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**Datasheet for the decision
of 11 March 2019**

Case Number: T 0403/18 - 3.3.01

Application Number: 10177093.1

Publication Number: 2322174

IPC: A61K31/41, A61K31/44,
A61K45/06, A61P9/00, A61P9/12

Language of the proceedings: EN

Title of invention:

Combined use of valsartan and calcium channel blockers for
therapeutic purposes

Patent Proprietor:

Novartis Pharma AG
Novartis Pharma GmbH

Opponents:

STADA Arzneimittel AG
Generics [UK] Limited

Headword:

Valsartan and amlodipine/NOVARTIS

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step - (no)

Decisions cited:

Catchword:



Beschwerdekammern
Boards of Appeal
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Case Number: T 0403/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 11 March 2019

Appellant: STADA Arzneimittel AG
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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 8 February 2018
rejecting the opposition filed against European
patent No. 2322174 pursuant to Article 101(2)
EPC**

Composition of the Board:

Chairman A. Lindner
Members: T. Sommerfeld
 L. Bühler

Summary of Facts and Submissions

I. European patent No. 2322174 is based on application 10177093.1, which was filed as a divisional application of the earlier European patent applications 07105179.1 and 99934647.1, the latter having been filed as an international application published as WO 00/02543. The patent is entitled "Combined use of valsartan and calcium channel blockers for therapeutic purposes" and was granted with two claims.

Claim 1 as granted reads as follows:

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

II. Seven notices of opposition and subsequently one notice of intervention (opponent 8) were filed against the granted patent, all opponents requesting revocation of the patent in its entirety. The grounds for opposition were Article 100(a) EPC for lack of novelty and inventive step, Article 100(b) EPC and Article 100(c) EPC.

III. By its decision announced at oral proceedings, the opposition division rejected the oppositions under Article 101(2) EPC.

- IV. All opponents except opponent 1 lodged an appeal against the decision of the opposition division. With their statements of the grounds of appeal, the appellants requested that the decision of the opposition division be set aside and that the patent be revoked in its entirety. Furthermore, appellants-opponents 2, 5, 7 and 8 requested acceleration of the appeal proceedings.
- V. Summons for oral proceedings before the board were issued, scheduling oral proceedings for 11, 12 and 13 March 2019.
- VI. In its reply to the statements of grounds of appeal, the patent proprietors (respondents) requested that the appeals be dismissed.
- VII. In the course of appeal proceedings, opponents 1, 2, 4, 6 and 7 withdrew their oppositions, and opponent 8 withdrew its intervention.
- VIII. Oral proceedings took place in the presence of both appellants-opponents 3 and 5 and of the respondents. At the end of oral proceedings, the chairman announced the board's decision.
- IX. The documents cited during the proceedings before the opposition division and the board of appeal include the following:

D1 Corea et al. 1996, Clin. Pharmacol. Ther. 60,
 341-346

D6 The Sixth Report of the Joint National Committee
 on Prevention, Detection, Evaluation, and
 Treatment of High Blood Pressure (1997): Arch.
 Intern Med. 157, 2413-2446

- D20 Hypertension Guidelines 1993: Hypertension J. Am. Heart Association 22, 392-403
- D28 FDA medical review application 20-838 for candesartan, pages 108 to 123
- D29 Neutel et al. 1996, Am. J. Med. 101, Suppl. 3A, 61S-70S
- D30 Weir 1998, Drugs of Today, 34(1), 5-9
- D32 Fujimura et al. 1995, Jpn. Pharmacol. Ther. 23, 87-93
- D48A Webb et al. 2000, Journal of Hypertension 18 (suppl. 4), S80, P4.33
- D49 1999 WHO - International Society of Hypertension Guidelines for the Management of Hypertension, Journal of Hypertension 17, 151-183
- D57 Extract from the FDA regulations in force at priority date
- D58 Note for Guidance on fixed combination medicinal products from the European Agency for the Evaluation of Medicinal Products, 1996
- D59 Crout, J. Clin. Pharmacol. May-June 1974, 249-254
- D61 Product label for Diovan HCTTM, from FDA approval documents for application nr. 20-818

X. The submissions of the appellants, in so far as they are relevant to the present decision, may be summarised as follows:

For appellant-opponent 3, D1 was the closest prior art because it disclosed successful therapy with valsartan and amlodipine, the only difference to the claimed subject-matter being the dosage form. In contrast, D61, while disclosing the use of fixed-combination doses, did not disclose treatment with the same combination but rather with an alternative combination. D61's disclosure was thus further away from the claimed subject-matter. D1's aim was to ascertain the new drug

valsartan and compare its therapeutic efficacy with that of the known drug amlodipine used in its standard dose. After eight weeks, additional therapy was introduced for the non-responders in both groups, namely a standard dose of amlodipine. Hence, after eight weeks of monotherapy, the non-responders of the valsartan group received a combination therapy valsartan-amlodipine while the non-responders of the amlodipine group were treated by doubling the amlodipine dose. This was in line with the conventional therapeutic approach to hypertension at the priority date, disclosed in e.g. D29 and D30 and apparent from the therapy guidelines D20 and D49. From D1's table II it was possible to conclude that the therapeutic effect was as good for the combination therapy as for the amlodipine group, while table III showed that the amlodipine-associated side effects (edema) occurred less in the combination group. The only technical difference was the dosage form, which might be linked to the effect of increased patient compliance and lower production costs (D30). The technical problem was formulated as the provision of a therapy against hypertension with improved patient compliance. The solution as claimed was obvious in view of e.g. D30, which disclosed the advantages of fixed-dose combinations. There were no reasons not to combine both drugs in one fixed-combination form, fixed-dose combinations being also envisaged even when there was no improvement in the therapeutic efficacy but fewer side effects, as explicitly stated in D58. This was exactly the situation of D1, which showed that the combination therapy was as effective in reducing hypertension as the amlodipine high-dose monotherapy with 10 mg, with fewer side effects. D28 did not teach away from the invention as it did not relate to valsartan but to candesartan. Moreover, the patent had

not shown that the invention even worked. The objective technical problem formulated by the respondent was incorrect because it was not the monotherapy but rather the combination therapy disclosed in D1 that was the closest prior art. When comparing D1's disclosure with the patent's disclosure, it was apparent that the patent did not provide any data, just allegations, and therefore it did not contain any evidence for the alleged improvement in efficacy over the monotherapies. So even if it were argued that D1 did not show an improvement for the combination therapy, the same was true of the patent. In fact, the post-published evidence to support the alleged effect, D48A, taught that the combination had a comparable antihypertensive activity with fewer side effects, as did D1. It was irrelevant to determine the contribution of each drug of the combination for the therapeutic effect.

As regards document D28, appellant-opponent 5 argued that this document was not common general knowledge and therefore would not even have been necessarily taken into account by the skilled person. The fact that sometimes clinical trials did not work was known and would not have led researchers to abandon the project. D28 was restricted to a specific study with a specific combination and would not have stopped development of other combinations.

XI. The respondents' arguments, in so far as they are relevant to the present decision, may be summarised as follows:

Document D1 was not the closest prior art because it was not directed to the same issues as the present invention. D1 only provided a comparison between the two drugs valsartan and amlodipine and did not aim at

studying the combination therapy in comparison with the monotherapy. Nor would the study design of D1 have allowed any such conclusions. Additional amlodipine was given solely for ethical reasons, as a rescue medication, namely to avoid leaving non-responding patients uncontrolled. It did not correspond to the traditional approach disclosed in D29, which related to what a doctor would do with approved and established therapies, while valsartan was a new drug, not yet approved at the time of D1. Table II presented a pooled data set, that did not separate the patients on the combination therapy from those on the monotherapy, so no conclusions could be drawn as regards any improvement of the therapeutic effect. Moreover, the patient group size for the combination therapy was very small and the observed drop in blood pressure was minimal, which thus did not allow a relevant statistical analysis. Finally, since the additional amlodipine, known to be efficacious, was given in an open fashion, a placebo effect could not be excluded. In view of the fact that the patients were non-responders to valsartan, any effect seen with the combination therapy could simply have been due to the amlodipine itself. As to the side effects, it was not possible to make meaningful comparisons between the different columns of table III, nor had this table been interpreted in D1. The lower incidence of edema in the combination group could be explained by the fact that these patients were only on amlodipine for a third of the time of those patients that had been on amlodipine monotherapy all the time. On the other hand, it was apparent that the other side effects (dizziness, headache) were more prevalent in the combination group. Starting from D1, the differences to the claimed subject-matter were the fixed-dose combination and its use for the treatment of hypertension. The claim being

a second medical use claim, the therapeutical effect was a technical feature of the claim, which had to be fulfilled by the claimed subject-matter, meaning that the two components of the combination had to contribute to the antihypertensive effect and therefore there had to be an improvement over the corresponding monotherapies. Even if such an effect was part of D1, it was nevertheless hidden. The objective technical problem was hence to be formulated as the provision of a medicament to treat hypertension which was an improvement over the medicament's individual active ingredients. The appellants' formulation of the objective technical problem was not realistic as it ignored the fundamental teaching of the FDA and EMA (D57 and D58), according to which fixed-dose combinations were only justified when each component made a contribution to the claimed effect, and the combination was safe and effective. Simply showing that there was an effect on hypertension and an absence of interactions was not enough, and advantages of patient compliance and convenience were only secondary considerations (D59). None of the documents on file suggested that the claimed combination would be advantageous so as to justify development of a fixed-dose combination, and in fact the only combination of an angiotensin receptor inhibitor and a calcium channel blocker tested in the prior art - D28, concerning candesartan approval - had been proven not advantageous. This was not an isolated failure, as evidenced by D32. There was thus not enough information in the prior art that would have led the skilled person to make the fixed combination, and the skilled person would have rather combined valsartan with a diuretic: D6, D29, D61. Contrary to the appellants' arguments, the patent did in fact provide reports of experimental analysis: SHR (spontaneous hypertensive rats) animals,

which were the gold standard animal model for hypertension and even better than humans due to less variability, were used. The experiments were discussed in detail in the patent (paragraphs [0018] to [0024]), and the conclusions, which were plausible even in the absence of results, were proven later in D48A.

XII. Appellants-opponents 3 and 5 requested that the decision under appeal be set aside and that European patent No. 2322174 be revoked.

The respondents (patent proprietors) requested that the appeals be dismissed and that the patent be maintained as granted.

Reasons for the Decision

1. The appeals are admissible.
2. In view of requests on file by former appellants-opponents 2, 7 and 8 and appellant-opponent 5, which were based on pending national proceedings and on the approaching expiry of the patent's term, the board decided to accelerate the appeal proceedings.
3. Inventive step (Articles 100(a) and 56 EPC)
 - 3.1 The present patent is directed to the therapy of hypertension, in particular combination therapy. In view of the multifactorial nature of hypertensive vascular diseases, combining drugs with different mechanisms of actions may have benefits (paragraph [0011]), which include the possibility of using lower doses of the individual drugs, leading to a reduction

in side effects (paragraph [0015]). The patent is directed to the use of a combination of the angiotensin receptor 1 (AT₁) antagonist valsartan with a calcium channel blocker, which is amlodipine (paragraph [0004]), granted claim 1).

Closest prior art

- 3.2 Documents D1 and D61 both disclose the therapy of hypertension with combinations of antihypertensive drugs. Document D1 discloses the combined administration of valsartan and amlodipine in a clinical study with hypertensive patients, while document D61 discloses the commercially available fixed-dose combination product Diovan HCTTM, comprising valsartan and the diuretic hydrochlorothiazide (HCT). Since the patent is directed to the use of valsartan with amlodipine, document D1, also disclosing the use of valsartan with amlodipine in the treatment of hypertension, is the most suitable starting point for the discussion of inventive step.
- 3.3 The respondents did not agree that document D1 was the closest prior art, essentially arguing that it was not directed to the same purpose as the invention. According to the respondents, the invention was directed to the provision of a combination therapy which was an improvement over the respective monotherapies. In contrast, D1 was merely directed at comparing two monotherapies, namely valsartan and amlodipine monotherapy, amlodipine being added to non-responder patients in the valsartan-treated group solely for ethical reasons, as a rescue therapy, and not as a component of a combination therapy.

3.4 According to established case law, the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring a minimum of structural modifications.

3.4.1 In the case of second medical use claims, the purpose of the invention is the treatment or prevention of a medical condition, which is, in the present case, hypertension. The board disagrees that the purpose has to be defined more restrictively than this because the only functional restriction of the claim is the treatment or prevention of hypertension. Hence, any document disclosing the treatment or prevention of hypertension is directed to the same purpose of the invention and can potentially be used as a starting point for the assessment of inventive step. This requirement is fulfilled by a number of documents on file, including D1.

3.4.2 A further consideration is that the closest prior art must also share the most relevant technical features with the claimed invention. In the present case, the subject-matter as claimed concerns a pharmaceutical combination comprising valsartan and amlodipine. Among the prior art documents on file disclosing the treatment of hypertension, the only one disclosing the use of such a combination is D1. Hence, D1 is not only directed to the same purpose, i.e. to the treatment of the same medical condition, it also shares the most relevant technical features with the claimed invention, namely, the claimed valsartan-amlodipine combination.

3.4.3 A number of other documents disclose the use of fixed-dose combinations (e.g. D61) but do not disclose the use of the valsartan-amlodipine combination. The board concurs with appellant-opponent 3 that the drug combination comprising the active drugs is a more relevant technical feature of the invention than the dosage form. This is also apparent from the application as filed, in which the latter feature is mentioned only once and is not even part of the examples.

3.4.4 Additionally, the fact that the aim of D1's study was not to assess combination therapies or even to compare them against monotherapies but rather to study the efficacy of valsartan as antihypertensive treatment is irrelevant in the determination of the closest prior art because this is also not the purpose of the claimed invention. Moreover, even if the concomitant administration of amlodipine and valsartan to the valsartan non-responders was done for ethical reasons, the fact is that the aim was nevertheless to treat hypertension. As noted by appellant-opponent 3, this was in agreement with the conventional therapy approach described in D29 and reviewed in the guidelines for the management of hypertension of 1993 and 1999 (D20 and D49, respectively), which comprised first starting a monotherapy and then, if required, adding a further drug.

Objective technical problem and solution

3.5 Starting from D1, the only distinguishing feature of the subject-matter claimed in granted claim 1 is the dosage form being a "one fixed combination combined unit dose form". There is no data in the patent allowing the conclusion that this difference is linked to any particular effect. However, taking into

consideration the known advantages of fixed-dose combination formulations in terms of improved patient compliance and decreased production costs (disclosed in D30, page 7, right-hand column, third paragraph), the objective technical problem may be formulated as the provision of an improved dosage form for the combination therapy with valsartan and amlodipine. The solution is the fixed-dose combination as claimed, and the board is satisfied that the technical problem is plausibly solved by the claimed solution.

3.6 The respondents argued that the claimed invention differed from the disclosure of D1 not only in regard to the dosage form but also in the use of the combination for the treatment of hypertension. This use implied that the two components of the combination had to contribute for the antihypertensive effect and therefore the obtained therapeutic effect had to be an improvement over the corresponding monotherapies. According to the respondents, such an improved effect could not be derived from D1 and was thus a further distinguishing feature. On the basis of these two distinguishing features, the objective technical problem should be formulated as the provision of a medicament to treat hypertension which was an improvement over its individual active components.

3.7 The board disagrees with this argumentation. First, a second medical use claim, in which the technical effect is a functional feature of the claim to be fulfilled by the claimed subject-matter, only requires the claimed product to have the claimed technical effect, without any further restrictions as to the contributions of each of the product's components for the technical effect. In the present case, the claimed combination has to be suitable for the treatment of hypertension,

and this has been shown in D1: table II, showing the effect on sitting diastolic and systolic blood pressures of treatment with valsartan or amlodipine alone for up to eight weeks, and afterwards also with the combination of valsartan and amlodipine. It is true that D1's study format (e.g. addition of amlodipine done in an open fashion, not double blind) and results presentation (data for the combination therapy pooled together with those for the valsartan monotherapy) do not allow comparing the efficacy of the combination therapy with that of the monotherapies. However, this is not required to render it plausible that the combination therapy has a therapeutic effect in hypertension. Second, whatever improvement in the therapeutic effect is allegedly linked to the combination therapy over the corresponding monotherapies is implicit to the combination therapy itself and was thus already part of D1's disclosure, regardless of whether it was explicitly stated or immediately recognisable.

Obviousness

3.8 The respondent argued that the provision of fixed-dose combinations was not trivial since such dosage forms were only justified when it was shown that each component made a contribution to the claimed effect, as was apparent from the extracts of the regulations for medicament approval of the U.S. Food & Drug Administration, FDA (D57, point §300.50, item (a)) and of the European Agency for the Evaluation of Medicinal Products, EMA (D58, "Justification" section, item 1.2). Furthermore, D59 explicitly stated that patient compliance and convenience were just secondary considerations, of relevance only when the other conditions were fulfilled (second and third sentences

of first page; page 250, right-hand column, first full paragraph and last paragraph; page 252, right-hand column, paragraph starting at line 3). None of the documents on file suggested that the claimed combination would be advantageous so as to justify developing a fixed-dose combination, and in fact the only combination of an AT₁-receptor antagonist and the calcium channel blocker amlodipine which had been tested in the prior art had proven not advantageous (D28). Similarly, combining valsartan with the calcium channel blocker nifedipine was not successful in that a potentiation of the antihypertensive effect of valsartan was not observed (D32). The skilled person would thus have been taught away from developing fixed-dose combinations with these two drugs and would instead have considered other combinations of valsartan with drugs from other groups, such as diuretics, as taught by D6, D29 and D61.

3.9 The board notes that the respondent has not argued that there would have been any technical difficulties that had to be overcome when attempting to provide fixed-dose combinations of the claimed combination. Rather, it referred to difficulties of a regulatory, non-technical, nature, which, as such, are normally not taken into account when assessing inventive step.

3.9.1 Moreover, the regulatory requirements cited by the respondent rely on intrinsic properties of the drug combination, which, as stated above (point 3.7), have to be considered implicit to the disclosure of D1. There is certainly nothing in D1 that would have taught away from considering providing the two drugs valsartan and amlodipine in a fixed-dose combination, even if, naturally, the skilled person would have probably performed other routine tests and even larger clinical

trials beforehand, which is the same as for the patent because the patent only discloses limited experimental data on an animal model for hypertension (spontaneous hypertensive rats, SHR), and no clinical data at all. Independently of the undisputable value of animal studies in determining a therapeutic effect, they do not replace clinical trials when it comes to assessing dosage, side effects and safety, parameters which would certainly have to be evaluated before providing a fixed-dose combination medicament. The post-published meeting abstract authored by the inventors D48A, filed to support the alleged advantageous effect, also only provides data obtained with the SHR animal model. The section "Conclusion" states that the results "demonstrate that chronic treatment with valsartan and amlodipine in SHR results in additive effects on blood pressure and cardiac mass" and concludes that "combination therapy may enable comparable antihypertensive efficacy to be achieved in patients while minimizing the side-effect profile of high dosage amlodipine monotherapy". The same conclusions can, however, also be derived from D1 (table II and page 345, right-hand column, lines 23 to 29).

- 3.9.2 Neither did documents D28 and D32 conclude that the combination therapy was not suitable for treating hypertension. Rather, they just concluded that there was no additive effect over the respective monotherapies. Moreover, even if disclosing combinations of the same groups of antihypertensive drugs, none of these documents relates to the specifically claimed combination. Therefore, the fact that no additive effect over the monotherapies was observed for the combination of candesartan and amlodipine (D28) or for the combination of valsartan and nifedipine (D32) would not have led the skilled

person to doubt D1's teachings that the combination of valsartan and amlodipine was effective in the treatment of hypertension. Documents D6, D29 and D61, on the other hand, refer to fixed-dosed combinations that were already on the market or under evaluation. The fact that the valsartan-amlodipine combination is not disclosed in these documents just means that the claimed subject-matter is novel over these documents. There is no disclosure in these documents teaching away from combining the two drugs, which had, in any case, already been combined, albeit not in a fixed-dose combination form, in D1.

3.10 As a consequence, the skilled person, motivated to provide an improved dosage formulation of D1's combination therapy, would readily have considered the possibility of formulating the two drugs in one fixed-dose combination, as was widely known from the prior art, e.g. D30. In the absence of any evidence for technical difficulties to produce such a formulation, the skilled person would just have had to make use of routine procedures and components to arrive at the claimed solution without the need for inventive skill. The subject-matter of claim 1 thus lacks inventive step.

3.11 Granted claim 1 is therefore not allowable for lack of compliance with Articles 100(a) and 56 EPC.

Order

For these reasons it is decided that:

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

The Registrar:

The Chairman:



T. Buschek

A. Lindner

Decision electronically authenticated