of European  
patent No. 0753298 in amended form  
(Article 102(3) EPC 1973).

**Composition of the Board:**

**Chairman:** U. Kinkeldey  
**Members:** M. Wieser  
R. Moufang

## Summary of Facts and Submissions

- I. The appeal was lodged by the Opponent (Appellant) against the decision of the Opposition Division, whereby the European patent No. 0 753 298 could be maintained in amended form according to Article 102(3) EPC (1973).
- II. The patent had been opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC) and under Article 100(b) EPC.

The Opposition Division had decided that claims 1 to 73 of the Patent Proprietor's (Respondent's) then main request met all requirements of the EPC. These claims were identical to claims 1 to 73 as granted (claims 74 to 76 as granted had been deleted).

- III. The Board dispatched a first written communication on 13 December 2005 in order to clarify a contradiction between the actual decision taken by the Opposition Division and the minutes of the oral proceedings before the Opposition Division.

In a second communication dated 9 May 2008 the Board expressed its preliminary opinion on substantive issues.

Oral proceedings were held on 11 December 2008 in the absence of the Appellant, who had informed the Board with letter dated 10 October 2008, that he will not attend the oral proceedings.

IV. The Appellant requested that the decision under appeal be set aside and that the patent be revoked.

The Respondent requested that the decision under appeal be set aside and the patent be maintained on the basis of the claims of the main request, or of one of auxiliary requests I to V, all filed with letter dated 10 October 2008.

V. Claim 1 of Respondent's main request read as follows:

"The use for the manufacture of a medicament for the prevention or treatment of atherosclerosis or xanthoma, of a first agent selected from the group consisting of HMG-CoA reductase inhibitors and a second agent selected from the group consisting of insulin sensitizers, said first and second agents being provided in a form in which they may be administered together or within such a period as to act synergistically together."

Dependent claims 2 to 73 referred to preferred embodiments of the use according to claim 1.

VI. The following documents are referred to in this decision:

(2) Biochim. et Biophys. Acta, vol. 960, 1988, pages 294 to 302

(3) Lancet, vol. 344, 1994, pages 1383 to 1389

(4) JP-A-07-041423, English abstract

- (5) US 4 728 739
- (6) WO 94/25026
- (7) EP-A-0 419 035
- (8) US 5 132 317
- (9) US 4 895 861
- (19) Statistical analysis, Prof. Freeman, 24 March 2003
- (26) Statistical comments, Prof. Andersen,  
15 April 2004
- (27) Dorland's illustrated medical dictionary,  
26th Ed., 1985, W.B. Saunders Comp., pages 119 to  
120
- (32) American J. Med., vol. 103, 1997, pages 491 to 497
- (33) Diabetes, vol. 53, 2004, pages 2169 to 2176
- (48) Statistical calculations regarding the data in  
table 4 of the patent in suit, submitted by the  
Appellant with letter of 25 November 2005
- (51) EP-A-0 604 853
- (52) EP-A-0 481 243

VII. The submissions by the Appellant may be summarised as follows:

The minutes of the oral proceedings before the Opposition Division were incorrect. The decision taken by the Opposition Division at the end of these oral proceedings was that the patent could be maintained with claims 1 to 73 as granted according to Article 102(3) EPC 1973.

The claims lacked an inventive step for various reasons. Neither the claims nor the description contained a definition of what was meant by the terms "HMG-CoA reductase inhibitors" and "insulin sensitizers". Claim 1, moreover, did not indicate which time period between administering the first and second agent fell within the scope of the claim.

The claims referred to a combination of two known types of agents which were each individually used to treat high lipid levels in blood. It was therefore *prima facie* obvious to combine these two types of agents. Even if a synergistic effect was obtained by this obvious step, which was not the case, this was merely a bonus effect which did not confer inventiveness.

Neither the patent nor Respondent's late filed evidence showed the existence of a synergistic effect. The data provided by the Respondent were scientifically irrelevant. As a result of the small number of tested animals, the p-value of the experimental results was much too high. Therefore, Respondent's experimental results were unreliable to support any credible conclusion. Even if the p-value were to be ignored,

which would be scientifically incorrect, also Respondent's best data failed to show the claimed effect. The five specific combinations which were actually tested, including two specific HMG-CoA reductase inhibitors and three specific insulin sensitizers, did not show a general synergistic effect.

The patent did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a skilled person (Article 83 EPC). The Respondent himself had argued that he did not provide experimental results which convincingly showed the presence of synergy, because it would be unrealistic to perform such experiments. This had the consequence that performing these tests, which were a must for working the claimed invention, would amount to undue burden. This was all the more so as the patent did not provide any reliable test to decide whether a particular compound fell within the definitions "HMG-CoA reductase inhibitors" and "insulin sensitizers".

VIII. The submissions by the Respondent may be summarised as follows:

The minutes of the oral proceedings before the Opposition Division were not correct. The Chairman of the Opposition Division announced at the end of the oral proceedings that the patent could be maintained in amended form on the basis of claims 1 to 73 as granted.

Claim 1 had to be interpreted to contain two different embodiments, one requiring that the two compounds were administered together, and the other that the two compounds were administered consecutively. This second

embodiment was further characterised by the feature that the time period between the administration of the first and the second compound was limited such that they still acted synergistically together.

At the date of filing insulin sensitizers were considered to be therapeutically ineffective. To combine a HMG-CoA reductase inhibitor with an insulin sensitizer was therefore far from being *prima facie* obvious.

The experimental tests carried out were not designed to prove the existence of a synergistic effect with statistical certainty. The number of test animals required for achieving such scientifically reliable conclusion would have been much too high. Nevertheless, the skilled person when cumulatively analysing the data provided, could determine an overall trend showing the existence of synergy.

The terms "HMG-CoA reductase inhibitor" and "insulin sensitizer" were known in the art. A skilled person had no problem to decide whether or not a specific compound fell under this definition.

The use of a medicament containing a HMG-CoA reductase inhibitor and an insulin sensitizer for the prevention or treatment of atherosclerosis or xanthoma was not known in the art. Therefore, the answers to the questions referred to the Enlarged Board of Appeal in decision T 1319/04 (22 April 2008) were not relevant for the present case.



## Reasons for the decision

### *The appealed decision*

1. According to the written reasoned decision, the Opposition Division, at oral proceedings held on 15 April 2005, had decided that the claims set out in Patent Proprietor's (Respondent's) then main request, namely claims 1 to 73 as granted, met all requirements of the EPC. Claims 74 to 76 as granted were no longer contained in this main request.
2. The minutes of the oral proceedings before the Opposition Division were in contradiction to this decision. In points (2.5), (3.7) and (4.3) thereof it was stated that the patent as granted met the requirements of Articles 54(2), 56 and 83 EPC. In point (5) it was said that the Chairman announced the decision to maintain the patent on the basis of the claims as granted and the adapted description. Finally on EPO form 2309.2 it was said that after deliberation of the Opposition Division and before closing the oral proceedings on 15 April 2005 at 13:31 hours the Chairman announced the following decision: **"The opposition is rejected"**.
3. The Board, in a communication dated 13 December 2005, has called the parties for their recollection of what the actual decision announced orally by the Chairman at the end of said oral proceedings was, as, in case this decision was as stated on EPO form 2309.2 of the minutes, this would be considered as a substantial procedural violation which would require the case to be remitted to the department of first instance according

to Article 10 of the Rules of Procedure of the Boards of Appeal (in their then applicable form).

4. Both parties answered on 11 January 2006 and stated that, to their recollection, the decision announced by the Chairman at the end of the oral proceedings before the Opposition Division was that the patent could be maintained with claims 1 to 73 as granted according to Article 102(3) EPC 1973. The minutes of the oral proceedings before the Opposition Division were incorrect in this respect.
  
5. The Board is therefore convinced that there was no divergence between the decision as announced at the end of the oral proceedings and the written reasons for the decision. Thus, no remittal to the department of first instance for further prosecution (Article 111(1) EPC and Article 11 of the Rules of Procedure of the Boards of Appeal) is required.

*Amendments - Articles 123(2) and (3) EPC*

6. Claim 1 of Respondent's main request refers to "the prevention or treatment of **atherosclerosis** or xanthoma" (emphasis added by the Board), while the granted claim referred to "the prevention or treatment of arteriosclerosis or xanthoma".

Basis for this amendment can be found throughout the description of the application as published, for example on page 2, line 6 and in examples 2, 3 and 4.

"Arteriosclerosis" is a general term used to define three distinct diseases, namely atherosclerosis,

Mönckeberg's arteriosclerosis and arteriolosclerosis (see document (27)). Thus, by restricting the use according to claim 1 to the prevention or treatment of only one of these three diseases, the scope of protection has been reduced.

The requirements of Articles 123(2) and (3) EPC are met.

*Sufficiency of disclosure - Article 83 EPC*

7. In a first line of argument the Appellant submitted that the patent actually provided data for only five specific combinations, each containing one out of two specific HMG-CoA reductase inhibitors (pravastatin and fluvastatin) with one out of three specific insulin sensitizers (troglitazone, pioglitazone and compound A). The terms "HMG-CoA reductase inhibitor" and "insulin sensitizer", although used in the art, were not clearly defined, so that the skilled person could not know which other agents are covered by these definitions. Metformin, for example, an antihyperglycemic agent, belonging to the group of biguanides, was described in documents (32) and (33) to increase insulin sensitivity in peripheral tissue. Moreover, the patent did not disclose that medicaments containing other active agents than those actually tested, were suitable for the claimed preventive or therapeutic purpose.
  
8. The members of the group of HMG-CoA reductase inhibitors are defined by their capability to inhibit the enzyme which reduces HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme-A) (see document (2), abstract).

This definition allows a skilled person to decide whether or not a compound is a member of this group.

Furthermore, during the opposition procedure in the letters dated 31 March 2003 and 14 February 2005 the Respondent already argued that the term "insulin sensitizer" defines PPAR- $\gamma$  (peroxisome proliferator-activated receptor-gamma) agonists. At the oral proceedings before the Board, the Respondent confirmed that each and every insulin sensitizer mentioned in the patent was either a thiazolidinedione, an oxazolidinedione or an oxathiadiazol, which all are PPAR- $\gamma$  agonists. Thus, also the definition "insulin sensitizer" allows a skilled person to decide whether or not a compound is a member of this group.

9. The active agents contained in the medicament to be manufactured according to claim 1 are defined by their activity, being either an inhibitor of a specific enzyme or an agonist of a specific group of transcription factors. The Board is not in possession of any piece of evidence from which it could be concluded that a medicament containing members of these two groups, different from the specific agents disclosed in the examples, was not suitable for the claimed preventive or therapeutic application.

Thus, the Board is not convinced by Appellant's first line of argumentation.

10. Claim 1 refers to the use of a HMG-CoA reductase inhibitor and of an insulin sensitizer for the production of a medicament for the prevention or treatment of atherosclerosis or xanthoma. With regard

to the administration of the manufactured medicament the claim encompasses two embodiments. The first thereof requires that two agents are provided in a form in which they are administered together. According to the second embodiment, the two agents are administered consecutively, one after the other, wherein the time period between the administration of the first and the second agent is limited such that they still act synergistically together.

11. Where a therapeutic application is claimed in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, attaining the claimed therapeutic effect is a functional technical feature of the claim (see G 6/88, OJ EPO 1990, 114, point 9 of the reasons). As a consequence, under Article 83 EPC the patent must disclose the suitability of the product to be manufactured for the claimed therapeutic application.

According to the first "administration-embodiment" (see point (10) above), wherein the two agents are in a form in which they are administered together, the claimed therapeutic application is the prevention or treatment of atherosclerosis or xanthoma. The therapeutic application of the second embodiment, wherein the two agents are administered consecutively, is the achievement of a synergistic effect in the prevention or treatment of atherosclerosis or xanthoma.

12. In the light of the experimental data provided in the patent, the Board is convinced that the medicament to be manufactured according to claim 1 is suitable for the prevention or treatment of atherosclerosis or

xanthoma. Thus, the patent discloses the first of the two embodiments of the claimed invention, as mentioned above, in a manner sufficiently clear and complete for it to be carried out by a skilled person, as required by Article 83 EPC.

13. Concerning the second embodiment, requiring the consecutive administration of the two agents within a certain period of time, it has to be examined if the medicament to be manufactured according to this embodiment of claim 1 is suitable to achieve a synergistic effect in the prevention or treatment of atherosclerosis or xanthoma.
14. The patent contains two examples, namely example 1 and example 4, wherein test animals obtained a HMG-CoA reductase inhibitor and an insulin sensitizer at different points in time.

According to example 1, a group of six heritable hyperlipidaemic rabbits (group D) obtained pravastatin orally by gavage at a dose of 50 mg/kg/day once-daily. Troglitazone was given in the diet in an amount of 100 mg/kg for 32 weeks. Blood was withdrawn from these animals, from the animals of a control group and from animals who received only one of the two agents, immediately before starting the study and after 4, 8, 12, 16, 20, 24, 28 and 32 weeks and the total cholesterol level was determined. The results are shown in table 1 on page 8 of the patent. Thereafter the animals were sacrificed and necropsied to examine the percent lesion area (%) in the total, thoracic and abdominal portion of aorta (table 2), the stenosis (%)

of the coronary arteries (table 3) and the incidence (%) of xanthoma in the digital joints (table 4).

Example 4 describes a test wherein hamsters, after a cholesterol diet, received a HMG-CoA reductase inhibitor with drinking water and an insulin sensitizer with the diet. Five animals received 3 mg/kg pravastatin and 30 mg/kg troglitazone, four animals received 3 mg/kg pravastatin and 100 mg/kg troglitazone and two animals were given 1,5 mg/kg fluvastatin and 30 mg/kg troglitazone. The arterial lesions of the test animals were evaluated by using a staining method and compared with the results of a control group and with the results obtained in animals receiving only one of the two agents (table 10 on page 16 of the patent).

15. The Appellant has submitted document (26), a "statistical comment" by Prof. Andersen, professor for biostatistics at the University of Copenhagen and put forward the following points of criticism with regard to these examples and to the significance of the results obtained:

The design of the experiments in the patent in suit did not allow proving a synergistic effect of the two agents used. At the best an additive effect of HMG-CoA reductase inhibitors and insulin sensitizers could be shown. Results having a p-value greater than 0,05 were generally considered to be too unreliable to support any credible conclusion by the scientific community. None of the results of example 1 had such low p-value. No p-values could be calculated for the results of experiment 4 shown in table 10 of the patent, as no detailed experimental data were provided. However,

considering the small numbers of animals tested, these data were inadequate to conclude that synergy was present.

Even if the p-value was to be ignored, which would be scientifically incorrect, the results shown in tables 2, 3 and 4 of example 1, did not allow to draw any conclusion that the combined application of a HMG-CoA reductase inhibitor and an insulin sensitizer gave rise to an synergistic effect in the prevention or treatment of atherosclerosis or xanthoma.

The results for the total aorta and the thoracic aorta in table 2, indicated the presence of antagonism of greater magnitude than the alleged synergy for the abdominal aorta. The results shown in table 3 for MRC, LAD and LCX showed no synergy but only an additive effect of the two agents administered. The results for LSP even suggested antagonism. Finally, the results of table 4 of the patent, when seen in the light of Appellant's calculations in document (48), did not suggest the presence of synergy, but merely were in agreement with the expected additive effect of the two agents used.

16. The Respondent has submitted document (19), a statistical analysis by Prof. Freeman, an emeritus professor of the University of Leicester, expert in the field of mathematical statistics, in order to substantiate his arguments. This analysis can be summarised as follows:

Although the size of the test groups, i.e. the number of tested animals, used in the examples was too small



and certain results were too extreme to allow the provision of statistically significant results with a p-value of less than 0.05, there was no justification for using an all-or-nothing cut-off in the present situation and to generally discredit the results obtained. The fact that Respondent's results do not achieve statistical significance was hardly surprising since the tests were not designed to detect such significance.

The individual experiments were not uniformly supportive of the assertion of synergy. However, instead of looking at each and every specific test isolated, the results had to be looked at cumulatively, which allowed the recognition of a synergistic effect in thirty-one out of forty-nine tests which was an indication of an overall trend pointing in the direction of synergism.

The Respondent has taken a considerable effort to investigate the claimed synergistic effect in vivo. Taking all the results provided in the examples together, forty-nine separate tests were conducted involving more than 120 test animals (rabbits and hamsters). An experimental design allowing obtaining statistically significant data for each and every test carried out, would have required a multiple of test animals which would have exceeded the limits of Respondent's investigations by far.

17. The Board notes that both parties have consulted eminent and highly regarded experts in the field of clinical statistics which have each filed a document containing a detailed and conscientious analysis of the

- experimental data provided in the patent in suit and the conclusions that may be drawn from these data under consideration of the necessary statistical requirements. The Board sees that the two experts arrive at different results when evaluating the relevance and reliability of the present data and concludes that the question of the statistical significance of experimental data is controversially discussed also among recognized experts in the field.
18. The Board is aware that the patent not exclusively discloses experimental data in favour of a synergistic effect achieved by the consecutive administration of a HMG-CoA reductase inhibitor and an insulin sensitizer for the prevention or treatment of atherosclerosis or xanthoma, but also individual data showing only an additive or even sub-additive result. However, in the field of medical in vivo tests practised on complex living organisms, the relevance of individual results when seen in the light of the overall, cumulative picture mirrored by a large amount of data, has to be relativized, so that at least doubts as to the informative value of individual results arise.
19. According to established case law of the boards of appeal the objection based on lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts. The mere fact that a claim is broad is not in itself a ground for considering the patent as not complying with the requirement of sufficient disclosure under Article 83 EPC (cf decision T 19/90 OJ EPO 1990, 476, point (3.3) of the reasons).

20. In the light of the uncertainty in the here relevant technical field, which is mirrored by the contradictory analyses of two acknowledged experts, the Board does not consider Appellant's arguments to be substantiated by verifiable facts.

Therefore, the Board decides that the requirements of Article 83 EPC are met.

*Inventive step - Article 56 EPC*

21. The present invention is concerned with the prevention or treatment of atherosclerosis or xanthoma.

Prior art documents (2) and (3) disclose the preventive effect of a HMG-CoA reductase inhibitor (pravastatin and simvastatin) on coronary atherosclerosis (see abstracts and discussion).

Thiazolidinediones, a group of insulin sensitizers, and their therapeutic applicability are disclosed in document (4) to (9). At least documents (5) and (6) explicitly mention the treatment of atherosclerosis.

22. Claim 1 is formulated in the so-called Swiss type form, referring to the "use of substance X for the manufacture of a medicament for therapeutic application Y".

The Enlarged Board of Appeal in decision G 5/83 (OJ 1985, 64) decided that the novelty of such claims is derived from their sole new feature, that is the new pharmaceutical use of that known substance. The Enlarged Board found that no intention to exclude

second (and further) medical indications generally from patent protection could be deduced from the terms of the EPC. As a result, the Enlarged Board considered that it was legitimate in principle to allow claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application, even where the process of manufacture as such did not differ from known processes using the same active ingredient.

23. With regard to the administration of the manufactured medicament, present claim 1 encompasses two embodiments. The first thereof requires that two compounds are provided in a form in which they are administered together. According to the second embodiment, the two compounds are administered consecutively, one after the other, wherein the time period between the administration of the first and the second compound is limited such that they still act synergistically together.

According to the first embodiment the claim refers to the provision of a new medicament containing two different active agents, according to the second embodiment the claim may possibly be interpreted as to encompass the use of two particular agents which are already known to treat a particular illness where the only novel feature of the treatment is the administration regimen.

24. The Board is aware of decision T 1319/04 of 22 April 2008, wherein Board 3.3.02 refers the following three questions to the Enlarged Board of Appeal (Article 112 EPC):

"1. Where it is already known to use a particular medicament to treat a particular illness, can this known medicament be patented under the provisions of Articles 53(c) and 54(5) EPC 2000 for use in a different, new and inventive treatment by therapy of the same illness?

2. If the answer to question 1 is yes, is such patenting also possible where the only novel feature of the treatment is a new and inventive dosage regime?

3. Are any special considerations applicable when interpreting and applying Articles 53(c) and 54(5) EPC 2000?"

While the first question generally asks if one and the same medicament can be patented twice (or more) for using it for the treatment of the same disease when only the form of the therapeutic treatment is new and inventive, the second question is focussed on the situation where the new and inventive treatment is a dosage regimen.

25. The Respondent argued that the three questions referred to the Enlarged Board of Appeal are of no relevance for the present case. Although the individual active agents of the manufactured medicament were known to be useful to treat the "particular illness", the "particular medicament" in the sense of question (1) of decision T 1319/04 (supra) consisted of a HMG-CoA reductase inhibitor **and** an insulin sensitizer. As such medicament was not known to be used for the prevention or treatment of atherosclerosis or xanthoma, the present

case differed from the one being the basis for decision T 1319/04 (supra).

26. The Board does not agree. Claim 1, according to its second embodiment (see point (23) above) covers the provision of a medicament consisting of two physically separate formulations, each containing one of the two active agents, wherein said two formulations are administered to a patient according to a regimen not disclosed in the prior art documents on file, namely within such a period as to act synergistically together.

Therefore, the Board considers the Enlarged Board's answers to the questions referred to it in decision T 1319/04 (supra) to be of relevance for the outcome of the decision with regard to inventive step in the present case.

27. In this situation the Board could decide to stay the procedure in the present case until the Enlarged Board of Appeal has answered the above questions. However, for reasons of procedural efficiency in the light of Article 15(6) of the Rules of Procedure of the Boards of Appeal, the Board has decided to proceed in the following way:

As the questions referred to the Enlarged Board are of no relevance for the issue of inventive step with regard to the first embodiment encompassed by claim 1, wherein the two agents, HMG-CoA reductase inhibitor and insulin sensitizer, are provided in a form in which they are administered together, the Board will examine this issue in the present decision.

However, it will refrain from dealing with the issue of inventive step with regard to the second embodiment covered by claim 1 and will instead remit the case back to the department of first instance for further prosecution (Article 111(1) EPC). The department of first instance will then have to decide, in the light of the conclusion reached below in the context of the first embodiment covered by the claim, the issue of inventive step of this second embodiment after the referred questions have been answered by the Enlarged Board of Appeal. This will, moreover, give the parties the possibility to be heard on this issue by two instances.

28. For the embodiment of the invention according to claim 1 which refers to the provision of a new medicament containing two different active agents which are administered together, document (2) is considered to represent the closest state of the art. The document, already in its title, discloses that pravastatin, being a potent HMG-CoA reductase inhibitor, has a preventive effect on coronary atherosclerosis and xanthoma (see also abstract and discussion).

The problem to be solved is seen in the provision of further potent medicaments for the prevention and treatment of atherosclerosis and xanthoma.

29. The Board, in the light of the experimental data disclosed in the patent, is convinced that this problem is solved by the subject-matter of claim 1, in so far as it refers to the embodiment of the invention which is under consideration here.

30. It has to be examined if the skilled person at the relevant date, when trying to solve the problem formulated above, would have combined the teaching in document (2) with the disclosure in any of documents (4) to (9) and would have arrived at the claimed subject-matter in an obvious way.
31. The Appellant argued that the combination of two agents known in the art to be effective in the treatment of atherosclerosis and xanthoma into one medicament was *prima facie* obvious and lacked an inventive step.
32. Thiazolidinediones are described in documents (4) to (9) to have various preventive and therapeutic applications. Document (4) mentions the treatment of arteriosclerosis (abstract), document (5) refers to the treatment of diabetes mellitus and cardiovascular disease states involved in elevated insulin levels such as atherosclerosis (abstract), document (6) mentions the treatment and prophylaxis of atherosclerosis and the regulation of appetite and food intake (claim 1), document (7) refers to the treatment and prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular diseases and eating disorders (claims 9 and 10), document (8) mentions the use as a medicament without indicating a particular disease state (claims 10 to 12) and document (9) refers to the treatment of diabetes mellitus and associated conditions (abstract).

However, firstly, none of these documents mentions the prevention or treatment of xanthoma and, secondly, none of them contains any experimental data substantiating



the alleged therapeutic capabilities of thiazolidinediones.

33. As argued by the Respondent, and emphasised in paragraph [0004] of the patent, the therapeutic efficiency of insulin sensitizers was not considered to be satisfactory at the priority date of the patent in suit. No insulin sensitizer had been approved for use in the treatment of any form of arteriosclerosis, and this was also true today.
  
34. In 1995, the year of priority of the patent, the skilled person was aware of a multiplicity of choices of different classes of compounds known to have some activity for the prevention or treatment of atherosclerosis or xanthoma which could have been used in combination a HMG-CoA reductase inhibitor, to solve the problem underlying the patent. Such compounds are for instance glimepiride, a sulfonylurea antidiabetic agent, disclosed in document (51) or acetyl-CoA:cholesterol acyltransferase (ACAT) inhibitors, disclosed in document (52). Other compounds, such as fosinopril, an ACE inhibitor, isradipine, a calcium channel blocker and avasimibe, another ACAT inhibitor, had either received marketing authorisations or were advanced in clinical trials for the treatment of atherosclerosis at the priority date of the patent in suit.
  
35. Thus, contrary to the situation underlying decision T 192/82 (OJ EPO 1984, 415) there was not a lack of alternatives which would have created a "one-way-street" situation leading to predictable and obvious advantages. Rather there seems to have been no

incentive for the skilled person to choose the way taken by the Respondent, namely to choose a class of compounds to be combined with HMG-CoA reductase inhibitors, which class was known to be of unsatisfactory efficacy, while at the same time he was aware of the existence of more promising candidate compounds already advanced in clinical trials.

36. Accordingly the Board decides that it was not obvious for a skilled person, trying to solve the problem underlying the claimed alternative here at issue, to amend the teaching in the closest prior art document (2) and to combine a HMG-CoA reductase inhibitor with an insulin sensitizer.

Therefore, claim 1, and dependent claims 2 to 73, as far as they refer to the provision of a medicament for the prevention and treatment of atherosclerosis and xanthoma containing a HMG-CoA reductase inhibitor and an insulin sensitizer, wherein the two active agents are administered together, involve an inventive step and meet the requirements of Article 56 EPC.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.
  
2. The case is remitted to the department of first instance for further prosecution on the basis of claims 1 to 73 of the main request filed with letter dated 10 October 2008.

Registrar:

Chair:

P. Cremona

U. Kinkeldey