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Datasheet for the decision of 18 September 2014

Case Number: T 0484/09 - 3.3.02

Application Number: 01982846.6

Publication Number: 1336407

IPC: A61K31/4178, A61K31/54, A61P9/12

Language of the proceedings: EN

Title of invention:
COMPOSITION CONTAINING AN ANGIOTENSIN II RECEPTOR ANTAGONIST AND A DIURETIC AND ITS USE FOR THE TREATMENT OF HYPERTENSION

Patent Proprietor:
Daiichi Sankyo Company, Limited

Opponents:
Teva Pharmaceutical Industries Ltd.
Actavis Group hf.

Headword:
Olmesartan medoxomil and hydrochlorothiazide/ DAIICHI

Relevant legal provisions:
EPC Art. 56, 104(1), 114(2)
RPBA Art. 12, 13

Keyword:
Inventive step - (no) improvement not established
Late submitted material - document admitted (no)

Decisions cited:

Catchword:
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European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0484/09 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 18 September 2014

Appellant: (Patent Proprietor)	Daiichi Sankyo Company, Limited 3-5-1, Nihonbashi Honcho Chuo-ku Tokyo (JP)
Representative:	Wallace, Sheila Jane Marks & Clerk LLP 90 Long Acre London WC2E 9RA (GB)
Respondent: (Opponent 1)	Teva Pharmaceutical Industries Ltd. 5 Basel Street, P.O. Box 3190 Petah Tiqva 49131 (IL)
Representative:	Gallagher, Kirk James D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Respondent: (Opponent 2)	Actavis Group hf. Reykjavikurvegur 76-78 220 Hafnarfjordur (IS)
Representative:	von Uexküll - Güldenband, Alexa Vossius & Partner Siebertstrasse 4 81675 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 29 December 2008 revoking European patent No. 1336407 pursuant to Article 101(2) EPC.**

Composition of the Board:

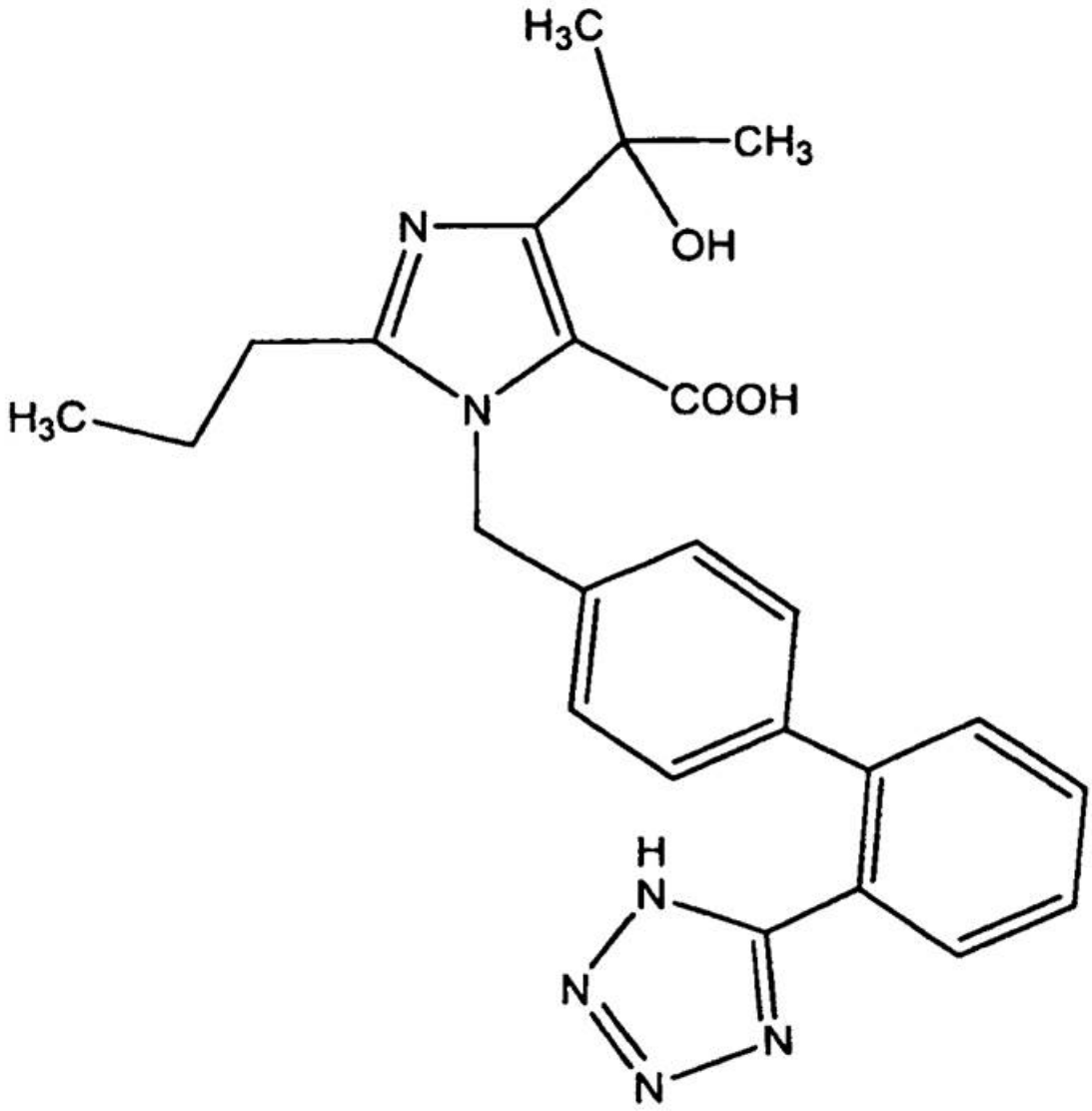
Chairman	U. Oswald
Members:	H. Kellner
	R. Cramer

Summary of Facts and Submissions

I. European patent No. 1 336 407, based on application No. 01 982 846.6 from international application No. PCT/JP2001/010095, published as WO 2002/041890 A1, was granted with twenty-eight claims.

Independent product claim 1 as granted read as follows:

"A pharmaceutical composition containing an angiotensin II receptor antagonist selected from the group consisting of a compound having a general formula (I),



(I)

pharmacologically acceptable salts thereof, pharmacologically acceptable esters thereof and pharmacologically acceptable salts of said esters thereof, and one or more diuretics as effective components, wherein said one or more diuretics are selected from thiazide derivatives."

During the following decision, the substance according to formula I is referred to as "olmesartan"; its particular (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester (see the later defined subject-matter of auxiliary request 3) is "olmesartan medoxomil", cited in many prior-art documents as "CS-866" (see *inter alia* the patent in suit, page 3, lines 26 to 28 and page 4, lines 35 to 37 in combination with appendix B to the appellant's letter of 6 June 2013, page 3).

II. Oppositions were filed against the granted patent on the grounds of lack of novelty and inventive step (Article 100(a) EPC).

III. The documents cited during the proceedings before the opposition division and the board of appeal include the following:

D8 "Conlin, P. et al., "Angiotensin II Antagonists for Hypertension: Are There Differences in Efficacy?", American Journal of Hypertension, April 2000; no. 13, 418-426",

D9 Graul, A. et al., "CS-866: Antihypertensive angiotensin II antagonist", Drugs of the Future, 1997, vol. 22, no. 11, 1205-1209

D10 EP 0 733 366 A2

D15 Critchley, J. et al., "A randomised, double-masked comparison of the antihypertensive efficacy and safety of combination therapy with losartan and hydrochlorothiazide versus captopril and hydrochlorothiazide in elderly and younger patients"; Current Therapeutic Research, 1998, vol. 57, no. 5, 392-407

D28 Experimental data filed with the appellant's letter of 4 July 2007: Examination of whether a combination of CS-866 and hydrochlorothiazide produces a synergistic effect in blood pressure lowering as compared with each drug alone and losartan-K

D29 Experimental data filed for the first time with letter of 31 March 2005 and again with the appellant's letter of 4 July 2007: Examination of whether the combination of CS-866 and hydrochlorothiazide produces a greater hypotensive effect as compared with combination of CS-866 and furosemide

D30 Webb, R. et al., "Effects of valsartan and hydrochlorothiazide alone and in combination on blood pressure and heart rate in conscious-telemetered spontaneously hypertensive rats (SHR)", American Journal of Hypertension, 1998, vol. 11, 59-65

D44 Koike, H. et al., "*In vitro* and *in vivo* pharmacology of olmesartan medoxomil, an angiotensin II type AT_1 receptor antagonist", Journal of Hypertension, 2001, vol. 19, (Suppl. 1), S3-S14 (post-published)

D48 First expert opinion of Mr. Birdsall, dated 24 April 2009 and filed with appellant's grounds of appeal of 8 May 2009

D54 US 5 656 650

D56 Wada, T. et al., "Combined Effects of the Angiotensin II Antagonist Candesartan Cilexetil (TCV-116) and Other Classes of Antihypertensive Drugs in Spontaneously Hypertensive Rats", Hypertens. Res., 1996, vol. 19, 247-254

D65 Test protocol filed with appellant's letter of 6 June 2013 concerning, according to page 3, paragraph 4 of the letter, "Details of a new experiment comparing the activity of a combination of olmesartan medoxomil and furosemide with a combination of olmesartan medoxomil and hydrochlorothiazide, including data demonstrating the basis for the selection of the dosage of furosemide"

D68 Second expert opinion of Mr. Birdsall, dated 4 June 2013 and filed with appellant's letter of 6 June 2013

D79 Ruilope, L. et al., "Clinical efficacy and safety of olmesartan/hydrochlorothiazide combination therapy in patients with essential hypertension", Vascular Health and Risk Management, 2008, vol. 4, 1237-1248

IV. By its decision pronounced at oral proceedings on 9 December 2008 and posted on 29 December 2008, the opposition division revoked the patent under Article 101(2) EPC.

With regard to Article 54 EPC, the opposition division held that the invention was not anticipated by the teachings of any of the documents on file, in particular not by D10.

However, regarding Article 56 EPC, inventive step, the opposition division found that taking either D8, D15 or D9 as closest prior art in conjunction with document D7, or alternatively for instance D9 in combination with document D8, prejudiced the patentability of claim 1 of the patent in suit.

Starting from document D8, the problem to be solved was to be seen as the provision of an alternative combination of an angiotensin II antagonist and hydrochlorothiazide. Furthermore, document D9 could also be taken as closest prior art.

The comparison data provided in documents D28 and D29 did not validly display an effect over documents D8 or D9, namely the combination of losartan and hydrochlorothiazide or olmesartan medoxomil and furosemide. The experimental data of the comparative experiments contained no effective doses of hydrochlorothiazide and furosemide that had been administered and therefore these data could not be used to prove an inventive step over the closest prior art.

V. The patent proprietor lodged an appeal against that decision and filed grounds of appeal together with a request that the patent be maintained according to its main request (claims as granted) or one of auxiliary requests 1 to 7.

The responses to the grounds of appeal were filed with letters dated 23 September 2009 and 18 November 2009.

VI. A first summons to oral proceedings was issued on 6 May 2013.

After that date, the patentee, with its letter of 6 June 2013, filed a number of documents containing data and their evaluation.

Respondent 1 requested the board not to admit most of these documents.

VII. In a communication dated 25 October 2013, the board stated that it intended to discuss the admissibility of these documents at the oral proceedings prior to the discussion of substantive issues. The board was of the preliminary view that the documents appeared highly relevant and could be regarded as a reaction to the responses to the grounds of appeal. However, they had been filed nearly four years after receipt of those responses and only after issue of the summons to oral proceedings.

VIII. The oral proceedings foreseen for 12 November 2013 were cancelled on reasoned request of the appellant and were rescheduled for 18 September 2014.

No further requests were filed after the date of the summons to these second oral proceedings.

IX. On the now scheduled date, oral proceedings took place before the board.

At the beginning of the oral proceedings, the appellant withdrew the main request and auxiliary requests 1, 4 and 5.

Therefore, the auxiliary requests 2, 3, 6 and 7 remained in the proceedings:

Claim 1 of auxiliary request 2 is worded like claim 1 as granted, with the thiazide derivative being hydrochlorothiazide.

Claim 1 of auxiliary request 3 is derived from claim 1 of auxiliary request 2 in defining the angiotensin II receptor antagonist as olmesartan medoxomil which is the (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester of the acid having formula (I).

Claim 1 of auxiliary request 6 is derived from claim 1 of auxiliary request 2 by adding the feature that the pharmaceutical composition is "formulated for oral administration".

Claim 1 of auxiliary request 7 is a combination of claims 1 of auxiliary requests 6 and 3.

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

Even if the oral proceedings had taken place on 12 November 2013, and all the more with regard to the current date, the respondents had had enough time to deal with the documents filed with letter of 6 June 2013; moreover, submission of the documents was only in reaction to the new arguments in the respondents' responses to the grounds of appeal.

The claimed subject-matter related to synergistic compositions of olmesartan and some of its derivatives with hydrochlorothiazide. Synergism was not predictable for these compositions because the olmesartan backbone was structurally distinct from the other relevant sartans and because all documents on file related to additive effects resulting from the combination of

sartans and diuretics of the state of the art. In the prior-art documents asserting synergism, the data and methods of evaluating them were flawed for different reasons.

Therefore, taking document D9 as the closest prior art, the problem to be solved was the provision of a synergistic composition of olmesartan medoxomil together with a diuretic.

The problem was solved by means of the provision of compositions according to the patent in suit and the solution was not obvious in view of the state of the art.

XI. The respondents' arguments, as far as relevant for the present decision, may be summarised as follows:

The documents filed after the issue of the summons to oral proceedings and specified in the letter of respondent 1 of 20 September 2013 should not be admitted because of the late filing *per se* and because they were not a reaction to the responses of the respondents to the statement of grounds of appeal. They dealt with issues which had been present since the proceedings before the opposition division.

Additionally, the respondents could not reasonably be expected to deal with these documents without adjournment of the oral proceedings because the documents were too voluminous and too complex. Finally, these documents were not even relevant to the proceedings, *inter alia* because they had been filed in order to support the synergism of the claimed pharmaceutical compositions, while the word synergism

or the assertion of such an effect did not appear in the patent.

It was well known from the basic teaching of the documents on file that sartans in the function of angiotensin II inhibitors were nearly always used together with diuretics, in particular hydrochlorothiazide. According to document D9, a combination of olmesartan medoxomil with furosemide was already disclosed and *inter alia* losartan was disclosed in combination with hydrochlorothiazide in document D8. Potentiating and synergistic effects were known to result from such combinations (the latter from documents D30, D54 and D56). Therefore, the skilled person was sufficiently motivated by the state of the art to combine olmesartan, in particular olmesartan medoxomil, with hydrochlorothiazide, rendering the subject-matter of the patent in suit obvious.

XII. The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of one of auxiliary requests 2, 3, 6 or 7 filed with the statement of grounds of appeal.

XIII. The respondents (opponents) requested that the appeal be dismissed.

The respondents further requested that Appendix B together with documents D61, D62 and D63; expert opinion of Mr. Birdsall (D68) and supporting documents D67 and D69 to D78; new data D47A and new experimental reports D64, D65 and D66 as referred to in the letter of respondent 1 of 20 September 2013 not be admitted into the proceedings. They requested apportionment of

costs in the event that these documents were not admitted into the proceedings.

XIV. If these documents were not admitted into the proceedings, the appellant requested that document D79 filed by respondent 1 not be admitted into the proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. Admissibility of evidence which was filed after the date of summons to the oral proceedings scheduled for November 2013

2.1 The following evidence was filed after the date of the summons of 6 May 2013 with letter of 6 June 2013:

Appendices A to E and documents D47A and D57 to D78.

Thus, these documents were filed nearly four years after receipt of the responses to the grounds of appeal and only after issue of the summons to oral proceedings. Article 13 of the Rules of Procedure of the Boards of Appeal (RPBA) applies. The discretion of the board to admit this evidence is to be exercised in view of *inter alia* the complexity of the new subject-matter submitted, the state of the proceedings and the need for procedural economy.

2.2 The question whether the board or the other parties could reasonably be expected to deal with these documents' contents "without adjournment of the oral

proceedings" (Article 13(3) RPBA) is to be considered without regard to the adjournment caused by the appellant's request filed with letter of 5 November 2013, six days before the oral proceedings initially were to be held. The fact that evidence was filed after the date of the summons remains *de facto* and the criteria in exercising the board's discretion also remain the same.

Under these circumstances, the answer to this question mainly depends on the complexity of the evidence filed.

2.3 Document D9 and the question of whether improvements were shown by the subject-matter under examination with respect to a pharmaceutical composition containing olmesartan medoxomil and furosemide (see document D9, sentence bridging pages 1206 and 1207) were crucial from the beginning of the assessment of patentability of the application which the patent in suit is based on. Therefore, in the proceedings before the examining division, the then applicant already filed the very same data of comparative experiments as it filed again as patent proprietor during the proceedings before the opposition division. The patent was granted on this basis (see letter of 30 March 2005, in particular annex 1, and letter of 4 July 2007, annex 2, which is document D29 in the opposition proceedings).

However, the opposition division, particularly on the basis of the submissions of opponent 1 with letter of 8 October 2008, paragraphs 3.2.2, 3.2.3 and 3.2.4, considered these comparative experiments to be deficient in that they did "not display an effect over the closest prior art, which would be the combination of losartan and hydrochlorothiazide at effective doses for losartan or the combination of CS-866 and furosemide

at effective doses for furosemide". They could not "be used to prove an inventive step over the prior art" (see decision of the opposition division, page 9, paragraph between points e) and a) and page 11, point d), second paragraph).

Thus, the appellant had been aware of the relevance of the comparative examples and of the deficiencies of the evidence on file at the latest since receipt of the decision of the opposition division.

The expert opinion D48, filed together with the grounds of appeal, did not refer to the experimental evidence of document D29 with respect to its status as comparative examples but only with respect to its data with a view to supporting synergism of a combination of olmesartan medoxomil with hydrochlorothiazide (see conclusion at the end of document D29 *vs.* document D48, sections 6.3 and 8). On this basis, the responses to the grounds of appeal contained nothing new about this status as comparative examples either. In addition, the appellant did not announce new comparative experiments in the grounds of appeal. Nor did it file such data within a reasonable time after the issue of the opposition division's decision.

Only with letter of 6 June 2013 document D65 together with comments in the expert opinion D68 was filed, one month after the initial summons to oral proceedings before the board and thus four and a half years after the appellant should have become aware of the deficiencies in document D29. The dose of furosemide reported in document D65 was amended to "exhibit a similar natriuretic effect to HCTZ" namely 30mg/kg in view of a dose of 3mg/kg administered in document D29.

However, the time frame for filing relevant evidence would rather have been that of Article 12(2) RPBA, requiring that the "statement of grounds of appeal and the reply shall contain a party's complete case". In view of the lapse of time between the relevant actions, the conditions under Article 13(1) RPBA for the board to use its discretion to admit late-filed evidence into the proceedings are therefore not met.

In addition, for the respondents to try to verify the data in documents D65 and D68 and to understand their evaluation as comparative examples and their ability to support the view that the claimed pharmaceutical composition was an improvement over the prior art would be *prima facie* a laborious and difficult task.

Thus, said evidence was filed surprisingly and late in the proceedings before the board and its complexity is high.

2.4 Under these circumstances, the board, in the exercise of its discretion pursuant to Article 114(2) EPC in conjunction with Article 13 RPBA, had no reason to admit the new experimental report D65 and the second expert opinion (document D68) into the proceedings.

Consequently, there is no need to consider whether this evidence shows an improvement of the claimed pharmaceutical combination over the prior art in document D9 or not.

3. Claim 1 of auxiliary request 2 as remaining highest ranking request; Articles 54 and 56 EPC

In accordance with the ruling of the opposition division in its decision regarding the patent in suit,

the novelty of the claimed subject-matter, in particular with respect to document D10, is acknowledged.

3.1 The subject-matter of claim 1 of auxiliary request 2 relates to

- a pharmaceutical composition containing
- olmesartan or a further specified derivative, e.g. CS-866 (olmesartan medoxomil),
- and hydrochlorothiazide.

3.2 The subject-matter of document D9 taken as the closest prior art relates to

- a pharmaceutical composition containing
- CS-866 (olmesartan medoxomil)
- and the non-thiazide diuretic furosemide

(see page 1208, right-hand column, paragraph headed "Clinical studies" and the chemical formula heading the article together with the sentence bridging pages 1206 and 1207).

3.3 In accordance with the view taken by the opposition division and ultimately not contradicted by the appellant (see the minutes of the oral proceedings before the opposition division, page 3, lines 11 to 13 and the appellant's grounds of appeal, page 13, last paragraph before the heading "Main Request"), the experimental results comparing the combination of olmesartan medoxomil and furosemide with the claimed pharmaceutical composition olmesartan medoxomil and hydrochlorothiazide (document D29) are found to be unable to show an improvement over the state of the art in the form of document D9. The experiments concerning

furosemide in document D29 are conducted with ineffective doses of furosemide. For example, in document D44 (see page S7, right column, "Potentiation by a diuretic agent") the inventors themselves administered the male spontaneously hypertensive rats with 20mg/kg i.m. of furosemide, i.e. more than six times the amount of furosemide given orally according to the comparative data in document D29 (3mg/kg).

Thus, in the absence of any valid example comparable to the closest state of the art, the problem to be solved is to provide another pharmaceutical composition containing olmesartan medoxomil and a diuretic.

3.4 The proposed solution according to the features of claim 1 of auxiliary request 2 is the selection of hydrochlorothiazide as the diuretic.

3.5 The board is satisfied that the problem is plausibly solved.

3.6 According to document D9, by way of pre-treatment of the spontaneously hypertensive rats (SHRs) used in the experiment with furosemide, the effect of olmesartan medoxomil is potentiated. This potentiation is stated to be indicative that olmesartan medoxomil, known to be an angiotensin II receptor antagonist, in fact lowers blood pressure mainly via interruption of the renin-angiotensin system (see the sentence bridging pages 1206 and 1207). Under the heading "Pharmacological Actions" (see page 1205, right column), olmesartan medoxomil (CS-866) is characterised as being deesterified in vivo to the active acid form to inhibit angiotensin II binding to the AT1 receptor.

Substances also known as angiotensin II receptor antagonists and also belonging to the class of sartans are described in document D8 (see first two sentences of the summary). They selectively antagonise the effects of angiotensin II at the angiotensin type 1 (AT_1) receptor (see paragraph bridging the left and the right column on page 418 of this document), being nothing else than the interruption of the renin-angiotensin system as indicated in document D9.

The known sartans, described in document D8 are losartan, valsartan, irbesartan and candesartan (see first two sentences of the summary). The comprehensive analysis contained in this document shows a "substantial potentiation of the antihypertensive effect with addition of hydrochlorothiazide" (see the last sentence of the summary).

Looking for another pharmaceutical composition containing the sartan olmesartan medoxomil and a diuretic, on the basis of the similarities set out in the paragraphs above and in view of the statement in the last sentence on page 423 of document D8 that "the dose response for blood pressure reduction with all AIIA (angiotensin II receptor antagonists; insertion by the board) is relatively flat and, in general, efficacy is enhanced significantly by adding low-dose (12,5mg) hydrochlorothiazide to the initial dose of AIIA rather than escalating the dose of the AIIA", it is obvious for the person skilled in the art to replace furosemide with hydrochlorothiazide.

Thus, he arrives without inventive effort at the subject-matter of claim 1 of auxiliary request 2.

4. *Claims 1 of auxiliary requests 3, 6 and 7; Article 56 EPC*

The additional features of all these auxiliary requests relate to restricting the olmesartan derivatives to olmesartan medoxomil and/or to restricting the pharmaceutical compositions per se to be formulated for oral administration.

All these features are fully addressed by the combination of documents D9 and D8 since D9 explicitly deals with oral preparations (see page 1206, left column, first paragraph) and D8 implicitly, and since document D9 relates to olmesartan medoxomil itself.

Thus, the argumentation under point 3 of this decision applies also to the subject-matter of claims 1 of auxiliary requests 3, 6 and 7 which, consequently, lack inventive step with respect to document D9 in combination with document D8.

5. Under these circumstances the appellant's further arguments on file cannot succeed:

The appellant sought to argue in favour of maintaining the patent in suit by defining the problem as being to provide a **synergistic** composition and by seeing the inventiveness solely in the assertion that such synergy was found in a combination of olmesartan(derivatives) and hydrochlorothiazide.

The problem in the approach of assessing inventive step is to be derived from the features in the claim in relation to the corresponding features of the state of the art with elements of the solution excluded. In a product claim it is to be distinguished whether the

problem concerns the provision of another, an alternative or an improved subject-matter and the problem must be solved convincingly on the basis of plausibility or of comparative experiments with respect to the closest prior art.

In pharmacy, synergy *per se*, however, is a phenomenon relating to the interaction of single substances in a composition in view of their pharmaceutic effect. With regard to state of the art disclosing such substances singularly and independently of each other, synergy - proved or made plausible by sufficient means - could characterise the composition in relation to the single substances in terms of being improved.

If the closest prior art already discloses a composition of substances similar to the claimed ones, the question whether the composition as claimed reflects an improvement with respect to the composition of the state of the art cannot be answered by the sole assertion of synergy in the claimed composition; further information concerning an improvement is needed.

In the current case, state of the art is a composition of olmesartan medoxomil and furosemide. The composition according to the patent assessed in the comparative experiment D29 is olmesartan medoxomil and hydrochlorothiazide.

For instance, if in the case of absolutely equivalent doses of the diuretics hydrochlorothiazide and furosemide (concerning e.g. their pharmacological effect including side effects) the dosage of olmesartan medoxomil could be reduced with hydrochlorothiazide as diuretic to achieve the same lowering of blood

pressure, there could be an improved composition. This might be due to synergism or not. *Vice versa*, even the occurrence of synergism for olmesartan medoxomil together with hydrochlorothiazide *per se* would not be sufficient to acknowledge that the problem of providing an improved composition has been solved.

Therefore, comparative experiment D29 being deficient, and documents D65 and D68 not being admitted, there is no basis to formulate the problem in such a way that any form of possible improvement might be included.

6. *Apportionment of costs; Article 104(1) EPC*

The board accepts that in particular the two documents D65 and D68, which were explictly not admitted into these proceedings, were certainly not drawn up in a short time. On this basis it cannot be excluded that the summons coincided with the completion of the documents. The board can therefore not establish an abuse of procedure on the part of the appellant.

Consequently, apportionment of costs is not equitable.

7. Since none of the claim requests meets the requirements of the EPC, the appeal must be dismissed.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The requests for apportionment of costs are refused.

The Registrar: The Chairman:

N. Maslin U. Oswald

Decision electronically authenticated