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Datasheet for the decision of 12 April 2018

Case Number: T 1063/15 - 3.3.07

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Language of the proceedings: EN

Title of invention:
RAPID DISSOLUTION FORMULATION OF CINACALCET HCl

Patent Proprietor:
AMGEN INC.

Opponents:
Actavis Group PTC EHF
RAFARM S.A.
ZBM PATENTS, S.L.

Headword:
RAPID DISSOLUTION FORMULATION OF CINACALCET HCl/AMGEN INC.

Relevant legal provisions:
EPC Art. 123(3), 100(b), 56

Keyword:
Extension of the scope of the claims
Sufficiency of disclosure
Inventive step

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 1063/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 12 April 2018

Appellant: (Patent Proprietor)	AMGEN INC. One Amgen Center Drive Thousand Oaks, CA 91320-1799 (US)
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Respondent: (Opponent 2)	RAFARM S.A. 12, Korinthou Str. GR15451 Neo Psychiko Athens (GR)
Respondent: (Opponent 3)	ZBM PATENTS, S.L. Pl. Catalunya 1 E-08002 Barcelona (ES)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 12 March 2015 revoking European patent No. 1663182 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: D. Boulois
C. Schmidt

Summary of Facts and Submissions

I. European patent No. 1 663 182 was granted on the basis of a set of 31 claims.

Independent claim 1 as granted read as follows:
"1. A pharmaceutical composition comprising
(a) from 10% to 40% by weight of cinacalcet HCl;
(b) from 45% to 85% by weight of at least one diluent; and
(c) from 1% to 5% by weight of at least one binder;
wherein the percentage by weight is relative to the total weight of the composition."

II. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that its subject-matter lacked inventive step, was not sufficiently disclosed, and extended beyond the content of the application as filed.

III. The appeal by the patent proprietor lies from the decision of the opposition division to revoke the patent. The decision was based on 7 sets of claims, namely the claims as granted as main request and the request filed with letter of 3 June 2014 as auxiliary request 1, filed during the oral proceedings as auxiliary requests 2-4, filed with letter dated 3 June 2014 as auxiliary requests 5-6.

IV. The documents cited during the opposition proceedings included the following:
D13: Franceschini, N. et al, "Cinacalcet HCl: a calcimimetic agent for the management of primary and secondary hyperparathyroidism", Expert Opin. Invetsig. Drugs, 2003, 12(8), pages 1413-1421
D14: "Pharmaceutics: The science of dosage form

design", 2nd Edition, Aulton, 2002, pages 404-408.
D15: "Remington: The science and Practice of Pharmacy", 20th Ed., Ch. 45, 2000.
D16: "Handbook of Pharmaceutical Excipients", 2nd, 1994, Pages 84-87, 143-144, 280-282, 392-399, 424-427 and 491-493.

V. According to the decision under appeal, the invention claimed in the main request was not sufficiently disclosed, since the description did not define exclusive lists of "diluents" and "binders".

The scope of protection of the invention claimed in auxiliary request 1 had been extended, and said request did not meet the requirements of Article 123(3) EPC. The previous requirement that the composition comprised 45-85% of at least one diluent and 1-5% of at least one binder had indeed been replaced by the requirement that the composition comprises 45-85% of at least a diluent selected from specific diluents and 1-5% of at least one binder selected from specific binders.

Auxiliary request 2 was modified by the features "wherein the at least one diluent was selected from..." and "wherein at least one binder was selected from..." and met the requirements of Article 123(3) EPC, as well as 123(2), 83 and 84 EPC. As regards inventive step, D13 which related to clinical trials involving unspecified oral compositions of cinacalcet, was considered as the closest prior art. The difference involved the specification of the further composition ingredients and their amounts. The experimental data EX-I did not demonstrate unexpected findings. The problem was seen as the provision of an oral dosage form containing cinacalcet HCl. The solution was obvious in view the common general documents D14-D16.

Auxiliary request 3 met the requirements of Articles 123(2) and 123(3) EPC. The claimed subject-matter did however not meet the requirements of inventive step, since the further selection of specific suitable types and specific amounts of excipients in the tablet formulation belonged to the capabilities of the skilled person. The data submitted in EX-I were not sufficient in demonstrating an effect, since it did not allow to determine whether the newly claimed ranges were purposeful in the sense that all formulations inside the scope of the claim performed better than all formulations outside the scope of the claim. The claimed subject-matter was not a purposeful selection of range and excipients and auxiliary request 3 was not considered allowable under Article 56 EPC.

Auxiliary request 4 met the requirements of Articles 123(2) and 123(3) EPC. As all added subject-matter, namely *inter alia* a mixture of starch and cellulose as diluent, povidone as binder and crospovidone, were considered as common for the skilled person, auxiliary request 4 also did not meet the requirements of Article 56 EPC.

Auxiliary requests 5 and 6 did not meet the requirements of Article 123(3) EPC for the same reasons as auxiliary request 1.

VI. The patent proprietor (hereinafter the appellant) filed an appeal against said decision. With the statement setting out the grounds of appeal dated 22 July 2015, the appellant submitted a main request and auxiliary requests 1-2.

Independent claim 1 of the main request read as follows, difference(s) compared with claim 1 as granted shown in bold:

"1. A pharmaceutical composition comprising
(a) from 10% to 40% by weight of cinacalcet HCl;
(b) from 45% to 85% by weight of at least one diluent; and
(c) from 1% to 5% by weight of at least one binder;
wherein the percentage by weight is relative to the total weight of the composition,
wherein the at least one binder is selected from povidone, hydroxypropyl methylcellulose, dihydroxy propylcellulose, and sodium carboxymethylcellulose, and wherein the at least one diluent is a mixture of microcrystalline cellulose and starch, and wherein the microcrystalline cellulose is present in an amount ranging from 40% to 75% by weight, and the starch is present in an amount ranging from 5% to 10% by weight, relative to the total weight of the composition."

VII. With a letter dated 12 February 2018, opponent 01 (hereinafter respondent 01) informed the Board and the other parties that it will not be represented at the oral proceedings.

VIII. A communication from the Board dated 15 March 2018, was sent to the parties. In this it was stated in particular that the main request met the requirements of Article 123(3) EPC, was sufficiently disclosed, and involved an inventive step over D13.

IX. Oral proceedings took place on 12 April 2018.

X. The arguments of the appellant, as far as relevant to the present decision may be summarised as follows:

As regards sufficiency of disclosure, the patent gave sufficient guidance as to the kinds of compounds that were understood as "diluents" and "binders". Moreover, the main request was now explicit as to the excipients to be selected.

As regards inventive step, the closest prior art was D13. The analysis of the opposition division considering that all formulations inside the scope of the claims had to perform better than all formulations outside the claims was wrong. The technical effect had to be demonstrated over the closest prior art and not over any embodiment not covered by the claims and not disclosed in the prior art. Experimental Report II provided a comparison that should have been considered for the assessment of the technical effect. The problem over D13 was the provision of a preparation of cinacalcet that provided rapid initial dissolution and disintegration. The cited prior art did not contain any teaching or motivation to select the claimed composition of starch, cellulose in the claimed proportions. The solution was therefore inventive.

XI. The arguments of the respondents, as far as relevant to the present decision, may be summarised as follows:

According to respondent 01, in view of the restriction to specific binders and diluents, the scope of protection of claim 1 of the main request had been extended and the main request did not meet the requirements of Article 123(3) EPC. A composition such as comprising:
- 25% cinacalcet
- 5% povidone (the defined binder)

- 50% microcrystalline cellulose and 8% starch (the defined diluent)
- 6% polyethylene glycol (as further binder)
fell within the scope of the main request, but not of the patent as granted.

The terms diluents and binders were functional definitions, and certain excipients are both diluents and binders, e.g. starch. The patent was found correctly insufficient, because whether or not a composition comprising and excipient which was both a binder and a diluent fell within the scope of that claim depended on an arbitrary decision on how to label that excipient.

As regards inventive step, the closest prior art was D13, which did not disclose specific compositions used in its disclosed trials. The distinguishing features were the proportions and nature of excipients and the proportion of cinacalcet. The problem was the provision of a preparation of cinacalcet that provided improved dissolution and disintegration. The evidence provided by the patentee, such as Experimental Report II was not sufficient to prove the existence of an effect linked with the claimed ranges of excipients. The excipients and the proportions defined by the main request were standard, and the skilled person would have selected these from the standard alternatives, as shown in D14 or D16. Hence, the subject-matter claimed by the main request was not inventive.

Respondents 02 and 03 did not provide any arguments.

XII. Requests

Appellant requests that the decision under appeal be set aside and the patent be maintained according to the set of claims filed as main and auxiliary requests 1-2 with letter of 22 June 2015.

Respondent 01 requests that the appeal be dismissed and the patent be revoked.

Respondents 02 and 03 did not provide any comment or request.

Reasons for the Decision

1. Main request – Article 123(3) EPC

1.1 In the present case, the objection against claim 1 of the main request arose from the limitation of the claimed component b), namely "at least one diluent", and component c), namely "at least one binder", to a qualitatively restricted specific list of said diluents and binders, whereas said "at least one diluent" and "at least one binder" were defined in the open composition of granted claim 1 only by their amounts without any qualitative specification.

1.2 An extension of the scope of the claims may indeed arise when a granted claim directed to a composition defined in an open manner, i.e. by means of the term "comprising", and including the presence of components belonging to a class of compounds, in a quantity defined by a range, is later amended by qualitatively limiting the class of compounds.

In such a case, in spite of the apparent limitation due to the explicit mention of some members of the class of compounds, the wording of the granted and the amended

claims may be such that the qualitatively restricted compounds are required to be present in an amount within a defined range according to the granted claim, while other compounds belonging to the same class of compounds, but not to the restricted list now claimed, may still be present, but with no limitation in quantity, according to the amended claim, therefore resulting in an extension of the protection conferred contrary to the requirements of Article 123(3) EPC.

1.3 Such possible infringement of the requirements of Article 123(3) EPC may be avoided by keeping in the amended claim the quantitative condition on the class of compounds as in the claim as granted and including an additional qualitative constraint on the nature (cf for instance T 1360/11).

1.3.1 In the present case, the Board considers that the wording of amended claim 1 of the main request makes it clear that, by means of the maintenance of the quantitative condition on the components b) and c), namely the claimed ranges of "*from 45% to 85% by weight of at least one diluent*" and the "*from 1% to 5% by weight of at least one binder*" with exactly the same wording as in granted claim 1 ,the protection conferred by the patent is not extended, in that both granted claim 1 and claim 1 of the main request require that the total amounts of any and all diluent(s) or binder(s) present in the composition are necessarily comprised in the respectively claimed quantities of the composition. A composition comprising any type of binder(s) or diluent(s) in a quantity outside the range is not covered by granted claim 1, but is also not covered by claim 1 of the main request.

1.3.2 Moreover, the additional features used in claim 1 of the main request, namely the features "*wherein the at least one binder is selected from povidone, hydroxypropyl methylcellulose, dihydroxy propylcellulose, and sodium carboxymethylcellulose*" and "*wherein the at least one diluent is a mixture of microcrystalline cellulose and starch*", in combination with the quantitative features already present in claim 1 as granted, namely "*(b) from 45% to 85% by weight of at least one diluent; and (c) from 1% to 5% by weight of at least one binder*" further restricts explicitly and qualitatively the presence of "*at least one diluent*" and "*at least one binder*" exclusively to those claimed in the list, and excludes the presence of further diluent(s) or binder(s), which would have been a cause of infringement of Article 123(3) EPC.

The feature "*wherein the microcrystalline cellulose is present in an amount ranging from 40% to 75% by weight, and the starch is present in an amount ranging from 5% to 10% by weight, relative to the total weight of the composition*" present in claim 1 of the main request restricts further the respective amount of the diluents, without any incidence on the conclusion raised above.

1.4 Claim 1 of the main request thus achieves the result of not extending the protection conferred by the patent while referring to a more limited group of compounds than the one indicated in granted claim 1. Consequently, the main request meets the requirements of Article 123(3) EPC.

2. Main request - Article 100(b) EPC

Claim 1 of the main request relates to a composition comprising a specified range of specified diluent(s) and binder(s) in combination with a specific range of cinacalcet HCl. Since claim 1 relates to a composition as such, the skilled person would not have any difficulty in preparing the claimed compositions.

The patent discloses therefore the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

3. Main request – Inventive step

3.1 The invention relates to pharmaceutical compositions of cinacalcet with rapid dissolution.

3.2 Document D13 was considered as closest prior art and discloses unspecified oral dosage forms of cinacalcet. D13 mentions indeed the use of single oral doses of 10, 25, 50, 75 or 100 mg cinacalcet HCl in trials for the management of primary and secondary hyperparathyroidism (see page 1416). The document does not specify the single oral dosage forms and does not specify the dissolution/disintegration profile of the mentioned doses.

3.3 According to the appellant and respondent 01, the problem is the provision of a preparation of cinacalcet HCl that provides an improved or rapid dissolution/ disintegration.

3.4 The solution is a composition as claimed with the specific ranges and specific combination of diluents and binder(s).

3.5 It has to be investigated whether there is sufficient evidence supporting the alleged effect.

3.5.1 The experimental report II filed on 21 November 2014 shows that a composition according to the claimed invention comprising 52.95% of cellulose and 10% by weight of starch as diluents, as well as 3% by weight of povidone as binder and 27.55% by weight of cinacalcet HCl has a dissolution rate of 39.8% after 5 minutes and 66.1% after 15 minutes. A comparative composition comprising 40.95% of cellulose and an excess of 22% by weight of starch, as well as 3% by weight of povidone , has a dissolution rate of about 22% after 5 minutes and 62.1% after 15 minutes.

The dissolution profiles of both the composition according to the invention and the comparative example appear to provide a rapid dissolution/disintegration and fulfil also the requirements of dissolution given in the description of the contested patent, namely a dissolution profile of at least 50%, at least 70% or at least 85% of the target amount of cinacalcet in 30 minutes (see par. [0036]).

The expected technical effect is therefore credibly demonstrated and there is thus no reason to doubt that the claimed compositions achieve a rapid dissolution/ disintegration.

3.5.2 As to the results provided by the examples of the contested patent and the experimental reports I, they have to be disregarded, since they are not relevant.

The compositions given in the examples of the contested patent presents indeed a rapid dissolution rate, while not falling under the scope of claim 1 of the main

request. The examples comprise indeed an amount of starch of 33.3% by weight, and have a dissolution profile of 80.8-85.3% after 15 minutes or 93.4-95.2% after 15 minutes.

Similarly, the experimental report I, which was cited by the opposition division in its decision, shows also a rapid dissolution of compositions not falling under the claimed scope presenting either an amount of diluent lower as the claimed 40%, or amounts of starch which are higher than 10% by weight as claimed in claim 1 of the main request.

Hence, it can be concluded from the examples of the contested patent and from experimental report I that a rapid dissolution profile is not the monopoly of the claimed compositions and that said property is shared by many compositions not falling under the scope of the claims. Said examples of the contested patent and experimental report I do however not provide any evidence that the claimed compositions do not achieve a rapid dissolution profile. The provision of evidence(s) that compositions falling outside the scope of the claims may also provide the desired technical effect, is irrelevant in the assessment of inventive step.

Inventive step has in any case to be assessed over the closest prior art, which is, in the present case, a document being silent on the compositions used therein and their corresponding dissolution profile. In view of the disclosure of D13, it appears sufficient to demonstrate credibly that the claimed compositions provide the expected technical effect; this is done by experimental report II.

3.6 It must then be determined whether the solution was obvious to the person skilled in the art.

Excipients such as microcrystalline cellulose, starch and the claimed binders are commonly used excipients, as demonstrated for instance by documents D14-D16.

There is however no document on file showing that a composition comprising cellulose, starch and a binder in the claimed range will systematically provide a rapid dissolution profile.

There is also no reason to expect that a skilled person would even try to modify the unspecified composition of D13 to arrive at the claimed subject-matter. The use of any kind of excipient or the achievement of any kind of dissolution is not suggested in or deductible from the teaching of D13.

The claimed solution is therefore not obvious in view of D13.

3.7 The main request meets the requirements of Article 56 EPC.

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 main request, filed with letter dated 22 July 2015 and a description to be adapted.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated