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Datasheet for the decision of 17 December 2009

Case Number: T 0788/06 - 3.3.02

Application Number: 96304291.6

Publication Number: 0747050

IPC: A61K 31/415

Language of the proceedings: EN

Title of invention:
Pharmaceutical compositions containing irbesartan

Patentee:
Sanofi-Aventis

Opponent:
(1) TECNIMEDE SOCIEDADE TECNICO-MEDICINAL S.A.
(2) Ratiopharm GmbH

Headword:
-

Relevant legal provisions:
EPC Art. 100(b), 123(2), 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main Request and auxiliary requests 1 to 3, disclosure - sufficiency - (no) - overlapping % ranges of functionally defined ingredients"
"Auxiliary request 4, amendments - added matter - (yes): particular combination of features not originally disclosed"
"Auxiliary request 5, inventive step (yes): non-obvious combination of known ingredients"

Decisions cited:
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Catchword:
-

Case Number: T 0788/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 17 December 2009

Appellant: (Opponent 01)	TECNIMEDE SOCIEDADE TECNICO-MEDICINAL S.A. R. Prof. Henrique de Barros, Edificio Sagres 3.A PT-2685-338 PRIOR VELHO (PT)
Representative:	Engelhard, Elisabeth Hoffmann Eitle Arabellastraße 4 D-81925 München (DE)
Respondent: (Patent Proprietor)	Sanofi-Aventis 174, avenue de France F-75013 Paris (FR)
Representative:	Thouret-Lemaitre, Elisabeth Sanofi-Aventis 174, avenue de France F-75013 Paris (FR)
Other Party: (Opponent 02)	Ratiopharm GmbH D-89070 Ulm (DE)
Representative:	Best, Michael Lederer & Keller Patentanwälte Prinzregentenstraße 16 D-80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 23 March 2006 concerning maintenance of the European patent No. 0747050 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
J. Van Moer

Summary of Facts and Submissions

I. European patent No. 0 747 050, based on the application No. 96 304 291.6 was granted with 14 claims.

Independent claims 1 and 11 as granted read as follows:

"1. A pharmaceutical composition, wherein said composition comprises, based on weight:

(a) from 20 to 70% irbesartan or a pharmaceutically acceptable salt thereof,
(b) from 1 to 70% diluent,
(c) from 2 to 20% binder,
(d) from 1 to 10% disintegrant,
(e) from 0.1 to 5% antiadherent,
(f) from 0.2 to 5% lubricant,
(g) from 0.2 to 6% surfactant,

wherein a tablet formed from said composition has a dissolution performance such that 85% or greater of the irbesartan or salt thereof contained in said tablet dissolves within 30 minutes.

11. A tablet formed from the composition according to any one of the preceding claims."

II. Opposition was filed against the granted patent under Article 100(a) EPC, novelty and inventive step, and Article 100(b) EPC, sufficiency of disclosure.

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

(1) "Handbook of pharmaceutical excipients", 1st ed., American Pharmaceutical Association, Washington, 1986, pages 5, 30, 36, 38, 45, 48, 53, 55, 56, 58, 84, 113, 115, 119, 131, 134, 137-139, 153, 161, 162, 181, 183, 207-209, 213, 234, 239, 253, 255, 257, 258, 271, 272, 278, 289, 293, 296-298, 300, 321, 349, 350

(7) US 5 270 317

(12) Lachmann, L. et al, "The Theory and Practice of Industrial Pharmacy", 3rd ed., Lea & Febiger, Philadelphia, 1986, pages 188, 189, 301-303, 324, 325, 327, 328, 480

III. The opposition division held that, for the main request before the opposition division, the requirements of Articles 123(2) and 83 EPC were fulfilled.

As far as Article 83 EPC was concerned, the opposition division did not deny that some specific ingredients may fall under more than one of the claimed functional categories at the same time, but it stated that the skilled person would know the category for which each ingredient was better suited.

In addition, the provisions of Articles 54 and 56 EPC were met.

Document (7) was the closest state of the art. There, the use of surfactants was discussed in general only or for other forms of medicaments and not for tablets; poloxamer was not mentioned.

The use of poloxamer to increase the dissolution rate of tablets containing irbesartan was acknowledged as the inventive solution contained in the patent in suit. In the relevant state of the art, in particular documents (12) and (1), poloxamer either was not mentioned or its use was proposed in larger quantities only.

IV. Appellant (opponent 01) lodged an appeal against that decision and filed grounds of appeal.

V. With a letter of 2 February 2007, the respondent submitted four sets of claims in addition to the main request; the main request referred to the set of claims as maintained by the opposition division; the wording of its claim 1 read (amendments with respect to the claim as granted in bold):

"A pharmaceutical composition **in the form of a tablet**, wherein said composition comprises, based on weight:

(a) from 20 to 70% irbesartan or a pharmaceutically acceptable salt thereof,
(b) from 1 to 70% diluent,
(c) from 2 to 20% binder,
(d) from 1 to 10% disintegrant,
(e) from 0.1% to 5% antiadherent,
(f) from 0.2 to 5% lubricant,
(g) from 0.2 to 6% surfactant, wherein the surfactant is a poloxamer,

wherein the tablet formed from said composition has a dissolution performance such that 80% or greater of the

irbesartan or salt thereof contained in said tablet dissolves within 30 minutes."

In the auxiliary request 1, the following passage was added at the end of claim 1:

", wherein the dissolution performance is measured using a tablet having a total weight of from 150 to 600 mg and USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37°C with a paddle speed of 50 rpm and measuring the irbesartan dissolved at 30 minutes".

In claim 1 of auxiliary request 2, particular groups of compounds were introduced defining the functional definitions of ingredients in terms of structural properties; it reads:

"A pharmaceutical composition in the form of a tablet, wherein said composition comprises, based on weight:

(a) from 20 to 70% irbesartan or a pharmaceutically acceptable salt thereof,
(b) from 1 to 70% diluent, wherein said diluent is selected from the group consisting of dibasic calcium phosphate, lactose hydrous, lactose anhydrous, and microcrystalline cellulose;
(c) from 2 to 20% binder, wherein said binder is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, gelatin, povidone, starch and pregelatinized starch;

(d) from 1 to 10% disintegrant, wherein said disintegrant is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, croscarmellose sodium, crospovidone, pregelatinized starch, sodium starch glycolate, and starch;
(e) from 0.1% to 5% antiadherent, wherein said antiadherent is one or more compounds selected from the group consisting of silicon dioxide, magnesium trisilicate, and talc;
(f) from 0.2 to 5% lubricant, wherein said lubricant is one or more compounds selected from the group consisting of calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate, stearic acid, hydrogenated vegetable oil, polyethylene glycol, sodium benzoate, and talc;
(g) from 0.2 to 6% surfactant, wherein the surfactant is a poloxamer,
wherein the tablet formed from said composition has a dissolution performance such that 80% or greater of the irbesartan or salt thereof contained in said tablet dissolves within 30 minutes."

In the auxiliary request 3, the same passage was added at the end of claim 1 as in auxiliary request 1.

Comprising more restricted definitions of ingredients, the wording of claim 1 in auxiliary request 4 was:

"A pharmaceutical composition in the form of a tablet, wherein said composition comprises, based on weight:

(a) from 20 to 70% irbesartan or a pharmaceutically acceptable salt thereof,
(b) from 1 to 70% diluent, wherein said diluent is lactose hydrous and microcrystalline cellulose;
(c) from 2 to 20% binder, wherein said binder is pregelatinized starch;
(d) from 1 to 10% disintegrant, wherein said disintegrant is croscarmellose sodium;
(e) from 0.1% to 5% antiadherent, wherein said antiadherent is silicon dioxide;
(f) from 0.2 to 5% lubricant, wherein said lubricant is magnesium stearate;
(g) from 0.2 to 6% surfactant, wherein the surfactant is poloxamer,
wherein the tablet formed from said composition has a dissolution performance such that 80% or greater of the irbesartan or salt thereof contained in said tablet dissolves within 30 minutes."

VI. On 17 December 2009, oral proceedings took place before the board.

During the oral proceedings, the respondent filed auxiliary request 5 which was admitted into the proceedings. It contains three claims.

Inter alia, the functionally defined ingredients are restricted still further to a few structurally defined groups of substances in narrower %ranges; the wording of the claims is:

"1. A pharmaceutical composition
in the form of a tablet, wherein
said composition comprises, based on weight:

(a) from 20 to 50% irbesartan,
(b) from 1 to 70% diluent, wherein said diluent is lactose hydrous and microcrystalline cellulose;
(c) from 10 to 20% binder, wherein said binder is pregelatinized starch;
(d) from 4 to 8% disintegrant, wherein said disintegrant is croscarmellose sodium;
(e) from 0.25% to 5% antiadherent, wherein said antiadherent is silicon dioxide;
(f) from 0.5 to 1.5% lubricant, wherein said lubricant is magnesium stearate;
(g) from 1 to 6% surfactant, wherein the surfactant is poloxamer 188,

wherein the tablet formed from said composition has a dissolution performance such that 80% or greater of the irbesartan or salt thereof contained in said tablet dissolves within 30 minutes, wherein the dissolution performance is measured using a tablet having a total weight of from 150 to 600 mg and USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37°C with a paddle speed of 50 rpm and measuring the irbesartan dissolved at 30 minutes.

2. The pharmaceutical composition according to claim 1, comprising, based on weight,
50 % irbesartan;
10.25 % lactose hydrous;
15.0 % pregelatinized starch;
5.0 % croscarmellose sodium;
3.0 % poloxamer 188;
15 % microcrystalline cellulose;

0.75 % silicon dioxide; and
1.0 % magnesium stearate.

3. The pharmaceutical composition according to claim 1, comprising, based on weight,
50 % irbesartan;
10.25 % lactose hydrous;
15.0 % pregelatinized starch;
5.0 % croscarmellose sodium;
3.0 % poloxamer 188;
13 % microcrystalline cellulose;
2.75 % silicon dioxide; and
1.0 % magnesium stearate."

VII. The appellant's submissions can be summarised as follows:

Concerning the main request and auxiliary requests 1 to 4, there were still objections with respect to Article 100(b) EPC because of overlap of functionally defined ingredients. With respect to the main request and auxiliary requests 2 and 4 no clear instructions were given in the opposed patent on how to measure the dissolution performance as claimed.

Claim 1 of auxiliary request 5 was also not allowable with respect to the provisions of Article 100(b) EPC. There were still millions of combinations of ingredients in different quantities to be formulated as a tablet and to be examined by the skilled person to determine whether the feature constituting the result to be achieved of improved dissolution performance, was in fact fulfilled. No guidance could be derived from the examples since they were only composed of very few

differing ingredients; furthermore even they did not demonstrate improved dissolution rates.

The subject-matter of auxiliary request 5 was also missing inventive step. There was, in particular, no evidence anywhere in the proceedings of a valid comparative experiment to show an improved dissolution profile of irbesartan with respect to the state of the art, for instance, document (7). In the patent itself, only speculative remarks could be found that tablets made of the examples' compositions might dissolve more rapidly and/or completely, and thus might exhibit an improved dissolution performance. In particular, there was no purposive selection made from the ingredients well known to the person skilled in the art resulting in any surprising advantage of the subject-matter as claimed.

VIII. The respondent contested the arguments of the appellant:

The overlap of functionally defined ingredients basically fell within the scope of Article 84 EPC which was no ground of opposition and which was not to be considered in context with features not amended with respect to the claims as granted.

The measurement of dissolution performance was well defined in the description of the patent in suit and the skilled person knew the primary function to be fulfilled by every ingredient in the composition and thus could determine the percentage of each ingredient in accordance with its functional definition.

With respect to inventive step, the respondent argued that in the claims as originally filed, the improved dissolution of irbesartan (active ingredient) was set out as a prerequisite for their subject-matter (see for instance original claims 1 and 2). When the patent was granted on that basis there was no doubt in this respect and the appellant, in his function of opponent, had not filed any evidence to the contrary. In addition, no such advantageous dissolution rate in context with irbesartan in tablet form was known from the state of the art.

Above that, in the patent's paragraph [0024], a whole bunch of advantageous features of tablets made in accordance with the teaching of the patent in suit was indicated and all these features were the result of the perfect combination of ingredients, in particular as claimed with auxiliary request 5 (being in line with table A to which paragraph [0024] referred).

The appellant (opponent 01) requested that the decision under appeal be set aside and that the European patent be revoked.

IX. The respondent (patentee) requested that the appeal be dismissed or, in the alternative, that the patent be maintained on the basis of the auxiliary requests 1 to 4 filed with letter of 2 February 2007 or auxiliary request 5 submitted during oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. *Admissibility of auxiliary request 5*

The amendments in this request are occasioned by the appellant's and the board's arguments during the oral proceedings.

In addition, they only contain combinations or deletions of dependent claims as maintained by the opposition division. They are clear-cut and *bona fide* attempts to answer the arguments brought forward during the oral proceedings.

Accordingly, the request fulfils the requirements of Rule 80 EPC and it is admitted into the procedure.

3. *Article 100(b) EPC; main request and auxiliary requests 1 to 3*

3.1 Article 100(b) EPC defines lack of the invention to be disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art as a ground for opposition. One of the provisions for the resulting requirements to be fulfilled is that the skilled person must be in a position to recognise whether or not the result of one of his reproductive experiments corresponds to the teaching of the patent in suit.

3.2 In the present case, claim 1 in all the requests seeks protection for a pharmaceutical composition as a product *per se*.

The pharmaceutical composition is characterised by %ranges for the ingredients selected from at least five groups of substances:

(b) diluents,
(c) binders,
(d) disintegrants,
(e) antiadherents,
(f) lubricants,

The %ranges are essential technical features in the corresponding claims since they characterise the limits within which the sums of percentages of different ingredients (substances) selected from any of the groups must remain.

In order to enable the skilled person to produce an embodiment as subject-matter covered by such a claim, the groups and the %ranges for them in the product as claimed must be defined unequivocally.

3.3 The groups from which the ingredients of a pharmaceutical composition are to be selected are characterised in terms of the functions that any ingredient should perform in the pharmaceutical composition and not in structural terms of chemical substances (main request and auxiliary request 1) or in structurally defined groups of substances with their function as additional remarks (auxiliary requests 2 and 3).

3.3.1 In the description of the patent, it is set out that a single compound may perform two or more functions (see paragraph [0021]).

In particular, from claim 4 of the main request and auxiliary request 1 and claim 1 of auxiliary requests 2 and 3 follows that

alginic acid, sodium alginate, carboxymethylcellulose sodium, starch and pregelatinized starch may be binder or disintegrant.

Microcrystalline cellulose may be diluent or disintegrant.

Talc may be antiadherent or lubricant.

3.3.2 If, under these circumstances, **for instance,** a pharmaceutical composition

- contains binder in an amount at the upper limit claimed for binder (20%) and
- the binder already contains starch
- and now a certain amount of additional starch is added,

there are two arbitrary ways of classifying this additional amount of starch:

- as a disintegrant or
- as further binder.

Depending on the outcome of that choice, the pharmaceutical composition resulting from the addition of starch is or is not contained in the claimed subject-matter.

If the additional starch is classified as a disintegrant and its percentage remains beneath the upper limit of the %range claimed for disintegrant

materials, the pharmaceutical composition resulting from the addition must be regarded as subject-matter as claimed.

If, however, the additional starch is classified as binder, the claimed range of binder is exceeded and the resultant pharmaceutical composition constitutes subject-matter which is beyond the limits of the claim.

Thus, two totally different conclusions can be reached in answering the question whether the pharmaceutical composition is subject-matter as claimed or not, despite the material having the identical composition. These two conclusions, one being the complete opposite of the other, are simply the result of the fact that some of the ingredients of the pharmaceutical composition can be classified arbitrarily.

3.3.3 The same effect is to be observed when the amount of ingredients of the different groups is changed slightly compared with the example mentioned above; for instance, it is not at all necessary to start with binder in an amount exactly equal to the upper limit as claimed. This special case has only been taken above for convenience and ease of explanation of the facts and effects.

3.3.4 Thus, in quite a lot of cases, the skilled person trying to carry out the teaching of the claims, i.e. the claimed invention, does not know whether or not he will get a pharmaceutical composition as claimed, which amounts to the problem that he cannot carry out the teaching at all.

3.3.5 The question of starch belonging to both the binder and the disintegrant groups applies to all of the main request and auxiliary requests 1 to 3. The same problem arises with the other functionally defined groups of ingredients as defined above under point 3.3.1 of this decision.

3.4 To summarise, for the skilled person, with respect to the main request and auxiliary requests 1 to 3, there is no unequivocal definition in the patent in suit of the %ranges for binder and disintegrant, for diluent or disintegrant, or for antiadherent or lubricant in the pharmaceutical composition as claimed. Consequently, this feature leaves the actual subject-matter covered by the claim in doubt. Therefore, in the board's judgement, claim 4 according to the main request and auxiliary request 1 and claim 1 of the auxiliary requests 2 and 3 fail to meet the requirement of sufficient disclosure imposed by the ground for opposition under Article 100(b) EPC.

3.5 Under these circumstances, there was no need to assess whether Article 84 EPC was relevant in this case.

4. In addition, the further argument of the respondent cannot succeed:

The skilled person may be able to recognise the primary function of an ingredient, but only in general terms when looking at a particular composition. A sound, clearly distinguishing correlation will not be possible for each and every percentage being claimed and for each and every environment as given by the percentages of the other ingredients. Moreover, even the wording

"primary function" already indicates that there may be a doubt as to whether or not the secondary function would have to be taken into account or even if it would prevail in a particular case.

Thus, the teaching with respect to the compositions as claimed supplies no clear and complete basis for carrying it out.

5. *Requirements of Article 123(2) EPC; auxiliary request 4*

Claim 1 of auxiliary request 4 concerns a pharmaceutical composition containing the %ranges of the ingredients of claim 3 as originally disclosed under the definitions of the groups of structurally defined substances from original claim 6.

There, however, the surfactant is already defined as poloxamer 188.

None of the claims as originally filed or the description as originally filed refer to the combination of the particular groups of ingredients of claim 1 of auxiliary request 4 or to a general choice of poloxamer instead of the specifically selected poloxamer 188. In particular, the passage in the description as originally filed introducing the group of surfactants (page 9, line 28 to page 10, line 3) does not contain a reference to the groups of ingredients of original claim 6 or, alternatively, a basis for conclusive generalisation.

In addition, claim 6 as originally filed refers back to claim 5, containing narrower %ranges than original

claim 3. There is no text in the description as originally filed that represents the claimed combination with its %ranges or would allow it by generalisation.

Therefore, it is compulsory to introduce the narrower %ranges of claim 5 as originally disclosed into the combination of claim 6 and claim 3, which was not done when formulating claim 1 of the current request.

Consequently, claim 1 of auxiliary request 4 contains an unallowable extension beyond the content of the application as originally filed (Article 123(2) EPC).

6. *Auxiliary request 5*

6.1 The three claims of auxiliary request 5 can be derived from original claims 1, 3, 5 and 6 as well as claims 7 and 8, together with page 1, lines 10 to 12 and page 5, lines 21 to 30 of the application as originally filed.

6.2 The board is satisfied that they also meet the provisions of Article 84 EPC, which was not denied by the other parties either.

6.3 Auxiliary request 5 is also allowable under Article 100(b) EPC:

6.3.1 The conditions for measuring the dissolution rate as the functional feature in claim 1 are exactly defined.

6.3.2 The appellant opponent not having delivered any example to the contrary, the board has to presume that the pharmaceutical compositions as claimed with auxiliary

request 5 in general fulfil the conditions of the claimed dissolution rate, in particular, since the subject-matter of this request represents a preferred embodiment of the patent as granted.

6.4 *Novelty*

6.4.1 The subject-matter of claim 1 of auxiliary request 5 concerns

a pharmaceutical composition in the form of a tablet

comprising particular structurally defined groups of substances in defined %ranges and
exhibiting a defined dissolution performance under defined conditions.

6.4.2 Document (7) discloses in column 13, lines 62 to 65 that solid compositions in the form of tablets can be prepared by mixing the main active ingredient with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like.

The differences in the teaching of claim 1 of auxiliary request 5 amount at least to the selection of a particular starch and lactose, the omission of gelatin, talc and gum arabic as compulsory ingredients and additionally the use of microcrystalline cellulose, croscarmellose sodium, silicon dioxide and poloxamer 188.

6.4.3 The other evidence on file refers to particular ingredients for use in tabletting, to irbesartan as active and its preparation or to the documentation of

experiments to assess dissolution rates. None of the documents discloses tablets containing irbesartan and the other substances as claimed together.

6.5 *Inventive step*

6.5.1 Document (7) represents the closest state of the art.

With respect to this document, the technical problem underlying the patent in suit is the provision of a medicament in the form of a tablet comprising irbesartan.

6.5.2 The solution to this problem is the provision of tablets according to the features of claim 1 of auxiliary request 5, in particular in the composition as disclosed in its specific combination of ingredients.

6.5.3 Having regard to the claims, the description and the examples of the patent in suit and in the absence of any counter-evidence provided by the appellants, the board is convinced that the problem has been plausibly solved.

6.5.4 None of the documents on file discloses, not even partially, the combination of ingredients in the claimed composition in a way that could complement the teaching of document (7) in the direction of the claimed tablet.

Thus, even if admitting that the participating ingredients as such are well known, their combination in the %ranges as claimed is not obvious from the state

of the art to produce a suitable tablet containing irbesartan.

6.5.5 Consequently, the board can only conclude that the subject-matter of claim 1 of auxiliary request 5 involves an inventive step.

7. Thus, the subject-matter of the main request and that of auxiliary requests 1 to 3 is not allowable because of the ground for opposition under Article 100(b) EPC, the subject-matter of the auxiliary request 4 does not meet the provisions of Article 123(2) EPC, but the subject-matter of auxiliary request 5 meets the requirements of the EPC.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the first instance with the order to maintain the patent with the following documents

- claims 1 to 3 of the auxiliary request 5 submitted during oral proceedings

- a description to be adapted.

The Registrar: The Chairman:

N. Maslin U. Oswald