Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 7 December 2021

Case Number: T 2413/18 - 3.3.07

Application Number: 12155251.7

Publication Number: 2465492

IPC: A61K9/00, A61K9/20, A61K9/70, A61K31/137

Language of the proceedings: EN

Title of invention:
Compositions comprising sphingosine I phosphate (sip) receptor modulators

Patent Proprietor:
Novartis AG

Opponent:
Pentafarma Sociedade Técnico-Medicinal S.A.

Headword:
FTY720 compositions / NOVARTIS

Relevant legal provisions:
EPC Art. 100(a), 56

Keyword:
Inventive step - (no)

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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

Case Number: T 2413/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 December 2021

Appellant: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Leon, Susanna Iris Novartis Pharma AG Patent Department 4002 Basel (CH)
Respondent: (Opponent)	Pentafarma Sociedade Técnico-Medicinal S.A. Rua da Tapada Grande, n. 2 2710-089 Abrunheira (PT)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 25 July 2018 revoking European patent No. 2465492 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	D. Boulois
Members:	E. Duval
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 2 465 492 (hereinafter "the patent") was granted on the basis of 2 claims. Claim 1 of the patent read as follows:

"A binary blend consisting of:
(i) 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol (FTY720) in free form or as a pharmaceutically acceptable salt thereof, and
(ii) one excipient selected from the group consisting of:
Lactose, Hydroxypropyl methylcellulose (HPMC), Hydroxypropylcellulose (HPC), Crospovidone, croscarmellose sodium, starch, and colloidal silicone dioxide."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, and it extended beyond the content of the (earlier) application as filed.

The opposition division took the decision to revoke the patent.

The decision was based on the patent as granted as the main request, on auxiliary requests 1-3 filed on 16 November 2017 (and renumbered during the oral proceedings whereby auxiliary request 2 was renumbered auxiliary request 1, and auxiliary request 1 became auxiliary request 2) and on auxiliary request 4 filed during the oral proceedings before the opposition division.

III. The decision referred to the following documents:

D1: WO 2005/025553 A2
D2: WO 2004/089341 A1
D3: "Die Tablette", Editio Cantor Verlag 2002, p.68

IV. In particular, the opposition division decided the following.

(a) The subject-matter of claim 1 of the main request lacked novelty over D1, which disclosed a composition made only of FTY720 and one excipient.

(b) The subject-matter of claim 1 of auxiliary request 1 was novel over documents D1-D3.

Regarding inventive step, the subject-matter of claim 1 of auxiliary request 1 differed from the binary blends of the closest prior art D1 by the specified level of impurities. The technical problem was the provision of an alternative composition. The claimed solution did not involve an inventive step over D1.

(c) Auxiliary request 2 did not meet the requirements of Article 84 EPC as a result of the relative term "stable".

(d) Auxiliary request 3 lacked novelty over D1 for the same reasons as for the main request.

(e) The subject-matter of claim 1 of auxiliary request 4 differed from the closest prior art D1 in that the selected disintegrating agent is croscarmellose. The technical problem was the provision of an alternative composition.

Croscarmellose being a well known excipient as shown in D3, the claimed solution did not involve an inventive step.

V. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division.

VI. With its statement setting out the grounds of appeal, the appellant defended its case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1-7 filed therewith.

In comparison with claim 1 of the main request,

- claim 1 of auxiliary request 1 limited the excipients to "Lactose, Hydroxypropyl methylcellulose (HPMC), croscarmellose sodium and starch",

- claim 1 of auxiliary request 2 contained the additional feature "wherein the level of impurities is not more than 4.5wt% and/or no more than 2wt% for an individual impurity",

- claim 1 of auxiliary request 3 combined the amendments of auxiliary requests 1 and 2.

- claim 1 of auxiliary request 4 limited the excipients to "Hydroxypropyl methylcellulose (HPMC) and croscarmellose sodium",

- claim 1 of auxiliary request 5 was limited to croscarmellose sodium as excipient, and defined the level of impurities as in auxiliary requests 2 and 3.

- claim 1 of auxiliary request 6 specified that the binary blend was a "stable" binary blend, and

- claim 1 of auxiliary request 7 limited the excipients to "Lactose, Hydroxypropyl methylcellulose (HPMC), Crospovidone, croscarmellose sodium and starch".

VII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA issued on 24 June 2021.

VIII. Oral proceedings were held before the Board on 7 December 2021, in the presence of the appellant, using videoconferencing technology.

IX. The appellant's arguments regarding inventive step may be summarized as follows:

(a) Main request

The invention related to formulations suitable for use as a dosage form, which were stable and could be transported and stored prior to final formulation. D1 did not represent a suitable starting point for the assessment of inventive step, because it related to a different purpose, namely to new therapeutic uses for FTY720. Only D2 could be a regarded as the closest prior art.

Even if D1 was taken as the closest prior art, the claimed compositions were not obvious. D1 (see page 24) generally disclosed FTY720 final formulations with excipients defined in seven lists. Final pharmaceutical compositions commonly contained ingredients from each of said seven ingredient categories. D1 did not, directly and unambiguously, disclose a binary blend of FTY720 and one excipient, and did not relate to stability. The problem was the provision of commercial

compositions of FTY720 with excellent stability. The only formulations exemplified in D1 were pre-clinical, liquid saline formulations for local administration, which taught away from the claimed solid formulations for systemic administration. Thus, the skilled person would have had no motivation to select a binary formulation with (only) one of the claimed excipients.

(b) Auxiliary requests

Regarding auxiliary request 1, the examples of the patent showed that the claimed compositions had good stability without significant degradation. The problem was the provision of a simpler composition with improved stability and better storage properties. The claimed solution to this problem was not obvious, because nothing in D2, D1 or D3 suggested that the binary formulations with the claimed excipients would lead to an improved stability.

Auxiliary requests 2-7 met the requirements of inventive step for the same reasons as for the main request. In particular, the disclosure of a 90% FTY720 purity in D1 was not enabling, and it was not derivable from D1 that such a composition would be stable.

X. The respondent's arguments regarding inventive step may be summarized as follows:

(a) Main request

D1 disclosed (see page 24, lines 20-26) tablets, pills, troches, capsules and the like containing a combination of FTY720 with one of starch, lactose and silicon dioxide.

Even if the subject-matter of claim 1 of the main request were considered novel over D1, the claimed compositions were obvious, because the claimed invention did not provide any technical effect over what was already achieved in D1. Example 1 of the patent showed that non-binary blends (mannitol + citric acid; mannitol + NaHCO3) were just as good as binary blends. Example 4 (Mannitol + Mg Stearate, not according to the invention) was even better than example 5 (silica, according to the invention). Therefore, the data in the patent did not make credible any advantageous technical effect. The objective technical problem was thus the provision of an alternative, and the claimed invention according to the main request amounted to an obvious alternative.

(b) Auxiliary requests

None of the auxiliary requests met the requirements of inventive step either.

In particular, despite the limitation of possible excipients in claim 1 of auxiliary request 1, the compositions according to this request were neither simpler nor provided any further improved stability or better storage properties. Therefore, the subject-matter of auxiliary request 1 was obvious essentially for the same reason as the main request.

As to auxiliary requests 2 and 3, the introduction of the feature relating to the level of impurity did not establish novelty, and the claimed subject-matter was obvious for the same reasons as for the main request.

In claim 1 of auxiliary request 4, the limitation to HPMC and croscarmellose as the possible excipients was

not associated with any surprising technical effect. Each of these excipients was an entirely common pharmaceutical ingredient, as evidenced by D3.

Auxiliary request 5-7 failed to meet the conditions of Article 56 EPC for the same reasons.

XI. The appellant requests that the decision under appeal be set aside and that the patent be maintained as granted (main request), or, alternatively, that it be maintained on the basis of one of auxiliary requests 1-7 filed with the statement of grounds of appeal.

XII. The respondent requests that the appeal be dismissed. The respondent further requests that auxiliary requests 1-7 not be admitted into the proceedings.

Reasons for the Decision

1. Main request (patent as granted), inventive step

1.1 The patent pertains to formulations of the S1P modulator FTY720. The compositions of claim 1 of the main request are binary blends, i.e. they consist of FTY720 and only one excipient chosen from the list of claim 1, namely lactose, HPMC, HPC, crospovidone, croscarmellose sodium, starch, and colloidal silicone dioxide.

The objective of the invention is to provide formulations for use as a dosage form (see paragraph [0002]). The patent further states that the binary blends of the invention are stable and may be transported and stored prior to final formulation without forming degradation products (see paragraphs [0026]-[0027]), and are preferably free of impurities

(see paragraph [0028]). The binary blend compositions of the invention are thus intended for use not only as intermediate compositions for the preparation of final FTY720 formulations, but also as final dosage forms themselves. This was confirmed by the appellant during oral proceedings, and is consistent with claim 2 which defines medical uses for these binary blends.

1.2 D1 discloses (final) pharmaceutical formulations comprising FTY720 (see page 10, lines 23-26, and pages 20-27), in particular solid FTY720 compositions such as tablets, pills, capsules or troches (page 24, lines 13-26). The purity of FTY720 in the composition is also a concern in D1 (see page 26 lines 7-8). Since D1 relate to the same or a similar technical problem, namely the provision of formulations of FTY720, the Board considers that D1 represents a suitable starting point for the assessment of inventive step.

The appellant expressed the view that D1 did not address the problem of stability. However, it is not a requirement for D1 to be considered as a starting point that D1 disclose all the problems mentioned in the patent. This applies particularly in the present case, where the problem (stability) is a usual consideration in the development of formulations, and where no effect in this respect turns out to have been achieved (see 1.6 below).

The appellant also contested the choice of D1 as closest prior art for the reason that D2 came closer to the problem of the invention and had the most features in common with the claimed formulations. The Board does not agree. Considering the Board's conclusion of lack of inventive starting from D1 (see below), D1 qualifies as the most promising springboard to arrive at the

claimed subject-matter, irrespective of the content of D2.

Lastly, the fact that the passage on page 24 of D1 is general, and that D1 contains no actual example of a solid FTY720 composition, does not mean in any way that the disclosure of D1 is defective or could not be reproduced.

1.3 As to the content of the FTY720 compositions, D1 indicates on page 24, lines 20ff, that:

"The tablets, pills, capsules, troches and the like can contain *any* of the following ingredients, or compounds of a similar nature: a binder such as [...]; an excipient such as starch or lactose, a disintegrating agent [...]; a lubricant [...]; a glidant [...]; a sweetening agent [...]; *or* a flavoring agent [...]." (*emphasis* and [deletions] by the Board)

Starch or lactose are among the excipients recited in claim 1 of the main request. Thus D1 discloses compositions comprising FTY720 and, at least, one of the recited excipient.

The appellant considers that D1 fails to disclose binary blends, i.e. compositions comprising FTY720 and only one of the recited excipients. The Board accepts that this passage of D1 does not specify the number of ingredients, and thus does not disclose, directly and unambiguously, a binary composition.

1.4 Nonetheless, the Board cannot share the appellant's view that the passage requires the presence of one component for each of the seven types of ingredients (namely a binder, an excipient, a disintegrating agent,

a lubricant, a glidant, a sweetening agent *and* a flavoring agent). The appellant's interpretation is neither supported by the expressions "*any* of the following ingredients", which leaves the number of excipients undefined, nor by the word "or" in the passage above. There is also no technical reason why a skilled person should regard all the recited ingredient types to be necessary for each of the dosage form listed. Likewise, D1 states that the oral compositions only "generally", but not necessarily, include an inert diluent or an edible carrier (see page 24, line 13). Additionally, starch and lactose can also be considered as carrier.

The Board concludes that the passage of D1 on page 24 allows for, but does not specifically disclose, binary blends.

1.5 Consequently, the compositions of claim 1 of the main request differ from the teaching of D1 in that they are binary blends, i.e. they are characterised by the absence of a further excipient in addition to e.g. the lactose or starch shown in D1.

1.6 The appellant did not show that this differentiating feature led to any particular technical effect. The examples of the patent do not allow for a meaningful comparison of a binary blend according to claim 1 with a composition comprising additional excipients. No conclusion can be drawn from the data on the FTY720 blends with mannitol alone or with additional ingredients (examples 1 and 4), because no difference in stability is exhibited under the test conditions when the additional ingredient is citric acid or sodium hydrogen carbonate. Additionally, mannitol is not among the excipients recited in claim 1.

The appellant submits that the excipients recited in claim 1 lead to a surprisingly high stability, whereas D1 provides no indication as to the stability of the formulations disclosed therein. The Board does not consider this argument to be convincing in the present case. In comparison with D1, the claimed invention is not characterised by the selection of the excipients listed in claim 1, but by the absence of further excipient. Considering the lack of evidence as to an effect resulting from the differentiating feature over D1, this alleged advantage cannot be taken into consideration in determining the problem underlying the invention and in assessing inventive step.

1.7 The objective technical problem is thus the provision of an alternative composition. The precision that these compositions should be commercial does not affect the conclusions below, since the same can be said of the final formulations of D1.

1.8 In the absence of an associated technical effect, the selection of binary compositions from the teaching of D1 does not involve an inventive step. As discussed above (see 1.4), D1 does not require that the compositions contain several excipients.

The appellant submits that D1 pointed to pre-clinical, liquid saline formulations for local administration, rather than the claimed solid formulations for systemic administration. However, the technical problem is formulated as the provision of an alternative, and the skilled person would consider the claimed binary blends covered by D1 as a solution to the problem. No inventive step can be derived from an absence of motivation in D1 to select the claimed solution.

1.9 Accordingly, the subject-matter of claim 1 of the main request does not involve an inventive step.

2. Auxiliary requests

The Board decided to admit auxiliary requests 1-7 into the appeal proceedings. Considering the conclusions reached below on inventive step, this admittance need not be discussed further.

2.1 Auxiliary request 1

The deletion of HPC, Crospovidone and colloidal silicone dioxide has no bearing on the assessment of inventive step given above for the main request, because it does not introduce any additional differentiating feature over the compositions comprising FTY720 and e.g. lactose or starch of D1. As for the main request, the binary blends of claim 1 of auxiliary request 1 do not differ from D1 by the choice of the particular excipients, but by the absence of further excipients. Since no effect is shown to arise from this differentiating feature, the same reasoning applies. Hence, auxiliary request 1 does not meet the requirements of inventive step.

2.2 Auxiliary requests 2 and 3

Auxiliary requests 2 and 3 comprises the feature that "the level of impurities is not more than 4.5wt% and/or no more than 2wt% for an individual impurity". This feature amounts to a statement of the desired purity (see paragraph [0029] of the patent), without otherwise limiting the claimed compositions or giving rise to any other effect with respect to e.g. stability. Purity is

commonly a concern in the formulation of active ingredient, as shown by the objective of 90% pure FTY720 mentioned in D1 (see page 26, lines 7-8). The skilled person would thus try to achieve the highest purity level for the composition, such as the arbitrarily defined levels of claim 1. Accordingly, auxiliary requests 2 and 3 do not meet the requirements of inventive step.

2.3 Auxiliary request 4

In claim 1 of auxiliary request 4, the excipient is selected from HPMC and croscarmellose sodium.

Compositions of FTY720 with HPMC or croscarmellose sodium are not mentioned in D1 (see page 24, lines 20-26). However, it is not shown, and the appellant did not assert, that HPMC and croscarmellose sodium perform any better than the lactose or starch formulations of D1 (see the examples of the patent).

Accordingly, starting from D1 as the closest prior art, the technical problem is still the provision of an alternative composition. As pointed out by the respondent, HPMC and croscarmellose sodium are common pharmaceutical ingredients. This is confirmed by D3 (see e.g. the disintegrating agent croscarmellose sodium in D3, Tables 2/4 and 2/5). Hence the skilled person would consider using these well-known additives as the binder or disintegrant generally mentioned in D1 (see page 24). The concentration ranges proposed in D3 for croscarmellose would not lead away from the claimed binary blends, since no concentrations are defined in claim 1 either. Accordingly, the criteria of Article 56 EPC are not met.

2.4 Auxiliary request 5

Claim 1 of auxiliary request 5 incorporates the feature relating to purity as in auxiliary requests 2 and 3, and selects croscarmellose sodium for the excipient. The considerations given above for auxiliary requests 2-4 apply correspondingly to auxiliary request 5. Thus auxiliary request 5 does not meet the requirements of inventive step.

2.5 Auxiliary request 6

Claim 1 of auxiliary request 6 specifies that the binary blends are stable. However, the claim does not define to what extent and under which conditions the compositions should exhibit this stability. The expression stable must accordingly be construed broadly, and does not represent an additional differentiating feature over D1, as a pharmaceutical composition must exhibit some level of stability to be suitable for that purpose. Accordingly, auxiliary request 6 does not meet the requirements of Article 56 EPC for the same reasons as for the main request.

2.6 Auxiliary request 7

As for auxiliary request 1, the deletion of HPC and colloidal silicone dioxide has no bearing on the assessment given above in respect of the main request regarding inventive step over D1. Hence this request must also be rejected for lack of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos D. Boulois

Decision electronically authenticated