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Datasheet for the decision of 7 March 2019

Case Number: T 2491/16 - 3.3.07

Application Number: 05810652.7

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Language of the proceedings: EN

Title of invention:
BILAYER TABLET COMPRISING TELMISARTAN AND AMLODIPINE

Patent Proprietor:
Boehringer Ingelheim International GmbH
Boehringer Ingelheim Pharma GmbH & Co. KG

Opponents:
ZAKLADY FARMACEUTYCZNE POLPHARMA S.A.
Oser, Andreas
KRKA, tovarna zdravil, d.d., Novo mesto

Headword:
Bilayer tablet / BOEHRINGER INGELHEIM

Relevant legal provisions:
EPC Art. 100(b), 56
RPBA Art. 13(1)

Keyword:
Sufficiency of disclosure - main request, auxiliary request 1 (no) - auxiliary request 2 (yes)
Inventive step - auxiliary request 2 (yes)
Late-filed documents - admitted (partially)

Decisions cited:
G 0005/83, T 0958/94, T 0890/02

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2491/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 March 2019

Appellant: (Opponent 1)	ZAKLADY FARMACEUTYCZNE POLPHARMA S.A. ul. Pelplinska 19 83-200 Starogard Gdanski (PL)
Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstraße 2 81541 München (DE)
Appellant: (Opponent 2)	Oser, Andreas Sohnckestrasse 12 81479 München (DE)
Representative:	Prüfer & Partner mbB Patentanwälte · Rechtsanwälte Sohnckestraße 12 81479 München (DE)
Appellant: (Opponent 3)	KRKA, tovarna zdravil, d.d., Novo mesto Smarjeska cesta 6 8501 Novo mesto (SI)
Representative:	Hoefer & Partner Patentanwälte mbB Pilgersheimer Straße 20 81543 München (DE)
Respondent: (Patent Proprietor 1)	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim (DE)
Respondent: (Patent Proprietor 2)	Boehringer Ingelheim Pharma GmbH & Co. KG Binger Strasse 173 55216 Ingelheim (DE)

Representative: Hoffmann Eitle
Patent- und Rechtsanwälte PartmbB
Arabellastraße 30
81925 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 20 September 2016 rejecting the opposition filed against European patent No. 1814527 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman P. Schmitz
Members: E. Duval
D. Boulois

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division to reject the three oppositions filed against the patent in suit (hereinafter "the patent").

II. European patent 1 814 527 B1 was granted on the basis of 13 claims. Independent claim 1 read as follows:

"A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix comprising a basic agent selected from alkali metal hydroxides, basic amino acids and meglumine, a water-soluble diluent and, optionally, other excipients and adjuvants and a second layer of amlodipine in a disintegrating or eroding tablet matrix".

Independent claim 12 read as follows:

"A method for the manufacture of a tablet of claim 1 to treat hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density

lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia".

III. Three oppositions were filed against the patent on the grounds that its subject-matter lacked inventive step and was not sufficiently disclosed.

IV. The following documents were cited *inter alia* during the first instance proceedings:

R1: Banker and Rhodes, Modern Pharmaceutics, 1979, p 397
R2: Lachmann et al, The Theory and Practice of Industrial Pharmacy, 1986, p 330-331
R3: E.A. Rawlins, Bentley's Textbook of Pharmaceutics, 1988, p 286
R4: Liebermann et al, Pharmaceutical Dosage Forms, 1989, p 179
R5: Banker and Rhodes in Modern Pharmaceutics, 1990, p 398
R7: Harano et al, Metabolism 44(3): p 315-319,1995
R10: Stangier et al, J of Clinical Pharmacology 40: p 1347-1354, 2000
R11: US 6,071,939
R13: US 6,162,802
R14: Mutschler Arzneimittelwirkungen, 2001, p 559-563 und 571-586
R15: RoteListe 2001 - Micardis®
R16: RoteListe 2001 - Norvasc®
R17: Sharma et al., Hypertension 40: 609-611, 2002
R21: RoteListe 2003 - Micardis®
R23: WO 03/059327
R26: WO 05/011680

R30: Abdoh et al., Pharm Dev and Techn, 9(1), p 15-24, 2004

V. The opposition division decided that:

(a) the expressions "dissolving tablet matrix" and "disintegrating or eroding tablet matrix" used in claim 1 were broad but clear and did not cause the claimed subject-matter to be insufficiently disclosed. As to claim 12 of the patent, it was not interpreted as a Swiss-type claim but as a method of manufacture, such that the medical indications listed therein were neither limiting nor relevant to the issue of sufficiency of disclosure. Hence the patent met the requirements of sufficiency of disclosure.

(b) R10 was seen as a suitable starting point for the assessment of inventive step because it disclosed the telmisartan - amlodipine combination; in contrast, R23 could not represent the closest prior art. Starting from R10, the problem to be solved was formulated taking into account not only improved patient convenience but also adequate amlodipine stability. The objections of lack of inventive step over a combination with R13, R23 or R11 were based on hindsight, because the problem of physical incompatibility of amlodipine in the presence of telmisartan with alkaline excipients was unknown at the date of priority of the opposed patent. Accordingly the patent met the requirements of Article 56 EPC.

VI. Each of opponent 1 (appellant 1), opponent 2 (appellant 2) and opponent 3 (appellant 3) lodged an appeal against this decision.

VII. With the reply to the statements setting out the grounds of appeal, the patent proprietors (respondents) defended their case on the basis of the patent as granted as main request, and on the basis of auxiliary requests 1 and 2, filed with said reply to the statements of grounds of appeal.

In auxiliary request 1, claims 1-11 were identical to those of the main request (see II. above), and claim 12 differed from claim 12 as granted as follows (amendments underlined by the Board):

"~~A method for the manufacture of a tablet of claim 1 to treat~~ Use of a tablet of claim 1 for the manufacture of a medicament for the treatment of hypertension either alone [...]"

In auxiliary request 2, claims 1-11 were identical to those of the main request, whereas claim 12 and its dependent claim 13 were deleted.

VIII. Further submissions were filed respectively by appellant 3 on 27 October 2017 and by appellant 1 on 30 November 2017 and 13 July 2018.

IX. By letter dated 9 November 2018, the respondents filed auxiliary requests 3-5 and objected to the admission of the documents R50-R55 filed by the appellants with the above further submissions.

X. In a communication pursuant to Article 15(1) RPBA dated 28 January 2019, the Board expressed its preliminary opinion.

XI. Oral proceedings were held on 7 March 2019.

XII. The following documents were among those cited during appeal proceedings:

R31: Textbook of Pharmaceutical Medicine, 3rd ed., pages 30, 33, 35, 36
R32: Stability Testing of Formulation Based on Disclosure in EP1814527
R34: expert declaration from Prof. Planinsek
R35: M, E. Aulton, Pharmaceutics: The Science of Dosage Form Design, Second Edition, 2002, pages 290-291 and 410-417
R36; J, T, Carstensen, Advanced Pharmaceutical Solids, Marcel Dekker, New York, 2002, pages 469-473
R38: Expert Opinion Prof. Frieß
R41: Excerpt from Europaisches Arzneibuch, 4th ed., 2002 (monographs 2.9.1 and 2.9.3)
R42: Excerpt from Pharmazeutische Technologie, 1st ed., 1978, p. 333
R45: Excerpts from the marketing approval documentation of the Twynsta® tablets
R46: Excerpt from original study report underlying the publication in R10
R48: ICH Guideline Q1A
R49: ICH Guideline Q3B
R50: Excerpt from Rote Liste 2013r MicardisPlus® (17 198)
R51: Experimental report from Elizabeta Tratar Pirc
R52: Stability Testing of Formulations Based on Disclosure in EP1814527
R53: WO 03/032954 A1
R54: Serajuddin et al., "*Selection of Solid Dosage Form Composition through Drug-Excipient Compatibility Testing*", Journal of Pharmaceutical Sciences, Vol. 88, No. 7, July 1999

R55: Laidler/Meiser, "*Physical Chemistry*, 1999, pages 454-458
R58: USP, 23rd edition, Monograph <701> DISINTEGRATION
R65: FDA Micardis® Drug Approval Package, Clinical Pharmacology Biopharmaceutics Review Part 2, pages 124-128
R68: Tiwari et al., Journal of Pharmaceutical Analysis, 2015, 5(1), pages 33-42

XIII. The arguments of the appellants, insofar as relevant to the present decision, can be summarized as follows:

(a) Documents R50-R55 should be admitted into the proceedings because they were *prima facie* relevant. Neither R50 nor R51 raised complex substantive questions. Furthermore, R51 represented a legitimate response to the respondents' submissions dated 12 June 2017.

(b) Claim 1 of the patent did not meet the requirements of sufficiency of disclosure, because the skilled person could not prepare a tablet comprising a "disintegrating or eroding tablet matrix" having instant release characteristics. Additionally, claim 1 was unduly broad, since it covered the use of any water soluble diluent in the dissolving tablet matrix and since it did not require the presence of a disintegrant in the disintegrating or eroding tablet matrix.

(c) Claim 12 of the patent did not meet the requirements of sufficiency of disclosure. The appellants debated whether claim 12 should be construed as a Swiss type claim or as relating to a manufacturing method. In both cases however, the suitability of the tablet for use in the vast range

of conditions recited in claim 12 was not shown in the application as filed.

(d) The claimed subject-matter did not involve an inventive step. The closest prior art R10 disclosed a study on the administration of telmisartan- and amlodipine-containing tablets. It was implicit, or at least immediately obvious, to the skilled person that the tablets used were the commercialised formulations Micardis® and Norvasc®. The claimed subject-matter differed from the teaching of R10 in that the known formulations were combined in a bilayer tablet. This combination did not result in any improved stability. The lack of stability of amlodipine in the presence of basic excipients of telmisartan was not plausibly shown in the application as filed. Additionally, either the documents R30, R53 and R68 did not suitably demonstrate that this stability problem existed over the whole scope of the claim, or R30 and R53 showed that the problem was known to the skilled person. Furthermore, the use of the claimed bilayer tablet did not result in sufficient stability level. The problem to be solved was to be formulated as the provision of a tablet form for co-administration of telmisartan and amlodipine having improved patient compliance and ensuring suitable solubility of telmisartan. In light of the common general knowledge as evidenced by R1-R5, or considering the teaching of R23, R11 or R13, it would have been obvious to combine the existing formulations in a bilayer tablet to improve patient compliance. The use of the commercialised telmisartan formulation Norvasc® ensured suitable solubility.

(e) The claimed subject-matter did not involve an inventive step either starting from R23 as closest prior art. R23 related to the same problem, namely the treatment of hypertension and the solubility of telmisartan, and was similar in structure as it showed a bilayer tablet comprising telmisartan. R14 showed that calcium antagonists such as amlodipine were an alternative to diuretics, such as the hydrochlorothiazide (HCTZ) of R23, in combination formulation for the treatment of hypertension. Since no effect resulted from the use of amlodipine instead of HCTZ, the problem to be solved was to provide an alternative tablet formulation for the treatment of hypertension. The claimed alternative was obvious in light of R10 or R14.

XIV. The respondents' arguments, insofar as relevant to the present decision, can be summarized as follows:

(a) Documents R50-R55 were filed late, namely only after the grounds of appeal, by appellants 1 and 3, and lacked *prima facie* relevance. These documents should accordingly not be admitted into the proceedings.

(b) The expressions "dissolving tablet matrix" and "disintegrating or eroding tablet matrix" used in claim 1 were standard language; their common understanding was not overruled by the description and they did not imply a particular release profile. The possibility that no disintegrant be present in the second layer did not contradict the alternative where this layer comprised an eroding tablet matrix. The subject-matter of claim 1 was thus sufficiently disclosed.

(c) Claim 12 should be construed as a Swiss type claim. However, even if the claim was interpreted as referring to a method of manufacture, no insufficiency of disclosure arose. The patent described how to prepare the claimed tablet. The skilled person could identify the tablet as dissolving, disintegrating or eroding system. No unjustified monopoly was granted by claim 12 since the tablet *per se* was in any case covered by claim 1. Lastly, the suitability of the combination of telmisartan and amlodipine for the treatment of hypertension was doubtless, and the effects of these agents on the concomitant conditions of claim 12 were known in the prior art.

(d) The closest prior art was R10. Amlodipine was not mentioned in R23, which could therefore not represent the closest prior art. R10 disclosed a clinical study in which telmisartan and amlodipine were administered in separate dosage forms. R10 did not disclose the content of these separate tablets. The choice of the claimed bilayer formulation addressed the problem of stability of amlodipine in the presence of the base present in the telmisartan formulation, as mentioned in paragraph [0009] of the patent. The problem to be solved was to be formulated as the provision of a formulation for the co-administration of telmisartan and amlodipine characterised by an adequate stability of amlodipine, in the sense that amlodipine should be made stable over the influence of the basic component in the telmisartan formulation. This problem was not disclosed in the prior art. Since the prior art did not contain any pointer to the claimed solution, the requirements of inventive step were fulfilled.

XV. Each of the appellant 1, the appellant 2 and the appellant 3 requested that the decision under appeal be set aside and that the patent be revoked.

XVI. The respondents requested that the appeals be dismissed, alternatively that the patent be maintained on the basis of one of the auxiliary requests 1 or 2, filed with the reply to the statements of grounds of appeal, or auxiliary requests 3 to 5 filed with letter of 9 November 2018. Additionally the respondents requested that documents R50 to R55 not be admitted into the proceedings.

Reasons for the Decision

Admission into the proceedings of documents R50-R55

1. The respondents were of the view that the documents R50 to R55 were not *prima facie* relevant and should therefore not be admitted into the proceedings.

R50 (an excerpt from Rote Liste), R51-R52 (experimental reports) and R53-R55 (prior art items) were submitted by appellants 1 and 3 after they had filed their grounds of appeal, they accordingly constitute amendments to their cases. Their admission is subject to the Board's discretion pursuant to Article 13(1) RPBA. The discretion shall be exercised in view of inter alia the complexity of the new subject matter submitted, the current state of the proceedings and the need for procedural economy.

For the Board, the experimental evidence R51 and R52 may be viewed as a reaction to the respondents' submission dated 12 June 2017, which not only criticised the absence of evidence regarding instability, but also introduced R45 to support such stability. Likewise, the filing of R50 may be seen as a reaction to the respondents' argument that, considering R46, Micardis® was not available at the time the study in R10 was conducted. R53 is relevant to the question of whether the instability of amlodipine in the presence of meglumine, which is one of the basic agents of claim 1, was known in the prior art. Moreover, the respondents were in a position to fully address the content of these documents in their letter dated 9 November 2018.

R54 and R55 were submitted, according to appellant 1, to support the relevance of R30 and of the testing conditions and results reported therein. R55 is evidence of the common general knowledge regarding hydrolysis of esters, and does not introduce complex new subject-matter. However, the same does not apply to document R54. The mere fact that it was cited in R30 does not justify its admission at a late stage of the procedure. Furthermore, this document introduces new considerations on the degradation mechanism of amlodipine, which had not been an issue before.

Accordingly, R50-R53 and R55 are admitted into the proceedings, whereas R54 is not admitted.

Main request

2. Article 100(b) EPC, sufficiency of disclosure of claim 12

2.1 The Enlarged Board of Appeal ruled in decision G 5/83 (OJ EPO 1985, 64) that a European patent may be granted with claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application. Following decision T 958/94, there is for that purpose no substantive difference between the *use of a substance or composition* for the manufacture of a medicament and a method to manufacture a medicament *characterised in the use of said substance.*

However, claim 12 is not characterised at all by the use of any substance or composition: claim 12 merely relates to a "method for the manufacture of a tablet of claim 1 to treat hypertension either alone or in combination with [additional conditions]". Contrary to appellant 1's assertion, the tablet of claim 1 is specified in claim 12 as the product of the manufacturing method, and not as the composition to be used. Accordingly, claim 12 cannot be construed as a Swiss-type claim, but only as a claim directed to a method of manufacture, irrespective of whether the claim explicitly defines any process steps. As a result, attaining the claimed therapeutic effects does not constitute a functional technical feature of claim 12.

2.2 Nonetheless, the treatment of hypertension either alone or in combination with the stated further conditions remains a feature characterising the subject-matter of claim 12, in the sense that the produced tablet must be

suitable for the stated uses. Consequently, and contrary to the conclusions of the opposition division, the achievement of the uses stated in claim 12 remains relevant to the issue of sufficiency of disclosure. The treatment of the stated conditions can also not be disregarded in the assessment of sufficiency of disclosure on account that claim 1 anyway confers absolute protection for the tablet, including any use thereof: the requirement of sufficiency of disclosure is only complied with if the disclosure of the invention allows the skilled person to perform, without undue burden, essentially all the embodiments covered by the claimed invention. The treatment of each of the stated conditions constitutes a particular embodiment of the claimed invention because it is explicitly recited in claim 12, irrespective of whether this feature is present in claim 1 or not.

2.3 The appellants pointed out that claim 12 covers a wide range of medical conditions to be treated in addition to hypertension, including cognitive decline, dementia, transient ischemic attack, stroke of type 2 diabetus mellitus. The Board concurs and notes that the patent does not disclose the suitability of the amlodipine-telmisartan combination for these therapeutic applications. The respondents relied on R7, R15-R17 and R26 to show the suitability of amlodipine/telmisartan for the treatment of hypertension together with the stated additional conditions. However, the articles and patent document R7, R17 and R26 neither reflect the common general knowledge nor appear to be cited in the patent in suit, whereas R15 and R16, as noted by appellant 3, merely mention hypertonia and chronic stable angina pectoralis. The suitability of the tablet of claim 1 for the treatment of several of the

conditions mentioned in claim 12 is thus not shown in the patent in suit or the evidence on file.

Accordingly, the main request does not fulfill the requirements of sufficiency of disclosure.

Auxiliary request 1

3. Sufficiency of disclosure

As a result of its rewording, claim 12 of auxiliary request 1 is to be construed as a Swiss-type claim in the sense of decision G 5/83. The treatment of the recited medical conditions accordingly constitute a functional feature of the claim. Since a sufficient disclosure is missing for some of these conditions (see 2.3 above), the criteria of sufficiency of disclosure are not met either by auxiliary request 1.

Auxiliary request 2

4. Sufficiency of disclosure

4.1 As a result of the deletion of claims 12 and 13, the objection of insufficiency of disclosure against these claims is moot.

4.2 Claim 1

4.2.1 The claimed pharmaceutical tablet comprises a layer of amlodipine in a disintegrating or eroding tablet matrix. According to appellant 3, a skilled person is not enabled by the patent or his common general knowledge to provide amlodipine in an eroding tablet matrix having instant release characteristics.

An objection of insufficient disclosure under Article 83 EPC cannot legitimately be based on an argument that the application would not enable a skilled person to achieve a non-claimed technical effect (Case Law of the Boards of Appeal of the European Patent Office, 8th edition, 2016, II.C.2). The Board notes that claim 1 does not explicitly recite any feature pertaining to instant release characteristics.

According to the appellants, the expressions "dissolving tablet matrix" and "disintegrating or eroding tablet matrix" must be construed based on the definitions provided for these expressions in paragraphs [0016] and [0017] of the description. Following these definitions, the dissolving tablet matrix and the disintegrating or eroding tablet matrix have instant release characteristics.

However, the Board notes that the concepts of disintegrating, eroding and dissolving tablets are well known and are discussed in e.g. R35 and R36, both of which may represent the common general knowledge. The Board shares the opinion expressed in declaration R38 (with respect to "eroding") that such expressions describe "the way of how a tablet falls apart *in vivo* or *in vitro* upon contact with a suitable dissolution medium", without being necessarily connected with specific release properties. Different tablet types are used to obtain different release profiles, e.g. immediate, extended or delayed release (see R35 page 410).

Consequently, under the present circumstances, the Board does not share the appellants' opinion that the expression "eroding tablet matrix" should be given the special meaning provided in the description: although

claim 1, by referring to dissolving, disintegrating or eroding tablet matrix, requires that the first layer be of a dissolving type, and the second layer of a disintegrating or eroding type, claim 1 contains no feature pertaining to the release profile to be achieved using these tableting techniques. The principle according to which the description may be used as the patent's "dictionary" cannot be used in the present case to read the additional feature "instant release characteristics" of the description (i.e. [0016] and [0017]) into claim 1, because this feature is neither recited nor can it be deducted from claim 1.

As a consequence, the incompatibility alleged by appellant 3 between the slow/extended release properties normally associated with eroding tablet matrix and the instant release characteristics is not relevant to the issue of sufficiency of disclosure because said instant release characteristics are not a feature of claim 1.

The skilled person, based on common general knowledge as reflected by R41 (for eroding tablets) and R58 (for dissolving or disintegrating tablets), can recognise whether a given tablet or layer dissolves, erodes or disintegrates. No reason was put forward by appellant 2 to explain why the alleged lack of clear distinction between such matrixes would prevent the skilled person from carrying out the invention. Since claim 1 is not limited in respect of *how* the layers dissolve, erode or disintegrate, or in respect of the release profile or any other parameter, any difficulty in achieving such release profile or parameter values as alleged by the appellants cannot prejudice the sufficiency of disclosure for claim 1.

4.2.2 The claimed pharmaceutical tablet also comprises a first layer of telmisartan in a dissolving tablet matrix comprising, *inter alia*, a water-soluble diluent.

For appellant 1, the breadth of the expressions "dissolving tablet matrix" and "water-soluble diluent" are not commensurate with the teaching of the examples, limited in this respect to sorbitol and mannitol. The Board does not agree: the patent in suit provides sufficient information regarding the composition of the first and second layers and the method for producing the bilayer tablets (see [0024]-[0029], [0030]-[0039] and [0046] ff). The Board stresses that the broadness of claim 1 cannot be contested on its own but only in conjunction with other criteria, here reproducibility. The alleged broadness of these expressions does not necessarily lead to the conclusion that it would represent undue burden for the skilled person to determine water soluble diluents that can be used to produce a dissolving tablet matrix.

4.2.3 The Board does not agree with appellant 3 that an insufficiency of disclosure arises from an alleged contradiction between the claim, requiring a disintegrating matrix, and the description (see paragraph [0039]), allowing for the presence of 0% disintegrant. As submitted by the respondents (and supported by document R42), the term "disintegrant" used in the description can be construed as referring to components *improving* the rapid decomposition of the tablet, such that no contradiction is seen between the absence of this [additional] disintegrant and the disintegrating tablet matrix. Furthermore, for the Board, the description could not be used to construe the claim such that the second layer comprises a disintegrating tablet matrix but contains no component

leading to this property, as this would not be a technically meaningful interpretation. Lastly, the possible absence of a disintegrant would in any case not contradict the alternative pertaining to an eroding tablet matrix.

5. Article 100(a) EPC, inventive step

5.1 The claimed invention

According to the patent, an object of the invention is to provide a fixed dose combination dosage form comprising amlodipine (a calcium channel blocker used to treat high blood pressure, angina and some arrhythmias) and telmisartan (an angiotensin II receptor antagonist developed *inter alia* for the treatment of hypertension). Following paragraph [0009], a "telmisartan formulation with acceptable *in vivo* performance has to comprise basic components like for example sodium hydroxide or meglumine whereas amlodipine is surprisingly not stable enough when it gets in direct contact with excipients to be used in a telmisartan formulation". The claimed invention addresses this problem by formulating telmisartan and amlodipine in a bilayer tablet as defined in claim 1.

The appellants submitted that this insufficient stability of amlodipine when formulated with basic agents was not made plausible in the patent, and that the first disclosure of this stability issue going beyond speculation was the post-published evidence R68. The Board cannot follow this view: as noted by the respondents, the patent (see [0009]) proposes a mechanism to explain this lack of stability in alkaline milieu, namely a hydrolysis of the ester bonds. Furthermore this fact is also derivable from the prior

art documents R30 and R53 (see 5.5.1). Accordingly the lack of stability of amlodipine in the presence of the basic excipients of the telmisartan formulation is plausible.

5.2 Choice of the closest prior art

Two documents have been cited as closest prior art, namely R10 and R23.

It is well established that, in selecting the closest prior art, a central consideration is that it must be directed to the same purpose or effect as the invention.

R10 discloses (see page 1349, left column) the concomitant administration of tablets of amlodipine (10 mg daily given as two 5 mg tablets) and tablets of telmisartan (120 mg daily given as one 80 mg and one 40 mg tablets) in a clinical trial. It is concluded that the combined administration is well tolerated without adverse effects.

R23 discloses bilayer tablets comprising telmisartan and a diuretic such as HCTZ. The choice of a bilayer tablet addresses the problem of lack of stability of HCTZ in the presence of the basic components used in the telmisartan formulation.

The Board does not consider R23 to be a realistic starting point for the following reasons: since the primary objective of the invention, as described in the patent, is to provide a fixed dose combination dosage form comprising the known compounds amlodipine and telmisartan, it is unrealistic to expect a skilled person to start from a disclosure pertaining to a

combination lacking amlodipine but containing instead a compound with a different mechanism of action.

Furthermore, the additional problem, mentioned in the patent, of the lack of stability of amlodipine in the presence of the basic components used in the telmisartan formulation, is also of relevance in the choice of the closest prior art. The choice of R23, which does not mention amlodipine, as a starting point for addressing the problem of lack of stability of amlodipine is all the more unlikely.

The Board does not agree with appellant 3 that, by relying on the technical problem mentioned in the patent, the determination of the the closest prior art is made in a subjective way. On the contrary, this determination is made objectively, taking into account the purpose or effect of the claimed invention as described in the patent.

The choice of R23 could only be based on the presence of technical features in common, in particular the bilayer tablet, without regard to the problem motivating the choice of these features in the patent, i.e. the stability of amlodipine. Such a choice would be based on hindsight.

Accordingly, R10 represents the closest prior art, whereas R23 is not suitable as a starting point.

5.3 Disclosure of R10

The appellants submit that the telmisartan and amlodipine tablets given in R10 must be those commercialised respectively under the names Micardis® and Norvasc®.

The use of Micardis® and Norvasc® in R10 may be said to be implicitly disclosed if a person skilled in the art, using common general knowledge, would directly and unambiguously deduce that these particular formulations have been used in this study. This is however not the case.

It is not demonstrated that commercial tablets were necessarily used for the purposes of the clinical trial described in R10. The correspondence between the doses given in R10 and the commercial tablet strengths cannot be seen as a direct an unambiguous disclosure that the Micardis® and Norvasc® tablets were used. This cannot be derived either from the absence of a statement to the contrary, i.e. the absence of a statement that the commercial tablets were not used.

The statement on page 1353 of R10 ("The results suggest that, if given in combination, both amlodipine and telmisartan may be administered once daily without need to adjust the dose of either agent") does not imply anything about the formulations used in the study.

For the Board, the disclosure of R10 cannot be ascertained by combining it with the separate items of the prior art R46 and R65. It is for this purpose not sufficient that the correspondence in the data reported in R10, R46 and R65 renders likely that all three documents relate to the same clinical study: R46 and R65 are neither cited in R10 nor can they be regarded as evidence of common general knowledge. In particular, R65 is an extract from the FDA Drug Approval Package for Micardis® reporting a telmisartan-amlodipine interaction study. Contrary to appellant 1's opinion, citing T 890/02 in this respect, the fact that R65

originates from the well known FDA database does not suffice for it to qualify as evidence of common general knowledge. The FDA database could not be anticipated by the skilled person to be an adequate source for obtaining information regarding not just Micardis® but its interaction with amlodipine. The criteria developed in T 890/02 are thus not fulfilled.

Accordingly, it is concluded that R10 discloses neither the formulation of telmisartan in a dissolving tablet comprising a basic agent selected from alkali metal hydroxides, basic amino acids and meglumine as well as a water-soluble diluent, nor the formulation of amlodipine in a disintegrating or eroding tablet.

5.4 Thus the claimed subject-matter differs from the concomitant administration of telmisartan and amlodipine of R10 by the formulation of both active ingredients in a fixed-dose combination in the form of a bilayer tablet as specified in claim 1.

5.5 Regarding the technical effect resulting from this difference, the Board comes to the conclusion that amlodipine exhibits a lack of stability in the presence of the basic components used in the telmisartan formulation, and that the bilayered formulation addresses this problem.

5.5.1 For the Board, the insufficient stability of amlodipine when formulated with the basic agents of claim 1 is credible considering R30 and R53: R53 (see example 3) describes the degradation of a particular amlodipine salt, namely a maleate salt, in the presence of meglumine. R30 relates to the stability of amlodipine in the presence of basic excipients (see pages 20-21 and table 3) or in basic (phosphate buffer) solution

(see pages 22-23). Although the test conditions in R30 do not involve an alkali metal hydroxide, basic amino acid and meglumine as specified in claim 1, and the degradation observed in R53 is specific to the maleate salt of amlodipine (see impurity 6 on page 10), the Board can accept that the skilled person would have derived from R30 and R53 the instability of amlodipine salts in basic conditions. The insufficient stability of amlodipine when formulated with said basic agents is further confirmed by the post-published evidence R68 (see abstract and page 35), which reports that amlodipine exhibits instability in alkaline conditions, as shown by subjecting amlodipine to basic conditions using sodium hydroxide under conditions which can be regarded as relevant stress conditions. Considering this general conclusion in R68, the same instability can be expected to arise with all the basic agents of claim 1.

5.5.2 The respondents filed R45 as evidence that the claimed bilayer tablets are stable. R45 shows data regarding the stability of the commercial bilayer tablet Twynsta®, comprising a layer of telmisartan formulated with basic agents (sodium hydroxide, meglumine) and a layer of amlodipine besilate. The Board is satisfied that the Twynsta® tablet is an embodiment falling within the scope of claim 1. The Board does not share appellant 1's opinion that the claims only cover formulations comprising amlodipine (i.e. free base) and not amlodipine salts, and therefore do not encompass Twynsta® as it contains amlodipine besilate. Since claim 1 contains no limitation as to the presence of salt-forming components, and since all the examples of the patent contain amlodipine salts, claim 1 on proper interpretation covers the Twynsta® tablet.

R45 thus demonstrates a sufficient stability for a tablet according to claim 1, i.e. it confirms that, for this embodiment, the physical separation of the incompatible ingredients avoids the loss of stability which would otherwise occur.

5.5.3 The appellants filed R32, R51 and R52 to show that claim 1 was so broad as to encompass formulations which did not exhibit an improved or given level of stability, such as those defined in R48 or R49. Appellant 1 also submitted that claim 1 does not limit the pH or exclude the presence of basic components in the amlodipine layer, in which case the required level of stability could not be achieved. However, it follows from the above that the relevant effect (avoiding the loss of stability resulting from the co-formulation of amlodipine with the basic components of the telmisartan formulation) credibly originates from the differentiating feature (the formulation of the components as a bilayer tablet). R32, R51 and R52 do not contradict this conclusion: these experimental reports demonstrate that formulations of amlodipine and telmisartan as bilayer tablet may exhibit some level of instability, but do not relate this instability to the presence of the basic excipients, i.e they do not show that the degradation of amlodipine caused by the basic excipients of telmisartan still occurs when the compounds are formulated as a bilayer tablet. It is accordingly not necessary to examine whether all claimed tablet exhibit a level of stability defined in absolute terms.

5.6 The problem to be solved is accordingly formulated as the provision of a tablet formulation containing telmisartan and amlodipine allowing for the co-administration of telmisartan and amlodipine and

avoiding the loss of stability of amlodipine associated with the basic excipients of telmisartan.

5.7 Turning to the obviousness of the solution, the Board agrees with both the respondents and the opposition division that the realisation of the incompatibility between amlodipine and the basic components used in the telmisartan formulation contribute to the inventive merit of the claimed invention.

Even if the insufficient stability of amlodipine in alkaline conditions was known at the priority date, the specific problem arising from co-formulating amlodipine and telmisartan was not known at the priority date. The realisation of this problem could only have been made by the skilled person by combining the teaching of R10 (which suggests the administration of amlodipine and telmisartan once daily at fixed dose, but without disclosing their respective formulations) with the choice of a formulation of telmisartan comprising a basic component (such as Micardis®, see R21) and the knowledge of e.g. R53 or R30 indicating that this may lead to stability issues.

The Board likewise does not agree that such a problem would be readily recognised in the course of routine work. As generally indicated in R31, the skilled person may observe instability problems upon testing of a particular formulation. However, this would suppose that the skilled person considers a formulation of amlodipine with telmisartan and basic components in the first place, which is not suggested in R10.

Consequently, the Board considers that the incompatibility between amlodipine and the basic

components used in the telmisartan formulation was unrecognized in the prior art.

5.7.1 A specific application of bilayered tablets to solve the problem of instability of amlodipine in the presence of basic components is neither derivable from R23 (because its teaching is limited to co-formulations of telmisartan with different components, namely a diuretic such as hydrochlorothiazide) nor from R13 (where only a physical incompatibility between benazepril and amlodipine is mentioned). It is however common general knowledge, as shown by R1-R5, that multilayer tablets permit the formulation of incompatible substances in separate layers. Nonetheless, the skilled person, without the knowledge of the incompatibility of amlodipine with the basic telmisartan excipients, would not be motivated to resort to the added complication of formulating the components as a bilayer tablet.

Accordingly, the subject-matter of claim 1 of auxiliary request 2 and of its dependent claims 2-11 involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the set of claims of auxiliary request 2 and a description to be adapted.

The Registrar: The Chairwoman:

B. Atienza Vivancos P. Schmitz

Decision electronically authenticated