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**Datasheet for the decision
of 5 December 2012**

Case Number: T 1626/08 - 3.3.02

Application Number: 00965906.1

Publication Number: 1216038

IPC: A61K 31/00

Language of the proceedings: EN

Title of invention:

Ramipril for the prevention of cardiovascular events

Patentee:

Sanofi-Aventis Deutschland GmbH

Opponent:

Teva Pharmaceutical Industries Ltd.
Hexal AG
BOEHRINGER INGELHEIM Pharma GmbH & Co KG

Headword:

Ramipril/SANOFI

Relevant legal provisions:

EPC Art. 54(3), 123(2)

Keyword:

"Novelty (no): all features of claim 1 anticipated"
"Partly: added subject-matter (yes): features not originally disclosed"

Decisions cited:

-

Catchword:

-



Case Number: T 1626/08 - 3.3.02

DECISION
of the Technical Board of Appeal 3.3.02
of 5 December 2012

Appellant: Sanofi-Aventis Deutschland GmbH
(Patent Proprietor) Brünigstraße 50
D-65929 Frankfurt am Main (DE)

Representative: Bösl, Raphael Konrad
Isenbruck Bösl Hörschler LLP
Patentanwälte
Prinzregentenstrasse 68
D-81675 München (DE)

Respondent I: TEVA Pharmaceuticals Industries Ltd.
(Opponent 2) 5 Basel Street, P.O. Box 3190
Petah Tiqva 49131 (IL)

Representative: Nachshen, Neil Jacob
D Young & Co LLP
120 Holborn
London EC1N 2DY (GB)

Respondent II: Hexal AG
(Opponent 3) Industriestrasse 25
D-83607 Holzkirchen (DE)

Representative: Hamm, Volker
Maiwald Patentanwalts GmbH
Jungfernstieg 38
D-20354 Hamburg (DE)

Respondent III: BOEHRINGER INGELHEIM Pharma GmbH & Co KG
(Opponent 4) Binger Strasse 173
D-55216 Ingelheim/Rhein (DE)

Representative: HOFFMANN EITLÉ
Patent- und Rechtsanwälte
Arabellastraße 4
D-81925 München (DE)

Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted 30 June 2008
revoking European patent No. 1216038 pursuant
to Article 101(3) (b) EPC.**

Composition of the Board:

Chairman: A. Lindner
Members: H. Kellner
 R. Cramer

Summary of Facts and Submissions

- I. European application No. 00 965 906.1 was granted as European patent No. 1 216 038 with eight claims, based on international application No. PCT/EP2000/008461, published as WO 2001/015674.

Independent claim 1 as granted read as follows:

"The use of ramipril or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the prevention or reduction of a cardiovascular event in a high risk patient with no evidence of left ventricular dysfunction or heart failure, where the cardiovascular event is stroke, cardiovascular death or myocardial infarction."

- II. Oppositions were filed against the granted patent under Article 100(a) EPC (novelty and inventive step), Article 100(b) EPC (sufficiency of disclosure) and Article 100(c) EPC (added subject-matter).

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

(18) WO 01/15673 A2 (Article 54(3) EPC)

(24) EP 1 437 131-A1 (Article 54(3) EPC, divisional of EP 1 212 081 based on document (18))

(25) Swedish application No. 9903028-0 (priority document relating to documents (18) and (24)).

III. By its decision pronounced at oral proceedings on 19 May 2008 and posted on 30 June 2008, the opposition division revoked the patent under Article 101(3)(b) EPC.

The opposition division held that the set of claims of the main request (claims as granted) was not to be objected under Articles 100(c) and 100(b) EPC.

However, with regard to Article 54(3) EPC the subject-matter of claim 1 of the main request was not novel over documents (18) and (24). In addition, several other documents prejudiced its teaching.

The same reasoning applied to auxiliary request 4.

Moreover, the opposition division held that auxiliary requests 1 to 3, 5 and 6 did not fulfil the requirements of Article 123(2) and/or (3) EPC.

IV. An appeal was lodged against that decision and grounds of appeal were filed together with a request that the patent be maintained according to its main request (claims as granted) or one of its auxiliary requests 1 to 11.

V. In a communication dated 8 August 2012, the board stated that the current requests appeared to require examination with respect to added subject-matter and with respect to the provisions of Article 84 EPC (the latter concerning the auxiliary requests only); specific problems in this context were indicated.

VI. On 5 December 2012, oral proceedings took place before the board in the presence of representatives of the

appellant and representatives of respondents I and II (opponents 02 and 03); duly summoned, respondent III (opponent 04) had informed the board in advance that it did not wish to attend.

VII. During the oral proceedings, withdrawing the requests on file the appellant filed eleven sets of claims as a main request and auxiliary requests 1 to 10, which were admitted into the proceedings.

These requests were based on the requests filed with the grounds of appeal, omitting the former main request that was annexed to the statement of grounds of appeal and deleting the passage "or a pharmaceutically acceptable salt thereof" from all claims.

Claim 1 of the current main request is based on claim 1 as granted and consequently reads as follows (amendments compared to claim 1 as granted shown in strikethrough):

"The use of ramipril ~~or a pharmaceutically acceptable salt thereof~~ for the preparation of a medicament for the prevention or reduction of a cardiovascular event in a high risk patient with no evidence of left ventricular dysfunction or heart failure, where the cardiovascular event is stroke, cardiovascular death or myocardial infarction."

In claim 1 of auxiliary requests 1 and 2, at the end of the text of claim 1 of the main request the text of claim 2 as granted is added in the following form:

"and where the patient is at risk having an cardiovascular event due to a manifest coronary heart disease, a history of transient ischaemic attacks or stroke or history of peripheral vascular disease."

In claim 1 of auxiliary request 3, at the end of a text identical to claim 1 of the main request, the passage

", wherein the medicament is to be administered for at least 2 years".

is added.

In claim 1 of auxiliary requests 4 and 5, the added text reads

"and where the patient is a diabetic."

Claim 1 of auxiliary request 6 is also worded like claim 1 of the main request, with the additional texts of auxiliary request 4 and auxiliary request 2.

In claim 1 of auxiliary request 7, also at the end of a text identical to claim 1 of the main request, the passage

"wherein the medicament also prevents cardiac arrest, heart failure and diabetic complications"

is added.

In claim 1 of auxiliary request 8, as a further disease to be prevented, "worsening or new angina" is added as compared to claim 1 of auxiliary request 7.

The wording added to the text of the main request in auxiliary requests 9 and 10 reads

"wherein the medicament also prevents cardiac arrest, **worsening angina**, heart failure, **diabetes** and diabetic complications" (diseases added in comparison with those of auxiliary request 7 in bold).

VIII. The appellant's submissions may be summarised as follows:

All sets of claims comprised only features that were disclosed in context with the other features in the respective claims as originally filed, at least in the original description if there were considered to be ambiguities with respect to disclosure in the original claims.

With respect to the state of the art, the documents on file did not contain all the features of the claims 1 of the requests and therefore were not novelty-destroying. In particular, nowhere in the state of the art was it reported that for instance in addition to "stroke, cardiovascular death or myocardial infarction" also all of "cardiac arrest, worsening angina, heart failure, diabetes and diabetic complications" were prevented, as was set out in auxiliary request 10 as an example for the meaning of the wording of auxiliary requests 7, 8, 9 and 10.

IX. The respondents' arguments may be summarised as follows:

There were *inter alia* problems with Article 123(2), Rule 80 and Articles 83 and 54 EPC.

In particular, there was added subject-matter with respect to dependent claims, and limiting the duration of treatment to two years was not disclosed in relation to all the kinds of treatment (prevention or reduction of symptoms) and not supported by facts of statistical relevance.

Objections under Rule 80 EPC were brought forward where only a sub-claim was deleted and claim 1 of the request remained unamended.

Inter alia, lack of a sufficient definition of the term "high risk patient" made the teaching of claim 1 of the main request impossible to be carried out by the skilled person (Articles 100(b) and 83 EPC respectively).

Finally, the opposition division was right in its conclusion with respect to novelty in relation to the documents as indicated.

X. The appellant requested that the decision under appeal be set aside and that the case be remitted to the department of first instance for further prosecution on the basis of the main request or alternatively on the basis of one of the auxiliary requests 1-10 filed during the oral proceedings on 5 December 2012.

XI. The respondents requested that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.
2. The amended claims filed as main request and auxiliary requests 1 to 10 during the oral proceedings are a *bona fide* attempt to respond to the arguments set out in the communication of the board and during the oral proceedings. Not being objected to by the respondents, and the board raising no objections of its own, these claims are therefore admitted into the proceedings.
3. *Claim 1 of the main request*
 - 3.1 *Article 123(2) and (3) EPC*
 - 3.1.1 The subject-matter of claim 1 of the main request relates to
 - the use of ramipril
for the preparation of a medicament
 - for the prevention or reduction
of a cardiovascular event
 - in a high risk patient
 - with no evidence of left ventricular dysfunction or
heart failure
 - where the cardiovascular event is
stroke,
cardiovascular death or
myocardial infarction.

3.1.2 The disclosure of the subject-matter of this claim in the application as originally filed is based on the first paragraph under the heading "Detailed description of the invention" (page 5, lines 3 to 10) which starts with the text "It has been surprisingly found ...", and therefore is to be regarded at least as closely related to the basic definition of the subject-matter to be claimed. It indicates the teaching that

- by use of an inhibitor of the renin-angiotensin system (RAS) (which can be *inter alia* ramipril (see page 7 of the description as originally filed, lines 11 to 13))
- cardiovascular events such as
stroke, ...,
cardiovascular death,
myocardial infarction,
...
- can be prevented
- in a broad population of high risk patients
- with no evidence of left ventricular dysfunction or heart failure.

Other events that can be prevented are also mentioned in this paragraph, the particular inhibitor ramipril is not indicated and the word "reduction" is missing in comparison to the features of claim 1 of the main request.

3.1.3 The "examples" set out in the application as originally filed (see page 14 ff.) are explained on page 15, line 22 containing the protocols and results of the large-scale clinical trial HOPE (Heart Outcomes Prevention Evaluation). Thus, they are meant to

represent the description of different aspects of this one study (see page 14, line 31) as conducted before the priority date of the patent in suit.

Consequently, these "examples" represent a combination of details of the study's conduct and of experimental results and conclusions drawn from the collected data, the results and conclusions representing a generalised teaching which is valid independently of all the details.

Such a conclusion is set out on page 15, lines 18 to 20 and relates to the teaching that

- ramipril significantly **reduces**
- cardiovascular events such as stroke, **mortality**, myocardial infarction, ... and prevents diabetic complications
- in a broad range of high risk patients
- without **low EF (ejection fraction)** or heart failure (ramipril is now cited specifically; other wording differing from the passage to be found on page 5 of the original description and cited under point 3.1.3 of this decision is shown in bold by the board).

3.1.4 These two passages, the first as a general definition of the subject-matter to be claimed (page 5 of the original description) and the second as a conclusion drawn from the exemplified study forming its basis (page 15 of the original description), are to be seen

as complements despite the differing wording indicated above, namely

- (a) "cardiovascular deaths" and "mortality"
- (b) "prevention" and "reduction"
- (c) "left ventricular dysfunction" and "low ejection fraction":

(a) According to lines 2 to 4 in the paragraph before the cited passage on page 15 of the description as originally filed, "The primary outcome was the first occurrence of the composite of cardiovascular (CV) mortality, myocardial infarction or stroke".

The paragraph continues by indicating certain numbers of patients that "experienced a primary outcome" as the basis for claiming "clear and significant reductions" relating to "CV deaths" (obviously used synonymously with "cardiovascular (CV) mortality") and myocardial infarction. Directly at the beginning of the following sentence, for the first of the "secondary outcomes" a figure for reduction of "total mortality" is presented (see page 15, line 11).

"Secondary outcomes" are characterised as comprising total mortality, revascularisation procedures, cardiac arrests, heart failure, and diabetic complications, and are also described as significantly reduced (see page 15, lines 10 to 15).

In the next and final paragraph of the text introducing the enumeration under the heading "examples", a conclusion from these particular results is drawn (page 15, lines 18 to 20 as cited above under point 3.1.3). This starts by mentioning "mortality,

myocardial infarction, stroke" as results in the context of primary outcome followed by "revascularization procedures, and heart failure" as secondary outcomes.

Consequently, the board is convinced that "mortality" in the context of this conclusion, at least as an indication of results including "total mortality", represents "cardiovascular (CV) mortality" or "CV deaths", i.e. the first primary outcome apart from myocardial infarction and stroke, just as is expressed in the first paragraph on page 5 of the original description and in claim 1 of the main request with the wording "cardiovascular death".

(b) As far as the feature "prevention or reduction" in claim 1 of the main request is concerned, the board is satisfied that "prevention" and "reduction" are used interchangeably, as can be seen from a comparison between the cited conclusion on page 15, lines 18 to 20 which relates to some effects to be reduced administering ramipril (e.g. myocardial infarction and stroke) and the passage on page 5, lines 3 to 10 in particular lines 4 and 3), according to which the same events are prevented by use of an inhibitor a the RAS system such as ramipril.

(c) According to the teaching of claim 1 of the main request, "left ventricular dysfunction" and "low ejection fraction" are features characterising the diseases of the patient sub-group to be excluded from the patient group to be treated. Thus, patients suffering from "low ejection fraction" are regarded as patients suffering from "left ventricular dysfunction",

the latter being a kind of generic wording for the disease suffered by a larger number of patients, including "low ejection fraction".

Therefore, there is no contradiction in the use of the terms "left ventricular dysfunction" and "low ejection fraction" in the respective parts of the original disclosure and current claim 1; the only consequence is that by mentioning the larger patient sub-group to be excluded from the patients to be treated the number of these patients is reduced to a greater extent and the subject-matter of the claim is narrower than a subject-matter excluding the patients suffering from "low ejection fraction" only.

3.1.5 Consequently, the features of claim 1 of the main request including the features

- (b) "prevention or reduction of a cardiovascular event",
- (a) e.g. "cardiovascular death", and
- (c) "left ventricular dysfunction" in characterising the patient-subgroup to be excluded

are to be found in the required meaning and context in the combination of the passages indicated above under point 3.1.4 of this decision and set out on pages 5 and 15 of the original description.

Taking into account that under these circumstances claim 1 of the main request differs in substance from the combination of these passages only in that there is a medicament for the prevention or reduction of a cardiovascular event concerning a reduced list of these

events, the whole teaching is directly and unambiguously derivable and the provisions of Article 123(2) EPC are met.

3.1.6 Since the patient group to be treated in comparison to claim 1 as granted is more reduced in claim 1 of the main request and since the other features are in principle the same, the provisions of Article 123(3) EPC are also met.

3.2 *Claim 1 of the main request; Articles 84 and 83 EPC*

3.2.1 *Article 84 EPC not under investigation*

Article 84 EPC is not under investigation in the current case because claim 1 of the main request, with the exception of the deletion of salts of ramipril, is identical to claim 1 as granted. As a further amendment, in the claim set of the main request only claim 8 as granted is deleted (according to the appellant it was omitted because it was not supported by the priority document).

3.2.2 *Article 83 EPC*

On the other hand, the board is satisfied that the teaching of claim 1 of the main request can be carried out by the skilled person, because nothing tangible to the contrary has been filed and ambiguity concerning the high risk patient, meaning the patient group to be treated, is a question of the clarity of the claim itself (Article 84 EPC) and not a question of sufficiency of disclosure regarding the patent in all

its parts, in particular including the description (Article 83 EPC).

3.3 *Claim 1 of the main request; Article 54(3) EPC novelty*

3.3.1 Undisputed by the parties and in line with the considerations and conclusions of the opposition division, document (18) is state of the art under Article 54(3) EPC. Its priority date being three days in advance of the priority date of the patent in suit, anticipation is restricted to subject-matter contained in document (18) as far as it represents the same invention as the priority document (25). In the current case, the relevant parts of document (18) are identical to the respective text in document (25).

3.3.2 The subject-matter of claim 1 of the main request relates to

- the use of ramipril
for the preparation of a medicament
- for the prevention or reduction
of a cardiovascular event
- in a high risk patient
- with no evidence of left ventricular dysfunction or
heart failure
- where the cardiovascular event is
stroke,
cardiovascular death or
myocardial infarction.

3.3.3 The teaching of document (18) is

- the use of ramipril (see document (18), page 10, lines 18 and 19)
for the preparation of a medicament
- for the prevention or reduction of a cardiovascular event (*ibid*, page 11, lines 1 to 3)
- in a high risk patient (*ibid*, page 10, lines 21 and 22)
- with no evidence of left ventricular dysfunction or heart failure (*ibid*, page 11, lines 13 and 14, setting out that the patients included in the study had no signs or symptoms of congestive heart failure (CHF) at its start, which means that clinically no congestive heart failure and - because of the common use of both terms for the same clinical picture in the sense of the patent in suit - no heart failure was to be diagnosed)
- where the cardiovascular event is stroke, cardiovascular death or myocardial infarction (*ibid*, page 11, lines 1 to 4 with heart attacks used as a synonym for myocardial infarction).

3.3.4 Thus, all features of claim 1 of the main request being anticipated by the teaching of document (18), the subject-matter of this claim is not new.

4. *Claims 1 of auxiliary requests 1, 2, 4, 5 and 6, Article 54(3) novelty*

4.1 Claims 1 of auxiliary requests 1 and 2 read identically to one another and, as compared to claim 1 of the main request include the further feature that the patient be

at risk of having a cardiovascular event due to particular diseases.

However, the argumentation concerning Article 54(3) EPC also applies *mutatis mutandis*. The subject-matter of these claims is not new because also the additional feature relating to the patients' risk due to a manifest coronary heart disease, a history of transient ischaemic attacks or stroke or history of peripheral vascular disease is prejudiced in addition in document (18), page 10, lines 22 and 23, with the one risk factor - stroke - being identical in wording and others being identical in meaning.

- 4.2 Claims 1 of auxiliary requests 4 and 5 read identically to one another and relate to the use of ramipril ... for the prevention or reduction of a cardiovascular event in a high risk patient ... and where the patient is a diabetic.

Auxiliary request 6 relates to high risk patients to be treated with ramipril, being diabetic and at risk of a cardiovascular event due to a manifest coronary heart disease, a history of transient ischaemic attacks or stroke or a history of peripheral vascular disease.

Thus, according to these claims in the context of diabetes, there are two groups of high risk patients to be treated, one suffering from diabetes and another risk factor not mandatorily related to cardiovascular problems (see page 16 of the original description, lines 2 to 7) and the other suffering from diabetes and a cardiovascular risk (due to ...).

This is confirmed by the text on page 25, lines 21 and 22, where 3578 diabetic participants were mentioned with 1100 of them having no clinical manifestations of cardiovascular disease (CVD).

In document (18) (and in document (25)) it is set out that "The study was stopped early because of a very clear reduction in the combined endpoint of cardiovascular deaths, heart attacks and strokes in patients taking ramipril. In addition to the above benefits, there was also a reduction of between a fourth and a fifth in the need for revascularisation procedures ... and diabetic complications" (see document (18), page 11, lines 1 to 6).

The results with regard to patients who had no diabetes at the beginning of the study but developed diabetes during the study are described later in document (18) (lines 16 and 17 on page 11).

Consequently, reduction of diabetic complications in document (18) means reduction of such complications in patients being diabetic from the beginning of the study that were treated with ramipril, some of them having clinical manifestations of cardiovascular disease (as deduced from the patient numbers cited above).

That is exactly the situation to which claims 1 of auxiliary requests 4, 5 and 6 are directed. This teaching is therefore not novel over document (18).

- 4.3 Accordingly, the subject-matter of claims 1 of auxiliary requests 1 and 2, 4, 5 and 6 is not new in view of document (18).

5. *Claims 1 of auxiliary requests 3 and 7 to 10;
Article 123(2) EPC*

5.1 *Claim 1 of auxiliary request 3*

Claim 1 of this auxiliary request contains the text of claim 1 of the main request with the addition "*, wherein the medicament is to be administered for at least 2 years*".

The relevant text containing the time period of two years is to be found in the description as originally filed under example 8, page 24, lines 5 to 10: "*The reduction in the primary outcome was evident within 1 year after randomisation ... and became statistically significant at 2 years ...*".

One message of this text is that effects start even before the end of one year of administration. Under these circumstances there is no sense in imposing the administration of ramipril for at least 2 years. The 2-years period as mentioned in the application in suit only expresses a value that is relevant for statistical conclusions with respect to the particular situation of the study, and even there only in context with a confidence interval (CI) to be defined (see example 8, page 24, line 8).

Therefore, a minimum administration of two years with respect to the use of ramipril as specified in the claim cannot be derived from example 8 as originally disclosed.

5.2 *Claims 1 of auxiliary requests 7 to 10*

The subject-matter of the main request was found not to contain added subject-matter because two paragraphs of the description as originally filed were read together that both had a general meaning in the application.

Whenever further details are introduced into a claim, the question arises whether such a detail can be generalised on its own or if it is connected with further details from the context of its disclosure that had to be included in the claim together with the first detail. This is the case, in particular, as soon as it is necessary to include parts of the example study into the assessment of the original disclosure of features of requested claims.

5.2.1 Auxiliary request 7

Claim 1 of this request relates to claim 1 of the main request where in addition to prevention or reduction of cardiovascular events of one of the primary outcomes stroke, cardiovascular death or myocardial infarction, **also** secondary outcomes, namely cardiac arrest, heart failure **and** diabetic complications were prevented (emphasis in bold by the board).

Disclosure of such features with primary and secondary outcomes connected by the word "also" can be found only on page 15, lines 10 to 15 of the application as originally filed. The other list of secondary outcomes in example 6 on page 22 of the application, which presents some of the secondary outcomes reduced or prevented by ramipril in the HOPE study in a similar

way as indicated in claim 1 of auxiliary request 7, is not connected to primary outcomes by the word "also" and therefore represents another meaning and cannot be used as a source for the respective features in the claim.

The subject-matter of claim 1 of auxiliary request 7 relates to cases where in addition to one of the primary outcomes stroke, cardiovascular death or myocardial infarction **all** of the mentioned secondary outcomes are to be reduced or prevented together.

This however is in contradiction with the text in the application as originally filed, where "secondary outcomes **such as** ..." have been reported to be "also significantly reduced", which means that one or a second or a third ... of them is concerned to be reduced or prevented together with one of the primary outcomes and not mandatorily all of them together.

In addition, the introductory remarks under point 5.2 of this decision apply because details of example 6 are introduced into the claim that are the consequence of the particular conduct of the study and therefore are not generalisable. Also for this reason claim 1 of auxiliary request 7 is in breach of Article 123(2) EPC.

5.2.2 Auxiliary requests 8, 9 and 10

The arguments and conclusions with respect to auxiliary request 7 also apply to claims 1 of the auxiliary requests 8, 9 and 10, since only single or multiple other secondary outcomes are added at random and also are meant to be prevented altogether in connection to

one of the primary outcomes. Thus, the claims' wording excludes the originally disclosed meaning that one or more of the secondary outcomes are prevented together with one of the primary outcomes.

6. Since none of the requests meets the requirements of the EPC, the appeal was to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

N. Maslin

A. Lindner