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Application No. / Patent No.	Ref.	Date
10 177 093.1 - 1114 / 2 322 174 /	O007799EP	08.02.2018
Proprietor Novartis Pharma AG, et al		

Decision rejecting the opposition (Art. 101(2) EPC)

The Opposition Division - at the oral proceedings dated 07.12.2017 - has decided:

The opposition(s) against the European patent EP-B- 2 322 174 is/are rejected.
The reasons for the decision are enclosed.

Possibility of appeal
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 and Rules 97 to 98 EPC.

Registered letter with advice of delivery
EPO Form 2330 12.07TRI

Opposition Division:

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2nd Examiner:	Hörtner, Michael
1st Examiner:	Estañol, Inma

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Enclosure(s): 27 page(s) reasons for the decision (Form 2916)
Wording of Articles 106 - 108 and Rules 97 - 98 EPC (Form 2019)
Minutes of oral proceedings
List of documents

to EPO postal service: 05.02.18

Facts and Submissions

I European patent No EP 2 322 174 B1 is based upon the European patent application No. 10177093.1.

Date of filing: 09.07.1999

Claimed priorities: 10.07.1998 US 09/113893

The mention of the grant of the patent was published in the European Patent Bulletin 2015/39 of 23.9.2015.

The title of the patent is "Combined use of valsartan and calcium channel blockers for therapeutic purposes".

The Proprietor of the patent (P) is Novartis Pharma AG, 4056 Basel (CH) for the designated contracting states BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE, IT,LI,LU, MC,NL,PT,SE; and Novartis Pharma GmbH, 1230 Wien (AT) for the contracting states AT.

The European patent No EP 2 322 174 B1 is a divisional application of 07 105 179.1 (EP 1 870 098 is deemed to be withdrawn). This application is in turn a divisional application of 99 934 647.1 (EP 1 096 932) which is based on the international application WO-A-00/02543. All applications claim priority of US 09/113893 filed on 10.07.1998.

II Seven notices of opposition have been filed against the identified European patent in its entirety by:

Opponent 1 (O1): Actavis Group PTC EHF, Reykjavikurvegur 76-78, 220 Hafnarfjordur, Iceland, on 3.3.2016

O1 based its opposition on the grounds that the subject-matter of the contested patent is not new and does not involve an inventive step (Art. 100(a) EPC) and extends beyond the content of the application as originally disclosed (Art. 100(c) EPC).

Opponent 2 (O2): Teva Pharmaceutical Industries Ltd., 5 Basel Street, Petach Tikva 49131, (Israel) on 19.04.2016.

O2 based its opposition on the grounds that the subject-matter of the contested patent does not involve an inventive step (Art. 100(a) EPC) and extends beyond the content of the application as originally disclosed (Art. 100(c) EPC).

Opponent 3 (O3): Stada Arzneimittel AG, Stadastr. 2-18, 61118 Bad Vilbel (Germany) on 9.06.2016.

O3 based its opposition on the grounds that the subject-matter of the contested patent does not involve an inventive step (Art. 100(a) EPC), is not sufficiently disclosed (Art. 100(b) EPC) and extends beyond the content of the application as originally disclosed (Art. 100(c) EPC).

Opponent 4 (O4): Huarte & Pi, C/ Veneçuela 67 (La Torreta), 08430 La Roca del Vallès (Spain) on 21.06.2016.

O4 based its opposition on the grounds that the subject-matter of the contested patent does not involve an inventive step (Art. 100(a) EPC).

Opponent 5 (O5): Generics [UK] Limited, Station Close, Potters Bar Hertfordshire EN61TL (United Kingdom) on 23.06.2016.

O5 based its opposition on the grounds that the subject-matter of the contested patent is not new and does not involve an inventive step (Art. 100(a) EPC), is not sufficiently disclosed (Art. 100(b) EPC) and extends beyond the content of the application as originally disclosed (Art. 100(c) EPC). Further O5 alleges that the claims of the contested patent are not entitled to priority.

Opponent 6 (O6): KRKA, D.D., Novo Mesto, Smarjeska cesta 6, 8501 Novo Mesto (Slovenia) on 23.06.2016.

O6 based its opposition on the grounds that the subject-matter of the contested patent is not new and does not involve an inventive step (Art. 100(a) EPC), is not sufficiently disclosed (Art. 100(b) EPC) and extends beyond the content of the application as originally disclosed (Art. 100(c) EPC).

Opponent 7 (O7): Kraus & Weisert, Patentanwälte PartGmbB, Thomas-Wimmer-Ring 15, 80539 München (Germany) on 23.06.2016.

O7 based its opposition on the grounds that the subject-matter of the contested patent does not involve an inventive step (Art. 100(a) EPC), is not sufficiently disclosed (Art. 100(b) EPC) and extends beyond the content of the application as originally disclosed (Art. 100(c) EPC).

III Notice of intervention has been filed by:

Opponent 8 (O8): Betapharm Arzneimittel GmbH, Kobelweg 95, 86156 Augsburg, Germany on 06.06.2017.

O8 based its opposition against the patent as a whole on the grounds that the subject-matter of the contested patent does not involve an inventive step (Art. 100(a) EPC).

IV O1 to O8 requested oral proceedings as an auxiliary measure in the event that the opposition division would intend to decide against their principle requests (Art. 116 EPC).

V O1, O2, O4, O6 and O7 requested to prioritize the opposition procedure and O2 further requested to accelerate the opposition procedure (The Guidelines Part D, VII, 1.2(i) and Part E, VII-4).

VI Further correspondence / requests

With letter of 13.12.2016, P responded to the notices of opposition and requested the rejection of the opposition and the maintenance of the patent as granted. P additionally requested that D19 and D19B not be admitted into the proceedings and oral proceedings as an auxiliary measure.

With letter of 27.09.2017 O5 filed further arguments and a new document D72.

With letter of 05.10.2017 O1 and O2 filed further arguments in response to the summons to attend oral proceedings. O1 filed two new documents D73 and D74.

With letter of 06.10.2017 P submitted further arguments and saw no need for further claim requests at that point. P requested nonetheless to be permitted to file new claim requests in response to any points raised by the opponents or the OD before or during the oral proceedings.

With letter of 06.10.2017 O3, O4, O6, O7 submitted further arguments in the preparation of the oral hearings.

With letter of 09.11.2017 P submitted new documents D75 and D76 in response to the argument of O1/O2 that D28 is not prior art. P requested not to admit D73 and D74 in the proceedings for being late-filed and not more relevant than the evidence on file. P commented D71/D71A filed in June 2017 as part of O8's intervention and filed a new version of this document of improved quality.

With letter of 4.12.17 O1 and O2 submitted a copy of the decisions in preliminary injunction proceedings of the Federal Patent Court of Switzerland, of the Commercial Court of Barcelona (and its English translation) and of the District Court of Düsseldorf 4c O 5/17 (D77-D79).

VII The parties were invited to attend oral proceedings with the summons of 27.02.2017.

Oral proceedings were held on 6-7.12.2017. During the oral proceedings O5 indicated that the objection of invalid priority was not maintained. P requested not to admit O1 and O2 latest submissions dated 4.12.17 and maintained its request not to admit documents D19, D19B, D73 and D74. The opposition division announced its decision at the end of the oral proceedings on 7.12.2017.

VIII Documents D1 - D79 were submitted during the procedure (annex).

IX Claim 1 as granted relates to a pharmaceutical combination composition for use in treating or preventing hypertension comprising the AT_1-antagonist valsartan (VAL) or a pharmaceutically acceptable salt thereof; amlodipine (AML) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, wherein the combination composition is in one fixed combination combined unit dose form.

X Summary of parties' arguments

The opponents essentially argued as follows.

Art. 76(1) / 123(2) EPC

The subject-matter of the contested claim 1 is the result of multiple selections and represents an intermediate generalisation without a clear pointer presenting the claimed combination as a preferred embodiment. The first selection is the disease (hypertension out of a list of 20 diseases). The second selection is the specific calcium channel blocker (CCB) which might be a dihydropyridine (DHP) or a non-DHP; both alternatives given equal weight. A third selection is AML from the group of DHPs. The fourth selection is the fixed combination unit dose form for which additionally two selections are also needed; the first being the unit dose and the second that the two compounds are combined in one fixed combination form in said unit dose. A fixed combination might be two tablets (page 8, paragraph 2 of D16 or in paragraph 31 of D15). T727/00 was cited.

Verapamil (VER) is the most preferred CCB because the results of survival rate are given in the reported study of pages 6-7 of D16.

Should the exemplified tablet be taken as basis for the combination of drugs, then it comprises specific amounts of the drugs and of the particular excipients (page 10 of D16 and in paragraph 39 of D15) and those technical features are not included in claim 1 of contested patent.

The therapeutic effect, namely the anti-hypertensive effect is neither disclosed in the parent application nor in the application as filed either in relation to rats (not concrete results in the preclinical study) or to humans. Neither was the claimed medical use.

Art. 83 EPC

For compliance of Art. 83 EPC in medical use claims, the therapeutic effect is a technical feature. In the contested patent the therapeutic effect is not the reduction of hypertension but the alleged improved effect of the pharmaceutical composition comprising the combination of VAL and AML. There is no evidence in the contested patent that makes it plausible that the combination therapy is better than either monotherapy. The therapeutic effect was not originally disclosed because the tests for approval of the combination showing that effect were not done at that time. A mere statement of the alleged effect is not enough for complying with the requirements of Art. 83 EPC. The skilled man with the information contained in the patent specification requires to perform a research program in order to reproduce the invention which amounts undue burden. The doses administered to the rats could not be standardised and it does not correspond to the claimed invention. The statements in the contested patent are purely speculative. The decisions G2/88, T609/02 and T967/09 were cited.

Art. 54 EPC

There is no effect shown in the contested patent for any of the 20 diseases disclosed. Should the same requirements in terms of plausibility be applied for the analysis of the contested claim 1 and the prior art documents, then D1 and D2 are both novelty destroying.

Since there is no definition in the contested patent of what the term "fixed combination unit dose form" is meant to cover, each of the documents disclosing the separate administration of fixed doses, namely D1 and D2, anticipates the subject-matter of the contested claim 1.

D19/D19B shows that part of the prescriptions written for Diovan^{R} (VAL) were co-prescribed with Norvasc^{R} (AML). To the extend that claim 1 covers VAL and AML administered separately in a fixed ratio with the term "one fixed combination combined unit dose form", then claim 1 lacks novelty over D19/D19B.

Similarly, claim 2 lacks novelty over D1 or D19/D19B because the only approved form of AML at the priority date of the opposed patent was AML besylate (D13).

Art. 56 EPC

The contested patent relates to a unit dosage form containing VAL and AML for use in the treatment or prevention of hypertension.

D1, D2, D3, D71 and D13 have the same purpose of lowering blood pressure and they might qualify as the closest prior art.

Compared to D1, the subject-matter of the contested claim 1 has only one distinguishing feature which is the galenic formulation. The objective technical problem starting from D1 is the provision of a more convenient administration form allowing better patient compliance and less production costs. D1 already discloses the advantages alleged in the opposed patent. Both table I and II of D1 disclose the combination, Table II on page 344 clearly discloses a combination therapy for patients with uncontrolled blood pressure at eight weeks; the therapy was not only envisaged in D1 but put into practice.

The effect has to be linked to the distinguishing feature and there is no effect linked to the fixed combination form in the contested patent. The problem has to be reformulated as an alternative. As an alternative, the solution of the opposed patent is obvious in view of the prior art disclosing combination anti-hypertensive therapies formulated in a fixed combination unit dosage form. The advantages of combination therapies in the treatment of hypertension are known at the priority date (D22, D29, D30, D32). Combinations of drugs that act by different mechanisms are preferred (D4, D49). At the priority date, VAL and AML were known as anti-hypertensive (D3, D6, table 8). Fixed combination forms comprising VAL and a diuretic (HCTZ) or comprising AML with a diuretic (HCTZ) or comprising an ACE inhibitor and CCBs are known from D4, D5, D61, D71. The skilled person would formulate VAL and AML as an alternative to the administration of the drugs in two unit dosage forms (D1) knowing the advantages disclosed in D4, D5 for better patient compliance and less production costs thereby arriving to the subject-matter of the contested patent without the involvement of an inventive merit.

Similarly, the contested claim 1 also differs in its subject-matter vis-à-vis D2 or D3 in the fixed combination form and could be equally taken as the closest prior art. Further, D2 carries out the tests in humans and shows no interaction between the two drugs VAL and AML. The arguments given for D1 as closest prior art equally apply for D2 or D3 taken as the closest prior art.

Starting from D71, the difference is the AT_1 receptor antagonist VAL. D71 discloses a combined therapy of two anti-hypertensive drugs (the ACE benazepril and AML) in a fixed combination form. Benazepril of D71 has the same physiological mechanism of action as VAL (D46). The effect is the reduction of side effects. The objective technical problem starting from D71 is the provision of an anti-hypertensive combination with less side effects. D3 discloses that AT1 antagonists have less side effects than ACE inhibitors. The skilled person would replace the ACE inhibitor by an AT_1 antagonist in order to reduce dry cough and combine it with AML thereby arriving to the subject-matter of the contested patent without the involvement of an inventive merit.

D13 discloses a fixed dosage form comprising AML. The difference is that in the contested patent AML is combined with VAL in a fixed combination form. The effect is the reduction of edema and the objective technical problem is the provision of an hypertensive with less side effects (edema). The results of less edema in the group taking the combination of VAL with AML in D1 would encourage the skilled person to combine both and reduce the side effects (edema) without an inventive merit.

Even if taking P's closest prior art D61, the subject-matter of the contested patent lacks an inventive step. D61 refers to fixed combinations of VAL and HCTZ. The distinguishing feature is AML in combined therapy not versus monotherapy. It is not plausible that the invention as claimed would actually achieve the purpose by the statement in the specification. The post-published evidence cannot be admitted, being the first disclosure beyond speculation. But even if taken into consideration, it is irrelevant because no comparison between the two combined therapies is reported. T2255/10 and T1329/04 were cited.

The proprietor's arguments may be summarized as follows.

Art. 76(1) / 123(2) EPC

Claim 7, dependent on claim 4 is the fundamental basis in D16 for the subject-matter of the contested claims. That AML and VER had equal weight might be true but it does not mean that the combination with AML is not disclosed. The therapeutic indication is hypertension and other conditions associated to hypertension. It is clear from page 4, first paragraph that the main object is hypertension. That the experiments are carried out with hypertensive rats confirm the allegation.

The sole fixed combination disclosed comprises VAL and AML; AML being in this way pointed out as preferred in the example (tablet) and in the experimental studies on hypertension. VER is used in the experiments dealing with hypertensive rats which additionally present diabetes.

The wording of page 8, paragraph 2 of D16 and of paragraph 31 of D15 was taken when claim 1 was modified in order to be one hundred per cent faithful to the disclosure of the previous applications.

Art. 83 EPC

In order to comply with the requirements of Art. 83 EPC the therapeutic effect of a pharmaceutical composition comprising two active agents known for the therapeutic purpose do not need to be proven in the patent unless there was a presumption of incompatibility of the two drugs. Even if according to the jurisprudence of the Boards of Appeal there is no need to provide evidence, the contested patent reports on real experimental studies using the standard model with hypertensive rats. In paragraphs 23-24 the results are given qualitatively. The experiments have been completed prior to the priority date and the information given in paragraphs 13-14 is not mere speculation (confirmed by D48). The fundamental technical contribution of the invention is that the combination therapy with VAL and AML has a beneficial effect over either monotherapy. The contested patent exceeds the threshold of disclosure required in the case law.

Art. 54 EPC

None of the prior art documents discloses a pharmaceutical combination composition comprising VAL and AML in one fixed combination form, let alone for its use in the treatment or prevention of hypertension.

Art. 56 EPC

Neither D1 or D2 or D3 or D71 or D13 is an appropriate starting point because none of these documents has the same purpose as in the opposed patent.

In D1 the aim is to compare the efficacy of VAL versus AML for approval of VAL monotherapy. In D1 AML was administered with VAL as rescue medication without any possible conclusion on the effects due to a combination therapy. Reference was made to the experts' declarations indicating that in view of the trial design and of the results provided in said document, the skilled person could not derive any information about the effect of the combined administration of VAL and AML. The Os' attack is the result of an ex post facto analysis of either the side effects or the efficacy of the combined administration.

D2 is a safety study of potential interactions between VAL and AML and D3 is a review of the pharmacology and therapeutic use of VAL in hypertension. The passage of page 1 of D3 refers to the addition of the "latter" being the diuretic HCTZ in patients with incomplete response to VAL.

D13 relates to AML monotherapy.

D71/D71A does not relate to VAL but to ACE inhibitors which have a different mechanism of action and so cannot be the closest prior art.

There is no information in any of these documents to allow the skilled person before the priority date to arrive to the conclusion that VAL combined with AML could improve the anti-hypertensive effect of either monotherapy. The contested patent provides preclinical studies with the combination and an exemplified tablet. Post-published documents are the confirmation of the technical contribution of the patent of an improved effect of the combination and may be taken into consideration. D48 discloses the same experiments described in the patent (post-published document) and confirms that the combined chronic treatment with VAL and AML elicited an additive decrease in blood pressure and cardiac mass in a SHR model of hypertension. This is the technical contribution of the opposed patent.

The skilled man would not combine the two active agents and formulate them in a fixed combination form unless the combination therapy is proven better than either monotherapy and this information was not available to the person skilled in the art without being aware of the information given in the opposed patent. Before the priority date the skilled person knows that other combination therapies exist (D22) but also that other trials of combination therapies failed (D28 and also D32). He would not combine the teaching of D1 (or D2 or D3) with that of D22, D4 or D5 or with that of D30, D49. Neither would he combine the teaching of D71 with that of D46 because ACE and angiotensin receptor blocker (ARB - AT_1 receptor inhibitors) have different mechanisms of action and any outcome is unpredictable.

D61 is the closest prior art. D61 discloses a tablet comprising VAL and hydrochlorothiazide (HCTZ). The purpose of D61 is to provide an anti-hypertensive combination therapy which is better than either monotherapy. It is the same purpose as in the opposed patent. The difference is the use of AML (CCB) replacing the diuretic of D61. In D46, the ACE inhibitor is combined with a CCB and an additive effect has been proven. It is not expected that an additive therapeutic effect will be obtained by another combination comprising a drug having another mechanism of action. The mechanism of action which is responsible to the additional effect is not known.

Reasons for the Decision

1) Admissibility of oppositions

The oppositions are admissible because they meet all the requirements of Articles 99(1) and 100 EPC and Rules 3(1) and 76(1)(2) EPC.

2) Intervention

The additional requirements of intervention of Bethapharm Arzneimittel GmbH (Rule 89(1)(2) EPC) were fulfilled and it became the Eighth opponent (O8) (Art 105(1)(a) EPC).

3) Procedural requests - Admissibility of D19/D19B, D73-D74 and D77-D79 (O1,O2's submissions dated 4.12.17)

3.1 D19 and D19B have been filed with the notice of opposition and during the opposition period under Art. 99(1) and Rule 76(2)(c) EPC. These documents form part of the procedure.

3.2 D73 and D74 have been filed after the time limit given under Rule 116 EPC.

D73 is an attempt to demonstrate public prior use of VAL and AML for the treatment of hypertension. However, it is neither made available to the public before the priority date nor has been sufficiently substantiated. That the collection of data ended on 30.06.1998 does not prove that the data was available in July 1998. Moreover, "available in July 1998" is not enough, given that the priority date of the contested patent is 10.07.1998. D73 is not conclusively shown to be prior art and it is not admitted into the proceedings.

D74 is an expert opinion and was filed with the purpose of showing that the skilled person would have recognised that by replacing ACE blockers by at least equally effective compounds such as AT_1 receptor antagonists, the opposed combination would avoid the side effect of persistent cough. D74 is however considered not more relevant than the evidence on file D1, D3, D71, D20 and D46. Further, it is late-filed, it could have been filed earlier and is therefore not admitted into the proceedings.

3.3 D77-D79 have been filed after the time limit given under Rule 116 EPC.

The three decisions in preliminary injunction proceedings of the Federal Patent Court of Switzerland, of the Commercial Court of Barcelona (and its English translation) and of the District Court of Düsseldorf 4c O 5/17 were issued shortly before the oral proceedings and OD decided to admit them into the procedure under its discretion, although late-filed.

4) This decision is based on the main and sole request which is the patent as granted.

4.1 Art. 123(2) / 76(1) EPC:

O1-O3 and O5-O7 put into question that the contested patent meets the requirements of Art. 76(1) / 123(2) EPC.

4.1.1 Claim 4 as filed in the WO 00/02543 publication (D16) reads:

"A pharmaceutical combination composition comprising (i) the AT1-antagonist VAL or a pharmaceutically acceptable salt thereof; (ii) a calcium channel blocker or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier".

Claim 5 discloses a list of diseases to be treated and it is dependent on claim 4. Hypertension is one of more than 30 diseases.

Claim 7 is dependent on claim 4 and discloses AML of a pharmaceutically acceptable salt as preferred calcium channel blocker.

Page 2, line 1 further defines the AML salt, namely amlidopine besylate.

4.1.2 Claim 1 as filed in the original application of the contested patent (D15) reads:

"A pharmaceutical combination composition comprising (i) the AT1-antagonist or a pharmaceutically acceptable salt thereof; (ii) a calcium channel blocker or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier".

Claim 2 is dependent on claim 1 and discloses the combined unit dose form.

Claim 3 is dependent on claim 2 and discloses that the combined unit dose form is a fixed combination.

Claim 5 is dependent on claim 4 and discloses the pharmaceutical composition of claim 1 for treating or preventing hypertension.

Claims 6 is dependent on claim 1 and claim 7 is dependent on claim 6. Claims 6-7 disclose that the CCB is AML and AML besylate, respectively.

4.1.3 Claim 1 as granted (D14) reads:

"A pharmaceutical combination composition for use in treating or preventing hypertension comprising (i) the AT1-antagonist VAL or a pharmaceutically acceptable salt thereof; (ii) AML or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, wherein the combination composition is in one fixed combination combined unit dose form".

4.1.4 The descriptions of D15 (application as filed) and D16 (grandparent application as filed) are identical, as is of 07105 179.1 (parent application as filed).

4.1.5 Art. 76(1) EPC

In D16, a pharmaceutical composition comprising (i) the AT1-antagonist VAL or a pharmaceutically acceptable salt thereof; (ii) a calcium channel blocker or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier is disclosed in page 1 and in claim 4. The CCB may be a DHP or a non-DHP, being AML the preferred DHP (claim 7) and VER the preferred non-DHP. The sole one fixed combination disclosed is in the form of a tablet comprising VAL and AML (page 10).

The preferred salt of AML is AML besylate (page 2, first line).

From page 3 to 4, it is clear that the main purpose of D16 is to address hypertension and to provide a more effective anti-hypertensive therapy. The text in line 4 of page 4 indicating that the combination is also useful in the treatment or prevention of diseases other than hypertension confirms it.

Further, the studies are carried out with spontaneously hypertensive rats (SHR) using VAL and AML as the active agents. In the study, four groups of SHR receive combination therapy; the two drugs being administered via the drinking water. It is alleged that the addition of the CCB AML confers additional benefit over the VAL monotherapy (page 5, last paragraph).

It is therefore considered that the amendments are convergent and that the pointers direct towards DHPs as preferred over non-DHPs, being AML the preferred DHP and hypertension the therapy of choice.

With regard to the feature of claim 1 of the contested patent "in one fixed combination combined unit dose form", reference is made to the passage in page 8, §2 of the original application (D16). In this passage, the two components can be administered (i) together, (ii) one after the other or (iii) separately and this can be done in (a) one combined single dose form or (b) in two separate unit dose forms. Thus, various alternatives are disclosed in said passage, one of them being that the two active agents are administered in one combined unit dose form, said combined unit dose form being a fixed combination.

Even if in the referred passage of page 8, there is no comma after the word "separately", the meaning of the term "in one combined unit dose form" cannot conceptually be linked to an alternative where the two active agents might be in separate unit dosage forms. The skilled person reading the text would inevitably identify that the alternative of the contested claim 1 is that of having the two drugs in one fixed combination. This alternative can only be in one single dose form and thus administered together and therefore represents only one selection.

OD therefore considers that the combination of features of claim 1 of the contested patent is not the result of a multiple selection but a convergent combination of preferred embodiments with only one selection, namely the selection of the administration "in one fixed combination combined unit dose form". In this respect, the decision T727/00 cited by O1/O2 does not apply in the present case.

Since the description and claims of D16 and of 07 105179.1 are essentially identical, the same conclusions equally apply for both the grandparent application as filed and the parent application as filed. The requirements of Art. 76(1) EPC are therefore met.

2.1.6 Art. 123(2) EPC

From D15, the basis for the subject-matter of claim 1 of the contested patent is to be found in claims 1-3, 12-13, 15. Claim 15 and paragraph 4 disclose DHPs and non-DHP represented by the most preferred in each case being AML and VER, respectively. It is however considered that equal weight is not given for both active agents. On the contrary AML is pointed in several passages as most preferred including the two exemplified tablets (paragraph 39). The mention in paragraph 25 that further representative studies are carried with the combination of VAL and VER indicates that the main CCB of the application is AML and not VER, at least at the publication date of the application. The medical use is disclosed in the application as filed and the treatment or prevention of hypertension singled out as the therapy of choice in claim 13.

In view of the above, it is considered that in the present case, the so-called multiple selection subject-matter is the result of the combination of preferred convergent embodiments; being the feature "the fixed combination unit dose" the sole selection disclosed in paragraph 31 and claims 2-3.

OD is therefore of the opinion that the requirements of Art. 123(2) EPC are met.

4.2 Art. 83 EPC:

O3 and O5-O7 objected sufficiency of disclosure of the contested patent.

It is the established jurisprudence of the boards of appeal that the level of disclosure in the application required for medical use claims is not the same as for a composition and that attaining the claimed therapeutic effect is a functional feature of the claim.

In T1616/09, the board pointed out that in the case of a claim directed to a pharmaceutical composition comprising two classes of compounds which had both already been used in therapy in the prior art, there was *a priori* no reason to doubt that such a pharmaceutical composition could be produced and no specific functional effect had to be demonstrated. In the case of second-medical-use claims, if the

claimed therapeutic effect was already known to the skilled person at the priority date and if there was no apparent reason to doubt that one compound would interfere in a negative way with the activity of the other, then it was not necessary to demonstrate it in the application (Reasons 6.2.2).

Claim 1 of the contested patent is a second-medical-use claim and its functional feature is the treatment or prevention of hypertension with a pharmaceutical composition comprising VAL and AML in one fixed combination combined unit dose form.

The OD makes a distinction between the above identified functional feature of the contested claim *versus* the alleged improvement of the therapeutic effect of the claimed combination therapy. Whereas the former is a matter of sufficiency, the latter relates to a technical effect which is not required in the claims and a matter of inventive step. This latter issue is therefore addressed in point 4.4 below.

For the analysis of the compliance of sufficiency of disclosure, the questions to be answered in the present case are:

- are the AT_1 antagonist VAL and the calcium channel blocker AML or a pharmaceutically acceptable salt thereof two compounds which are already known to the skilled person at the priority date and had both already been used in the treatment or prevention of hypertension?

- are there substantiated doubts that the therapeutic effect is attained?

Before the priority date, VAL and AML were known as anti-hypertensive agents (D1, D3 and D13, respectively). Other combination therapies comprising either VAL or AML in a fixed combination form were further known to be suitable for the treatment and prevention of hypertension (D61, D71).

The decision T609/02 was cited by O3 and O7. In that decision, the patent specification did neither identify any steroid hormone as binding to the hormone receptor in such a way that the so-formed complex would disrupt AP-1 stimulated transcription nor any data indicating that such an hormone (if it were identified) could have an impact on any of the listed specific diseases.

Contrary to the case in T609/02, the combination therapy of the contested patent comprises two classes of compounds which were known and had been used in therapy for the claimed therapeutic effect at the priority date.

Furthermore, there are no reasons to doubt that a therapeutic effect for the treatment or prevention of hypertension could be attained with the claimed combination of VAL and AML in one fixed combination combined unit form.

O3 cited T967/09. However, this decision does not apply to the present case. In T967/09, respondent III substantiated, by means of verifiable facts, serious doubts that the DNA measurement method for an influenza antigen vaccine disclosed in that patent could allow reliable detection of the host cell DNA level claimed (<=25pg/dose) in a sufficiently clear and complete manner.

In the present case however the patent specification does not provide a simply statement but guidance on how to perform an experimental test in spontaneously hypertensive rats (SHRs) which is the model normally used for testing the efficacy of anti-hypertensive drugs (D6, page 2418). The study is conducted with VAL and AML (paragraphs 13-24), which are known anti-hypertensives at the filing date. Further in paragraphs 31-33, the patent specification discloses an example of a tablet comprising the two compounds in a fixed combination combined unit form.

Hence, the technical effect of lowering the hypertension by means of the administration of the two active agents in a fixed combination form is credible and reproducible by the skilled person with the information disclosed in the contested patent and there are no doubts that an hypotensive therapeutic effect can be attained.

It is therefore concluded that the patent sufficiently discloses the invention for the skilled person to reproduce it without undue burden and that the requirements of Art. 83 EPC are met.

4.3 Art. 54(1)(2)(3) EPC:

O1, O5, O6 put into question that the subject-matter of the contested claim 1 is new over D1, D2 or D19.

D1 discloses a comparative study of the efficacy of VAL compared to AML in the treatment of hypertension. A group of patients whose blood pressure was not adequately controlled after 8 weeks of treatment received in addition to the initial monotherapy of 80 mg of VAL simultaneously and daily 5 mg of AML. The results of blood pressure of the whole population are in Table II under the group 12 weeks/VAL.

The two active agents in D1 are concomitantly administered between the weeks 8 and 12 in separate dosage forms. The requirements of Art. 54 EPC are met because in the contested claim 1 the anti-hypertensive drugs VAL and AML are formulated in one fixed combination combined unit dose form.

D2 discloses a clinical trial for evaluating the pharmacokinetic interactions between VAL and AML in healthy subjects. Healthy volunteers concomitantly received a single dose of 160 mg VAL (capsule) and a single doses of 5 mg AML (tablet). The subjects are healthy and D2 does not disclose any results on blood pressure but on the

pharmacokinetic parameters AUC, C_{max}, T_{max} and $T_{1/2}$. Thus, D2 neither discloses the two drugs in one fixed combination form nor its use in the prevention or treatment of hypertension. Consequently, the requirements of Art. 54 EPC are also met vis-à-vis D2.

D19 is an indication that Diovan^{R} (VAL) was co-prescribed with other drugs, e.g. Norvasc^{R} (AML). This document is classified as "Confidential". However, the confidentiality requirement does not need to be evaluated at this point because even if this information would have been available to the public before the priority date of the contested patent, D19 does not anticipate the subject-matter of the claims of the contested patent simply because in D19 the two active agents are not in a fixed composition.

The OD's opinion is therefore that the subject-matter of the contested claim 1 has not been disclosed in one specific embodiment of the prior art and that the requirements of Art. 54 EPC are met.

4.4 Art. 56 EPC:

The contested invention relates to the combination therapy of the AT_1-antagonist VAL and the calcium channel blocker AML in one fixed unit dosage form for use in the treatment or prevention of hypertension.

Selection of the closest prior art

In accordance with the established case law of the Boards of Appeal the closest prior art for assessing inventive step is the prior art document disclosing subject-matter conceived for the same purpose as the claimed invention and having the most relevant technical features in common.

Several documents have been identified as the most promising starting points for assessing the involvement of an inventive step of the opposed patent, namely D1, D2, D3, D71, D13 and D61.

D1 is a study of the efficacy and safety of VAL for the treatment of essential hypertension. The objective is clearly indicated in page 341, abstract, and it is to compare the anti-hypertensive efficacy of the new angiotensine II antagonist, VAL, with a reference therapy AML. It does not address the problem of providing a combination therapy as alternative to VAL monotherapy. It aims to evaluate whether VAL, a new anti-hypertensive drug, is at least as effective as AML, the standard anti-hypertensive therapy at the filing date. The clinical study of D1 comprises two arms : VAL monotherapy and AML monotherapy. During the study, patients non-respondent to VAL or to AML were identified and a rescue medicine was additionally given from

week 8 to week 12 (end of the study), namely 5 mg AML. This rescue medicine was administered to any of said non-responders, irrespective of whether they were in VAL or AML monotherapy.

The accidental combined administration to non-responding patients to either monotherapy does not mean in this case the same as a combined treatment. A combined therapy would be the co-administration of a specific dose of each drug from day 1 of the study and the corresponding periodic evaluation of the patients belonging to a differentiated group. The patients in D1 did not however receive both drugs with the purpose of studying the efficacy of the combination versus either monotherapy, but with the purpose of not leaving the non-responders without adequate anti-hypertensive medication during the trial with the consequent risk of uncontrolled hypertension. It is common practice in clinical trials with diseased patients to complement treatment of non-responding patients with an established effective medication for ethical reasons.

Thus, the purpose of administering VAL plus AML or of two-fold dose of AML in D1 was to control blood pressure of non-responders and not to analyse the effect of the combination VAL / AML or the effect of a higher dose of AML in either non-responding group. The results of D1 allow for concluding that VAL is at least as effective in the treatment of hypertension as AML and this confirms that the purpose of D1 was to compare either monotherapy and not to study the efficacy of the combination therapy.

OD considers that the technical teaching of D1 has been misinterpreted. The technical disclosure in a prior art document should be considered in its entirety and by a person skilled in the art without deriving therefrom technical information which is different from the integral teaching of the document. In the case of D1, the analysis of said document by the opponents is an ex post facto analysis, deviating from the proper technical teaching of the disclosure in order to arrive at the claimed subject-matter.

This is why OD does not consider D1 as the closest prior art.

The same is found to be true for D2. D2 discloses safety studies on potential interactions between VAL and AML in healthy subjects. This study does not have the purpose of evaluating the anti-hypertensive efficacy of the combination. Neither are treating or preventing hypertension addressed in the study. The purpose of D2 is the evaluation of whether the two drugs might be safely administered together. The conclusion of D2 that there are no interactions reported does not amount in the clinical field to presume that the combination therapy would result in an additive effect over either monotherapy.

Thus, OD does not consider D2 as the closest prior art.

D3 is a review of the pharmacology and the therapeutic use of VAL in hypertension. The efficacy of VAL monotherapy is reported. D3 discloses that the addition of HCTZ ("the latter") reduced blood pressure in patients which did not respond sufficiently to VAL monotherapy. The purpose however was not to provide a combination therapy which was better than the monotherapy and thus it is not considered as the closest prior art. A combination with a CCB (nifedipine) was not encouraged, let alone with AML. D3 refers to the clinical trials of D1 and the same arguments given for D1 equally apply for D3.

D3 is therefore not considered as the closest prior art.

D13 discloses a fixed dosage form of AML. There is no mention of a possible combination therapy with VAL or with any other anti-hypertensive and equally it thus not qualifies as the most promising starting point.

OD is of the opinion that D1, D2, D3 and D13 do not have the same problem to solve as the opposed patent and although these documents belong to the field of hypertension and might have a great number of features in common such as the incidental co-administration of VAL and AML as in the case of D1 (or D2) under certain circumstances, these documents are not aimed at providing a new combination therapy for hypertension which is better than either monotherapy.

The problem-solution approach presupposes that the skilled person has a purpose in mind from the very beginning of the inventive process and with regard to D1 or D2, D3 or D13 that purpose was not the same as in the opposed patent. Furthermore, the formulation of the problem and the intended use are given usually more weight than the maximum number of identical technical features, according to the established jurisprudence of the Boards of Appeal. Consequently, the skilled person would not start from D1 (or D2 or D3 or D13) in order to solve the problem of the provision of a new combination treatment using the newly approved drug VAL.

OD considers that the skilled person would start from documents having the problem of finding new hypertension combination therapies which are better than either monotherapy .

The documents of the prior art referring to this problem are D61 disclosing VAL / HCTZ; D32 disclosing VAL /HCTZ, VAL / nifedipine (calcium channel blocker) and VAL / propanolol (beta-blocker) and D71 disclosing AML / benazepril (ACE). Among them, only in D61 and in D71 the two drugs are formulated in a one fixed combination form. D71 is considered less promising than D61 because the skilled person at the priority date would take the newly approved anti-hypertensive VAL which was at least

as effective as AML as the starting point and not AML which although being the reference therapy had the known drawback of its side effects. For these reasons, OD considers D61 as the closest prior art.

Nonetheless, the involvement of an inventive step of the contested patent is assessed, according to the established jurisprudence of the Boards of Appeal, starting from any document considered equally eligible by the parties as the most promising starting point.

Technical effect and formulation of the problem

The difference between the contested patent and D1 or D2 or D3 or D13 is the combination therapy of VAL and AML in hypertension and the fixed combination unit dosage form.

The difference between the contested patent and D61 or D71 is the combination therapy of VAL and AML in hypertension.

In view of any of the potential closest prior art, the technical contribution of the opposed patent is the improved combination therapy of VAL and AML over monotherapy. This effect is considered not only disclosed but also credibly supported in the patent specification. The reasons are:

The contested patent discloses a beneficial effect of the combination of the AT1 antagonist VAL with the CCB AML over either monotherapy. This statement of purpose in the opposed patent specification is read in conjunction with the claims and has been shown not to be a mere allegation. The contested patent discloses a pre-clinical study with SHRs and gives the protocol for administration and testing. This animal model is the standard test model for hypertension and according to the established case law of the boards of appeal there is no requirement of human tests in this case. The alleged beneficial effect of the combination is made credible by reference to the results of the factorial designed study using the standard animal model which were clearly directed to compare the combination therapy with either monotherapy in view of the study arms included. The seven treatment groups are (i) VAL monotherapy, (ii) AML monotherapy, (iii) to (vi) combination therapies with VAL plus AML at different concentrations and (vii) a vehicle control. Furthermore, the opposed patent discloses examples of fixed combination galenic forms (paragraphs 13-24 and 32-33). From the patent disclosure it is therefore considered plausible that the experimental tests have been done and that the better effect of the combination is attainable throughout the whole claim.

Hence, having regard to the state of the art and the technical contribution of the opposed patent, the objective technical problem is regarded as the provision of a new combination therapy for hypertension which is better than either monotherapy.

In view of the above, the problem does not need to be reformulated and post-published evidence can be taken into account to support the claimed solution.

Several documents have been filed to illustrate the effect alleged in the contested patent, *inter alia* D56 and D48. In particular, the declaration in D48 and the journal abstract attached serves to confirm that the experiments disclosed in the opposed patent were completed before the priority date and that the additive effect on blood pressure and cardiac mass (regressed vascular hypertrophy ratios and regressed left ventricular hypertrophy) together with a reduction of the side-effect profile of high AML therapy were attained by the combination therapy of VAL / AML as already reported in the patent specification.

Obviousness

OD considers that the opposed patent is the first to report an improved combination therapy of VAL and AML and that this is the fundamental technical contribution of the contested patent over the disclosures and teaching of the prior art before the filing date.

The remaining question is thus whether the additive effect could be derived from the teaching of the prior art at the filing date.

Starting from D1

The difference between the opposed patent and D1 is considered not to be the fixed combination form only, as indicated by the opponents. OD considers that a further relevant technical difference is the technical information which the skilled person might derive from D1 with regard to the effect of the combination of VAL and AML.

In D1 the technical effect of efficacy or side effects of the combination are not disclosed. Further, the skilled person cannot conclude therefrom that the combination of VAL and AML has a better effect on reducing hypertension than either monotherapy. The values given in Table II for the 12 week group indicate a mean value for the whole population including responders and non-responders to VAL. This value is the cumulative data obtained (i) at week 8 from patients receiving VAL only, (ii) at week 12 from patients receiving from week 8 to 12 VAL only and (iii) at week 12 from patients receiving from week 8 to 12 VAL plus AML. No data can be extracted corresponding to the combination group only. Thus, no conclusion can be drawn from the pooled data of Table II of D1 on the efficacy of a combination therapy with VAL

and AML. Neither can be from the fact that non-responders took both drugs from week 8 to 12. Both study arms (monotherapy of VAL versus monotherapy with AML) continued to be compared after week 8 and until week 12 for the whole population. In fact, the sole information available in D1 is that the mean value for the whole population is within normal values at week 12.

The incidence of most frequently reported side effects of Table III does not allow for any conclusion either. The total number of patients were 168 divided in two groups of 84, one of VAL monotherapy (column 1) and the other of AML monotherapy (column 3). In Table III, the incidence of side effects for the whole population of each arm were reported. In addition, side effects of the non-respondents to VAL and non-respondents to AML were marked (columns 2 and 4). The monotherapy group in column 1 also includes non-responders who might have shown a side effect within the first 8 weeks of VAL monotherapy. These cases would be thus in column 1 and not in column 2. The same is true for non-responders to AML who might have shown side effects during the first 8 weeks and would then not be included in column 4 but in column 2. Another consideration is the size of the groups and the number of event frequencies. The small number of patients in the VAL / AML group (n=24 - column 2) is lower than the frequency of edema events observed in patients receiving VAL alone (1 per 42 patients in column 1) and in patients receiving 5 mg AML alone (1 per 28 patients in column 3). It is therefore not possible to draw any conclusion as to any reduced edema side effect for the combination group. Neither is it possible to conclude that the group taking both VAL and AML from week 8 to week 12 has fewer side effects than either monotherapy because additionally more headaches and dizziness events were observed within the VAL / AML combination therapy group.

For these reasons, OD concludes that without the technical input disclosed in the patent specification indicating that the combination claimed confers additional benefits (paragraphs 23-24), the skilled person would not interpret the values given in D1 as a hint to start the therapy from time zero with both drugs and with the expectation of obtaining an additional effect. The technical contribution disclosed in the contested patent is not disclosed in D1 and could only have been elucidated with hindsight.

Neither is this information derivable from the fact that VAL and AML might be prescribed and administered together before the priority date, as stated by the opponents citing D19 and D73. This argument was brought with the intention to show what the skilled person could have done before the priority date. The public availability of these documents is not proven. Furthermore, co-prescribing VAL and AML to some patients would not teach more than what the skilled person could conclude from D1 and the alleged additive effect of the combination as claimed cannot be derived from these documents either, should they belong to the prior art.

Without this teaching the skilled person would not be prompted to formulate the two drugs in a fixed combination form either. But even if he nonetheless would have been, and the galenic form would be the distinguishing feature vis-à-vis D1 (or D2), OD considers that formulating two drugs in a new fixed combination unit dosage form is not an obvious task but a problem *per se* in the pharmacological / galenic field. The results are neither predictable nor there is a reasonable expectation of success even if other combinations of anti-hypertensives are formulated in fixed combination forms in the prior art (D4, D5, D30). The skilled person could have had a try and see attitude, but with no particular expectation of success. The provision of a fixed combination form comprising VAL and a second drug AML (tablet of paragraphs 32-33) is thus not a straightforward routine procedure which might be derived from prior art disclosing fixed combination forms with other anti-hypertensives. This is in line with D8 which discloses the difficulties to make oral formulations of even only one of the two drugs claimed, namely VAL in the form of tablets in a reliable and robust way.

The skilled person would not combine D1 with D3 either. D3 is a review of the pharmacology and the anti-hypertensive use of VAL in monotherapy. Although one passage of D3 refers to the addition of HCTZ in page 3 for reducing blood pressure in patients not responding to VAL monotherapy, this document does not encourage the skilled man to try combination therapies with VAL, let alone with a CCB and AML in particular in order to obtain an additive effect over the monotherapy.

The OD concludes that the subject-matter of the contested patent involves an inventive step starting from D1 as the closest prior art.

Starting from D61

D61 discloses combination tablets of VAL and HCTZ (diuretic) - Diovan HCT ™ for use in hypertension therapy. The difference between the contested patent and D61 is that the fixed combination form comprises VAL and AML.

OD considers that the skilled person would not be prompted to replace HCTZ by AML at the priority date for solving the problem posed. There is no reasonable expectation of pharmacological success in combination therapies for obtaining an additive effect if one drug is changed, unless there is a clear indication in the prior art to do so. This is however not the case.

The skilled person at the priority date was aware of anti-hypertensive combination therapies from several documents (D4, D5, D30, D32, D33, D60).

D30 reviews the combination of HCTZ diuretics with practically every class of anti-hypertensives. It also indicates the advantages of the combination of ACE inhibitors with CCB based on the premise that each class provides an effect through different mechanisms of action and allows the utilisation of lower doses of the two or more agents providing satisfactory reduction of blood pressure without the increased risk of adverse effects caused by higher doses of individual monotherapies (page 8). However no indication of combinations with AT_1 receptor antagonists is reported.

VAL was a new anti-hypertensive drug belonging to the AT_1 receptor antagonists (ARB) and also combinations of VAL with other anti-hypertensives having different mechanisms of actions were evaluated in the state of the art before the filing date (D32, D29, D33, D61).

D32 evaluates the anti-hypertensive effect of VAL alone or in combination with HCTZ (thiazide diuretic), with nifedipine (calcium channel blocker) and with propanolol (beta-blocker) in experimental SHRs. D32 concludes that systolic blood pressure was depressed by single p.o administration of VAL monotherapy (3 mg/kg) and in combination with sub-therapeutic doses of HCTZ and nifedipine (NIF). However, no potentiation of the hypertensive effect of VAL was observed by these combinations. It also concludes that the development of hypertension in SHRs was significantly suppressed with the combination with HCTZ but not with NIF. Taking the teaching of D32, the skilled man would at the most combine VAL with HCTZ but not with a CCB.

This is in line with the teaching of D29 (page 3A-68S), with the teaching of D33 and confirmed by D61, wherein the sole oral fixed-dose combination therapy containing VAL which is more effective than the respective monotherapies is the fixed form with HCTZ.

D60 is a review of the hypertensive drugs and anti-hypertensive therapies shortly before the priority date (May 1998) and reflects the knowledge of the skilled person at that date. There is no suggestion in this document of VAL at all or of AML as preferred CCB. Compared to AML, mibefradil was reported to have a better profile in terms of side effects (fewer withdrawals for adverse effects and less edema than AML- page 162). Mibefradil was considered equal to nifedipine and superior than enalapril in its efficacy and producing less side effects. Taking into consideration the known side effects of edema by AML, the skilled man would probably have chosen mibefradil instead of AML as more appropriate CCB in combinations with VAL, should VAL be combined with a CCB. For the ACEs, telmisartan and irbesartan were reported (page 162); however there is no reference to AT_1 antagonists, let alone VAL.

Thus, should the skilled person look for a CCB in order to combine it with VAL, he would not select AML but mibefradil or less preferably nifedipine in view of the teaching of D60 and D32.

Some combinations reported in the prior art were not satisfactory VAL/NIF (D32) and this is an additional proof of the non-predictability of a pharmacological effect in combination therapies.

Moreover, D1 does not provide any clear information on the technical effect of the combination of VAL and AML on hypertension (see the arguments above) and D2 does not allow to conclude that the combination is either effective nor additive. Thus there is no teaching in the prior art that would have prompted the skilled person to combine VAL with AML with the expectation that the combination would result in an additive effect over either monotherapy.

The OD therefore considers that the subject-matter of the contested patent involves an inventive step starting from D61 as the closest prior art.

Starting from D71

D71 discloses a capsule comprising benazepril (BEN) and AML for use in hypertension therapy. The difference between the contested patent and D71 is the fixed combination form comprising VAL and AML for use in hypertension.

The problem in view of D71 was formulated by the opponents as how to provide a formulation for hypertension with less side effects, i.e less cough.

According to the opponents, the teaching of D46 would motivate the skilled person to combine D71 with D46. Figure 1 of D46 explains the renin-angiotensin system and its pharmacologic blockade illustrating the mechanism of action of ACE and AT_1 antagonists. This document suggests that AT_1 receptor antagonists as a class are as effective as ACE inhibitors, especially in hypertensive diseases and may best be used as alternative therapy to ACE inhibitors in patients who are intolerant of ACE inhibitors per se (eg, side effects of cough or angioedema). This document however does not suggest to replace ACE by AT_1 antagonists in combination therapies and concludes that there is insufficient clinical experience to elucidate about clinical benefits of AT_1 receptor antagonists. The sole reference to a possible combination of AT_1 antagonists is with ACE inhibitors themselves but not with any other class of anti-hypertensives (page 1366). Thus, the skilled person starting from D71 would not be motivated to replace benazepril, an ACE inhibitor, by VAL, an AT_1 antagonist with the expectation to provide a combined therapy for hypertension with beneficial effects.

D34 also discloses novel fixed combinations of ACEs and calcium channel blockers *inter alia* AML. However in the examples a synergistic effect is only shown for diltiazem (CCB) and losartan (ACE) and no reference is disclosed to possible combinations of CCB with AT_1 antagonists, let alone to the combination of VAL and AML.

D71 was further combined with D3. However D3 is a document about VAL and not about combination therapies of VAL. The sole CCB disclosed in D3 was nifedipine and this was in the context of comparison of the anti-hypertensive effect within monotherapies. The sole indication of a possible combination of VAL in D3 was with HCTZ (page 3). Although in D3 VAL is associated with a significantly lower incidence of dry cough than ACE inhibitors, this information alone is not enough to expect that the association of AML with VAL instead of with an ACE as in D71 would result in an additive hypotensive therapeutic effect over the monotherapy. As explained above, in the pharmacological field an additive effect is not predictable.

Also if D71 would be combined with D4 or D5 which propose combinations of ACE and CCB, these documents cite BEN/AML combination (Lotrel^R), enalapril/felodipine (Lexxel^R) and trandolapril/verapamil (Tarka^R), the last being a non-DHP. The skilled person would also not find any suggestion in these disclosures to combine CCB with AT_1 antagonists, let alone of AML with VAL.

Hence, there is no indication in any cited document which would encourage the skilled man to combine the AT_1 receptor antagonist VAL with AML instead of a representative of ACE inhibitors. This modification is possible (could) but not derivable (would) in the absence of any pointer and only knowing the technical information disclosed in the opposed patent would the skilled person arrive to the solution claimed.

In view of the above, OD concludes that the subject-matter of the contested patent also involves an inventive step starting from D71 as the closest prior art.

Starting from D2

D2 discloses that VAL and AML may safely be administered together. There are no results on the efficacy of the combination, the tests were carried out in healthy subjects and this document is silent about any expectation of an additive effect of the combination over either monotherapy.

D5 is a review from 1996 which discloses new approaches to anti-hypertensive therapy and the use of fixed-dose combination therapy of ACE inhibitors / calcium antagonists. Reference is also made in D5 to several studies which indicate that for some combinations the anti-hypertensive efficacy of the components is additive. The combinations disclosed are (i) nitrendipine and cilazapril - both are equally effective

and the combination is more effective than either individual therapy; (ii) felodipine and ramipril; (iii) AML and benazepril - first time that FDA approves an anti-hypertensive in combination which does not comprise a diuretic; (iv) enalapril and diltiazem and (v) enalapril and felodipine and in Europe (vi) verapamil and trandolapril. This document reflects the common general knowledge of the skilled person before the priority date and it is silent about any combination therapy comprising an AT_1 antagonist.

The same is true for D60 (see also above). D60 is published shortly before the priority date (May 1998) and reviews the knowledge of the skilled person on anti-hypertensive drugs and anti-hypertensive therapies at the priority date. There is no suggestion in this document either of VAL or of AML as preferred CCB. Among CCBs, mibefradil was reported to have a better profile in terms of side effects compared to AML (fewer withdrawals for adverse effects and less edema than AML- page 162) and considered equal to nifedipine, superior than enalapril both in its efficacy and in less side effect incidence.

The skilled man would not have any incentive to select AML among other known CCBs. From the teaching of D60, mibefradil would be a better CCB candidate, should VAL be combined with a CCB. The ACE inhibitors disclosed in D60 were telmisartan and irbesartan (page 162); however AT_1 antagonists were not foreseen.

Thus, starting from the safety study of the combination in D2 the skilled person could not predict any technical effect of said combination on hypertensive patients, let alone an additive effect over either monotherapy. This information could not be deduced either from D1 or from D3 (see the arguments above). Without such information the skilled person would not be prompted to formulate both drugs in a fixed combination form and thus arrive to the claimed solution. None of the documents on file could fill this gap of information for the reasons given above and only with an ex post-facto analysis would the skilled person arrive at the claimed solution. Thus, also starting with D2 as the closest prior art the subject-matter of the opposed patent involves an inventive step.

Starting from D3

D3 is a review of the pharmacology and the anti-hypertensive use of VAL in monotherapy.

The difference between the opposed patent and D3 is the combination of VAL with AML and the fixed combination form.

The combination therapy of VAL with a CCB is however not foreseen in D3. The concept of adding a second anti-hypertensive drug to VAL is only found in page 3 of D3 and it refers to the addition of HCTZ, not to the addition of a CCB. D3 further refers to the clinical study of D1 and the arguments given for D1 as closest prior art

equally apply. The object is also the reduction of blood pressure in patients not responding to VAL monotherapy. This document does not encourage the skilled man to try combination therapies with VAL, let alone with a CCB and AML in particular. Hence, the skilled person would not arrive to the claimed solution with a reasonable expectation of success by combining the teaching of D3 with any other cited document. Reference is further made to the arguments given above when D1 was considered as the closest prior art. It is therefore considered that the opposed patent involves an inventive step also starting from D3 as the closest prior art.

Starting from D13

D13 discloses a tablet of AML besylate (Norvasc^{R}).

The difference between the opposed patent and D13 is the fixed-dose combination therapy with VAL as the second anti-hypertensive.

None of the documents of the prior art suggests a combination therapy wit AML and VAL in a fixed dose formulation, including D1 and D2. The sole fixed-dose combination therapy comprising AML is disclosed in D71 and D5 with BEN. For the same reasons given above when D71 was considered as the closest prior art, the skilled person starting from D13 would not arrive to the claimed solution with a reasonable expectation of success.

In view of the above, the OD considers that only with hindsight knowledge of the technical contribution of the invention would the skilled person have been able to arrive to the solution proposed in the opposed patent. Merely with the teaching of the prior art at the priority date it was not possible to predict with a reasonable expectation of success that the combination of VAL and AML exhibits an additive anti-hypertensive effect over either monotherapy in a fixed combination unit dosage form.

The subject-matter of the opposed patent therefore involves an inventive step starting from any closest prior art document and the requirements of Art. 56 EPC are met.

5) For these reasons the opposition division is of the opinion that none of the grounds for opposition prejudices the maintenance of the European patent and the oppositions are rejected (Art. 101(2) EPC).