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**Datasheet for the decision
of 5 July 2011**

Case Number: T 1750/07 - 3.3.02

Application Number: 96115146.1

Publication Number: 0753301

IPC: A61K 31/4184

Language of the proceedings: EN

Title of invention:

Combination of a benzimidazole having angiotensin-II
antagonistic activity with a diuretic

Patentee:

Takeda Chemical Industries, Ltd.

Opponents:

STRAWMAN LIMITED
Hexal AG

Headword:

Combination of AT II - Antagonist with a diuretic/TAKEDA

Relevant legal provisions:

EPC Art. 100(a), 56

Relevant legal provisions (EPC 1973):

EPC R. 67

Keyword:

"Inventive step - no: Further combination of active substances
obvious"

Decisions cited:

-

Catchword:

-



Case Number: T 1750/07 - 3.3.02

DECISION
of the Technical Board of Appeal 3.3.02
of 5 July 2011

Appellant: STRAWMAN LIMITED
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Appellant: Hexal AG
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Respondent: Takeda Chemical Industries, Ltd.
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 18 September 2007 rejecting the opposition filed against European patent No. 0753301 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
L. Bühler

Summary of Facts and Submissions

- I. European patent No. 0 753 301, based on application No. 96 115 146.1 and being a divisional of application No. 94 108 687.8, was granted with two claims.

Independent claims 1 and 2 as granted read as follows:

"1. Use of a combination of
(±)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-
[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-
benzimidazole-7-carboxylate or a pharmaceutically
acceptable salt thereof with hydrochlorothiazide for
the manufacture of a medicament to be used as a
prophylactic or therapeutic drug for hypertension.

2. A pharmaceutical composition for the treatment of
hypertension, which comprises
(±)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-
[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-
benzimidazole-7-carboxylate or a pharmaceutically
acceptable salt thereof in combination with
hydrochlorothiazide."

The IUPAC-formula contained in the claims as granted
represents the compound candesartan cilexetil. That
compound is referred to by that name in this decision.

- II. Opposition was filed against the granted patent under
Article 100(a) EPC, lack of inventive step.

The following documents were cited *inter alia* during
the proceedings before the opposition division and the
Board of appeal:

- (1) EP-A-400 835
- (2) US 5 196 444 A
- (3) American Journal of Hypertension, 1992, volume 5, number 12, part 2, pages 247S-251S
- (5) Physician's Desk Reference; 47th ed, pages 1741-1743, 1112-1114, 2356-2359, 902-904, 1457-1460, 1591-1593, 1621-1624, 2359-2362, 1593-1597, 1615-1618
- (10) US 4 880 804 A
- (14) Kaplan, N.M., Clinical Hypertension, fifth edition, Williams & Wilkins, Baltimore 1990, page 239
- (21) WO92/10097 A1
- (22) Kaplan, N.M., Clinical Hypertension, fifth edition, Williams and Wilkins, Baltimore 1990, pages 71-73, 189-193
- (26) Jahnecke, J., "Stufenplan der Hochdrucktherapie", Verh. Dtsch. Ges. Kreislaufforschg., 43, 1977, pages 115-119
- (28) Mizuno, K. et al., "Hypotensive activity of TCV-116, a newly developed angiotensin II receptor antagonist, in spontaneously hypertensive rats", Life sciences, volume 51, number 20, 1992, pages PL 183-187

III. The opposition division held that none of the grounds for opposition prejudiced the maintenance of the European patent, so the opposition was rejected.

The opposition division considered that, even taking into account that document (21) already mentioned hydrochlorothiazide as enhancing the hypotensive effect of angiotensin II receptor antagonists in general, the

selection of the particular antagonist candesartan cilexetil and its remarkably pronounced synergism effect provided for inventive step of the subject-matter of the patent in suit.

IV. The appellants (opponents) 01 and 02 each lodged an appeal against that decision and filed statements of grounds of appeal. Appellant (opponent) 02 requested reimbursement of the appeal fee (Rule 103(1)(a) EPC).

V. On 5 July 2011, oral proceedings took place before the Board.

During the oral proceedings, the respondent attempted to file an auxiliary request containing claim 1 as granted as a single claim. This request was not admitted into the proceedings.

In the course of the discussion, the respondent submitted EP-A1-0 459 136 (cover page and pages 58 and 59). It was not admitted into the proceedings.

VI. The appellants' arguments during the proceedings can be summarised as follows:

Document (21) referred to a single experiment applying hydrochlorothiazide as a diuretic together with compound A as an angiotensin II receptor antagonist. Based on this experiment, the well-founded teaching of document (21) was "that diuretics enhance the hypotensive efficacy of angiotensin II receptor antagonists". This teaching was to be acknowledged as disclosure of a "class" effect and directly led to the combination of the diuretic hydrochlorothiazide with

candesartan cilexetil, a substance well known to be highly active. All assumptions of an unpredictably pronounced and therefore remarkable effect represented by the teaching of the patent in suit were based on incomparable experiments and, even if such an effect existed, it resulted from the known high potency of candesartan cilexetil itself.

Further effects like the reduction of side effects such as hypokalemia could only be regarded as bonus effects and could not be taken as a basis for acknowledging inventive step.

VII. The respondent contested the arguments of the appellants:

The experiment set out in document (21) taught that antihypertensive activity was increased when the specific angiotensin II receptor antagonist (E)-3-[2-n-butyl-1-((4-carboxyphenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl]-2-propenoic acid, named compound A, was combined with hydrochlorothiazide.

The teaching of the document as a whole, however, was that it was advantageous that

- "the angiotensin II blocking compounds of formula (I) - (IX)"
in a preparation comprising a pharmaceutical carrier and
- a second therapeutic agent selected from a diuretic, a calcium channel blocker, a β -adrenoceptor blocker, a renin inhibitor, or an angiotensin-converting enzyme inhibitor

would be present in an amount to treat hypertension in a subject in need thereof.

Consequently, in document (21), the replacement of the specific angiotensin II receptor antagonist (compound A) by candesartan cilexetil in combination with hydrochlorothiazide was neither disclosed nor suggested. Even considering the prior art as a whole, there was no convergent teaching leading the skilled person to combine candesartan cilexetil with hydrochlorothiazide in order to obtain any synergistic or other effect.

This was particularly true, since in document (21) each of the components, namely compound A and hydrochlorothiazide, exhibited a zero-effect when administered alone, while in the patent in suit, the angiotensin II receptor antagonist had a measurable effect when used alone which was **reinforced** by co-administration of hydrochlorothiazide. Therefore, the problem to be solved with respect to document (21) related to the - even synergistic - improvement of the antihypertensive activity by **increasing** the existing activity of the individual compounds when combining them and not just switching it on by starting the renin-angiotensin feedback loop of blood-pressure.

In addition, the teaching in document (28) led the reader away from replacing compound A (an imidazole derivative) by candesartan cilexetil (a benzimidazole derivative), because it was silent on combinations of an angiotensin II receptor antagonist with other active compounds and because it stressed that candesartan cilexetil caused the relatively slow onset of antihypertensive action with respect to losartan, which

was an imidazole derivative (like compound A) in contrast to the benzimidazole derivative candesartan cilexetil.

Moreover, synergism of two components was defined as an over-additive effect and it was never predictable. Accordingly, the teaching of numerous documents pointed arbitrarily in the direction of an additive, over-additive or even non-existent effect of combining an angiotensin II receptor antagonist or an angiotensin converting enzyme inhibitor (as a similarly acting substance) with other blood-pressure lowering substances (see in particular document (1), page 26, lines 21 to 36; document (3), paragraph bridging pages 250S and 251S; document (5), referring to different angiotensin-converting enzyme inhibitors in combination with diuretics, in particular hydrochlorothiazide; document (10), column 45, lines 4 to 9; document (14), page 239, last sentence in the paragraph under the headline "Combination therapy"; document (22), page 193, first two paragraphs under the headline "Combination therapy"; document (26), page 118, last sentence of the first paragraph).

Finally, with respect to the teaching of document (21), the skilled person could select the substitute for compound A, an angiotensin II receptor antagonist, from the countless candidates offered by the state of the art. Only one of them, without any preference for it, was candesartan cilexetil.

In this context, it was requested not to admit document (28) into the proceedings, because it could have been filed during the proceedings before the

opposition division and because it did not provide any more information than the documents already on file, in particular document (2).

The appellants (opponents) requested that the decision under appeal be set aside and that the European patent be revoked. Appellant (opponent) 02 requested reimbursement of the appeal fee.

VIII. The respondent (patentee) requested that the appeals be dismissed.

Reasons for the Decision

1. The appeals are admissible.

2. Document (28) was introduced together with the statement of grounds of appeal and has to be regarded as an answer to the considerations and conclusions of the opposition division set out in its decision; therefore it is admitted into the proceedings.

Document EP-A1-0 459 136 (cover page and pages 58 and 59), even if representing the European Application relating to document (2), a US Patent which has already been introduced into the proceedings, was not admitted into the proceedings as a late filed document, because it firstly contained only two pages of the whole document, leaving a doubt as to whether there was any information to the contrary in the rest of the document, secondly the full document apparently contained more than 58 pages which was too much to consider at this stage of the proceedings, and finally because it

contained no additional relevant information exceeding the evidence on file.

3. *Admissibility of the auxiliary request*

Independent claim 2 as granted, having been under attack already in the grounds for opposition of appellant (opponent) 02 (pages 12/13), and the deletion of this claim 2 not setting out an answer to relevant objections raised during the proceedings, the auxiliary request was not admitted into the proceedings.

4. *Claim 1 of the main request; Article 56 EPC (inventive step)*

4.1 Regarding its claim 1, the patent in suit relates to

- the use of a combination of
- candesartan cilexetil with
- hydrochlorothiazide
- for the manufacture of a medicament to be used as a prophylactic or therapeutic drug for hypertension.

4.2 In the present case, there is no reason when determining the document of closest prior art to deviate from the reasoning and conclusions of the opposition division. The closest prior art is document (21).

Document (21) relates to

- the use of a combination of
- (E)-3-[2-n-butyl-1-{(4-carboxyphenyl)methyl}1H-imidazol-5-yl]-2-(2-thienyl)methyl]-2-propenoic acid

(compound A, an angiotensin II receptor antagonist) with

- hydrochlorothiazide (page 22, lines 29 to 35)
- for the manufacture of a medicament to be used as a prophylactic or therapeutic drug for hypertension (page 22, line 34 to page 23, line 2, with the hypotensive effects of the experiment set out in table 1 on page 23)

and, as a consequence, it relates to the teaching that the results of the experiment indicate that diuretics enhance the hypotensive efficacy of angiotensin II receptor antagonists (see in particular page 22, lines 29 to 35 of document (21)).

- 4.3 Nothing in the evidence on file contradicts the generalisation from the experiment in document (21) because no combination of an angiotensin II receptor antagonist and hydrochlorothiazide is reported with the enhancement of the hypotensive effects of the individual compounds missing.
- 4.4 In the absence of any comparative experiment showing superior features of the subject-matter of claim 1 of the patent in suit over the subject-matter represented in document (21) (combination of compound A with hydrochlorothiazide), the problem to be solved is to provide a further combination of hydrochlorothiazide and an angiotensin II receptor antagonist for the manufacture of a medicament for treatment of hypertension.
- 4.5 The solution to this problem is to replace compound A by candesartan cilexetil.

- 4.6 In the light of the "Test example 1" demonstrating "Antihypertensive activity in spontaneously antihypertensive rats (SHR) by the co-administration with a diuretic drug", the Board is satisfied that the problem is solved.
- 4.7 According to documents (2) and (28), candesartan cilexetil is a well-known angiotensin II receptor antagonist exhibiting quite low toxicity, being clinically useful in treating *inter alia* hypertension (see document (2), column 2, lines 34 to 48), and being about tenfold more active than the equally well-known losartan (see document (28), page PL-186, second paragraph, first two lines).
- 4.8 Being aware of documents (2) and (28), in the present situation it was obvious to use the well-known angiotensin II receptor antagonist candesartan cilexetil instead of compound A together with hydrochlorothiazide to produce a further combined medicament for the treatment of hypertension (Article 100(a) EPC, lack of inventive step).
5. In addition, the further arguments of the respondent cannot succeed:
- 5.1 *Correct starting point*

The overall content of document (21) is broader than the experiment, while the experiment represents the basis of the document's teaching. However, it is normal practice to treat an experiment contained in a document and in particular a single one as a distinct disclosure

with its own and particular teaching. Insofar, comparing the teaching of the experiment on pages 22 and 23 of document (21) to the teaching of the patent in suit is a correct basis on which to assess the inventive step of this patent.

5.2 *Additional further arguments*

5.2.1 The respondent submitted that "synergism" was well defined as an effect of the combination of drugs being more than additive with respect to the effects of the individual substances, while the documents on file mostly presented not such synergism but only vague speculation or information on additive effects; in particular prediction of a "class" effect was not possible with respect to a very distinctive phenomenon like synergism.

Additionally, the effects described in document (21) represented no synergism at all, because the hypotensive effect was simply activated on adding hydrochlorothiazide; this was a decisive difference to results of the experiments set out in the patent in suit, where an existing hypotensive effect was reinforced in a synergistic way.

Finally, so many angiotensin II receptor antagonists were shown in the documents of the state of the art, in particular document (1) but also document (21) itself, which appeared ready for selection for combination with hydrochlorothiazide according to the teaching of the experiment in document (21); there was no reason to take candesartan cilexetil and not another angiotensin II receptor antagonist.

5.2.2 All these arguments, however, cannot succeed, because there is no comparative experiment setting out that the enhancement of the blood-pressure lowering effect due to the combination of the active substances referred to in the patent in suit is superior to the enhancement presented by the experiment in document (21) (see page 22, line 25 to page 23, line 2 and page 23, table 1). The experiments conducted according to the patent in suit and the experiment disclosed in document (21) are not comparable for various reasons (other values for blood-pressure measured, other rats used in another environment; design of application different, e.g. intravenous and oral administration).

On the other hand, "enhancement" of the hypotensive efficacy of an angiotensin II receptor antagonist as set out in document (21) means nothing other than claiming an over-additive effect, thus representing a synergistic effect in terms of the patent in suit. Such an effect is demonstrated by the information set out in table 1 of document (21) irrespective of the underlying mechanism. The conclusion drawn about the "class" effect with respect to all angiotensin II receptor antagonists in combination with diuretics results from the experiment in the light of the common general knowledge that such combinations are always preferred medicaments (see for instance document (26), page 116, "Stufe III"). The respondent could not call into question this conclusion to the extent that it was relevant in the present case, because none of its examples of only additive effects or non-existent effects related to a combination of an angiotensin II

receptor antagonist with hydrochlorothiazide in particular.

That relatively low amounts of candesartan cilexetil in absolute terms can be administered successfully is due to the substance's good performance per se, which was already known to the skilled person before the priority date of the patent in suit (see document (2), column 2, lines 37 to 40 and document (28), page PL-186, second paragraph, first two lines) and not due to co-administration with hydrochlorothiazide as an indication of a superior extent of the enhancement effect. Thus, the experiment set out in the patent in suit cannot support the statement of superior synergism.

Consequently, the problem to be solved relates only to another combination of hydrochlorothiazide and an angiotensin II receptor antagonist which in turn has the consequence that any known angiotensin II receptor antagonist may be combined with hydrochlorothiazide without inventive effort insofar as it was known before the priority date (see documents (2) and (28)). No particular incentive to select candesartan cilexetil has to be indicated.

6. *Request of appellant (opponent) 02 for reimbursement of the appeal fee (Rule 67 EPC 1973)*

The appellant (opponent) 02 argued that the opposition division had ignored its arguments as regards document (2) being the closest prior art.

In its decision, however, the opposition division set out its reasons to choose document (21) as the closest

prior art (section 2.3 of the decision). From this section and a later statement on document (2) (section 2.8.2) it can be inferred, why the opposition division did not consider document (2) to represent the closest prior art. Thus, although not explicitly refuting the reasoning of appellant (opponent) 02 with respect to document (2) as the closest prior art, the opposition division cannot be said to have ignored or disregarded an argument of the appellant (opponent) 02. The Board sees no objection to an opposition division limiting itself to the arguments relevant for the decision and omitting a detailed analysis of pieces of prior art that are less relevant.

Under these circumstances, the conditions for reimbursement of the appeal fee on the grounds of a substantial procedural violation are not met, and the request is to be refused (Rule 67 EPC 1973).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.
3. The request for reimbursement of the appeal fee is refused.

The Registrar:

The Chairman:

N. Maslin

U. Oswald