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Datasheet for the decision of 18 June 2024

Case Number: T 2205/21 - 3.3.07

Application Number: 14721256.7

Publication Number: 2988733

IPC: A61K9/20, A61K31/506

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITION CONTAINING CRYSTALLINE MACITENTAN

Patent Proprietor:
Sandoz AG

Opponent:
Gill Jennings & Every LLP

Headword:
PHARMACEUTICAL COMPOSITION CONTAINING CRYSTALLINE MACITENTAN/ Sandoz AG

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(2)

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It can be changed at any time and without notic

Keyword:
Main request and auxiliary request 2 - Inventive step (No)
Auxiliary request 1 not admitted

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Case Number: T 2205/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 18 June 2024

Appellant: (Opponent)	Gill Jennings & Every LLP The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Representative:	Gill Jennings & Every LLP The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Respondent: (Patent Proprietor)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 25 October 2021 rejecting the opposition filed against European patent No. 2988733 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	A. Jimenez

Summary of Facts and Submissions

I. European patent No. 2 988 733 was granted on the basis of a set of 14 claims.

Independent claim 1 as granted read as follows:

"1. A pharmaceutical composition, which is an oral solid dosage form, and comprising crystalline macitentan free base characterized by an X-ray powder diffraction pattern showing peak maxima at 2 theta/° values of 11.4±0.2, 13.0±0.2, 16.1±0.2, and 25.4±0.2 when a radiation wavelength of 1.5419 Å is used; and at least one excipient; wherein said pharmaceutical composition is packaged in a packaging material having a moisture vapour transmission rate of at least 0.4 $g.m^{-2}d^{-1}$ as measured according to standard DIN 53122-1."

II. An opposition was filed under Article 100 (a) and (b) EPC on the grounds that the subject-matter of the patent lacked inventive step and was not sufficiently disclosed.

III. The appeal lies from the decision of the opposition division to reject the opposition.

IV. The documents cited during the opposition proceedings included the following:

D6: Bauer, Kurt et al., "Pharmazeutische Technologie" Georg Thieme Verlag Stuttgart, 31 December 1993, pages 102-104 and 402-410
D7: WO 2007/031933 (A2), 22.03.2007

D9: Bolli, Martin et al., "The Discovery of N.[5-(4-Bromophenyl)-6- [2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4- pyrimidinyl]- N'-propylsulfamide (Macitentan), an Orally Active, Potent Dual Endothelin Receptor Antagonist" Journal of Medicinal Chemistry, 31 December 2012, 55, 7849-7861
D9a: Supporting information of D9
D12: Applicant's submission dated August 04, 2017
D13: Applicant's submission dated July 11,2018

V. According to the decision under appeal, the claimed invention was sufficiently disclosed.

With regard to inventive step, D7 was considered to represent the closest prior art. The subject-matter of claim 1 differed in the crystalline form of macitentan and the moisture vapour transmission rate of the packaging material. The objective technical problem was defined as the provision of an oral solid dosage form comprising macitentan with improved storage stability in conditions of elevated temperature and high humidity. The claimed solution was not obvious.

VI. The opponent (hereinafter the appellant) filed an appeal against said decision.

VII. With its reply to the statement of grounds of appeal dated 1 July 2022, the patent proprietor (hereinafter the respondent) filed auxiliary requests 1 and 2.

VIII. A communication from the Board, dated 29 February 2024, was sent to the parties. In it, the Board expressed *inter alia* its preliminary opinion that D7 or D9 could be considered as closest prior art for the assessment of inventive step.

IX. With a letter dated 27 May 2024, the respondent submitted new auxiliary requests 1. The previous auxiliary request 1 was resubmitted with the same letter and renumbered as auxiliary request 2.

In comparison to claim 1 of the main request, claim 1 of the new auxiliary request 1 had been amended by the further feature **"wherein the oral solid dosage form comprises at most 5 % by weight of amorphous macitentan free base, and wherein the solid dose form is a tablet"**.

In comparison to claim 1 of the main request, claim 1 of auxiliary request 2 had been amended by the further feature **"wherein the crystalline macitentan free base has a particle size distribution having a D98% of at most 680 pm, a D50% of from 3 µm to 250 µm and a D5% of at least 0.5 µm"**.

X. Oral proceedings took place on 18 June 2024.

XI. The arguments of the appellant may be summarised as follows:

Main request - Inventive step

D7 served as a suitable starting point and claim 1 differed from D7 in that macitentan was provided in crystalline polymorph Form I and in the claimed packaging material.

Neither the patent in suit, nor the comparative data presented in D13, showed that the packaging material used would have had any influence on the stability of the pharmaceutical composition, as shown for instance by D6. Moreover, although the patentee claimed that the

polymorph of macitentan specified in claim 1 was more stable than other forms, claim 1 did not include any quantitative limitations on the amount of Form I present, or the exclusion of other forms or material. Hence, any alleged advantage accruing to Form I macitentan could not be plausibly achieved at such low levels as allowed by the claim and any disadvantages accruing to amorphous or other polymorphic forms of macitentan must also be suffered by claim 1 which notionally covers all such forms. Finally it seemed that only a combination with specific excipients could provide the desired stability.

The problem was therefore the provision of an alternative oral solid dosage form of macitentan.

Claim 1 of D7 disclosed a morphological form of the free base of macitentan. No selection was required to get to this starting point. Thus, the only choice to make was the specific morphological form specified in claim 1. This criteria was met by combining D7 with D9, which disclosed the polymorphic form I of macitentan, and used it in clinical trials.

If the problem was defined as an improvement, the conclusion was the same in view of the combination of D7 and D9. The skilled person would have been motivated to assess the stability properties of the known polymorphic forms and would have used the most stable.

Auxiliary request 1 - Admission into the appeal proceedings

This request was filed very late in the absence of any exceptional circumstances, since D9 was cited as possible closest prior art in the statement of grounds

of appeal. Moreover, it was *prima facie* not allowable with regard to inventive step. A new issue on Article 123(2) EPC had also to be discussed.

Auxiliary request 2 - Inventive step

The features introduced in claim 1 did not have any incidence on inventive step and did not relate to the particle size of macitentan in the final product, but only in the starting product.

XII. The arguments of the respondent may be summarised as follows

Main request - Inventive step

D7 was the closest prior art and differed from the subject-matter of claim 1 of the opposed patent in that: macitentan was provided in a specific crystalline form and in a specific packaging material. Example 3 of the patent showed that the choice of a packaging material had an impact on the stability of the packaged product. D13, as well as D12, showed that other crystalline forms of macitentan, or macitentan in its amorphous form, did not exhibit the desired physical or chemical stability when stored in a packaging material with high moisture vapour transmission rate. In consequence, both distinguishing technical features contributed to the unexpected technical effect of improved chemical and physical stability of a macitentan product packaged in a packaging material as claimed.

Auxiliary request 1 - Admittance into the appeal proceedings

This request has been filed in response to the preliminary opinion of the Board which envisaged the possibility to take D9 as closest prior art, which came as a surprise to the respondent. The subject-matter of claim 1 was simple to analyze, which was in favour of the procedural economy.

Auxiliary request 2 - Inventive step

The respondent referred to the effect disclosed in paragraph [0046] of the patent with regard to the particle size distribution.

XIII. Requests

The appellant requested that the decision under appeal be set aside and that the patent be revoked. They also requested that auxiliary request 1 be not admitted into the appeal proceedings.

The respondent requested that the appeal be dismissed, alternatively that the decision under appeal be set aside and the patent be maintained according to one of the sets of claims filed as auxiliary requests 1 and 2 with the letter of 27 May 2024, wherein auxiliary request 2 corresponded to auxiliary request 1 filed with the reply to the statement of grounds of appeal.

Reasons for the Decision

1. Main request - Inventive step

1.1 The claimed invention relates to a pharmaceutical composition comprising macitentan and exhibiting improved chemical stability upon storage, in particular at conditions typical for tropical countries (cf. par. [0009], [0012] or [0013] of the specification).

1.2 Document D7 was considered to represent the closest prior art by the opposition division in its decision. The appellant agrees with this choice, even if it added also D9 as possible alternative closest prior art.

1.2.1 Document D7 discloses stable oral dosage forms of macitentan or any salt, hydrate or morphological form thereof, but does not specify which form is used (see page 1, first paragraph and see the examples or the claims). The solid compositions are stable for at least 6 months or 12 months when kept at a temperature of 5 to 50°C (see page 12 third paragraph).

D7 does not disclose the claimed crystalline polymorph form I and the property of the packaging material.

1.3 The opposition division defined the problem as the provision of an oral solid dosage form comprising macitentan with improved storage stability, i.e. chemical and physical stability, in conditions of elevated temperature and high humidity. The respondent agrees with this definition of the problem.

The appellant disagrees with the opposition division and defines the problem as the provision of an alternative oral solid dosage form of macitentan.

1.4 The claimed solution to any of these problems is an oral dosage form comprising the crystalline polymorph Form I of macitentan in a packaging material having the claimed moisture vapour transmission rate.

1.4.1 The respondent mentioned the examples of the contested patent and documents D12 and D13 in support of a technical effect, while the appellant considered that the problem of improved stability had not been solved across the scope of the claims.

1.4.2 Examples 2-4 of the patent compare the chemical stability and storage stability of coated tablets comprising the claimed polymorphic form I of macitentan, said tablets being packaged in polypropylene blisters in example 3, to coated tablets comprising the amorphous form of macitentan. The tablets are stored at 25 or 40°C at 70% relative humidity during 4 weeks, and the examples mention a significant better stability of the tablets prepared with the polymorphic form I of macitentan, without giving quantitative results. Example 4 studies furthermore the stability of coated tablets comprising the Form I of macitentan with a particular particle size distribution obtained by milling. The dissolution rate is determined after 4 weeks of storage at 40°C and 70% relative humidity, again without giving quantitative results.

D12 tests the physiochemical properties and physical stability of macitentan crystalline form I compared with two crystalline solvate forms of macitentan, designated macitentan Form II and form III, which are respectively a crystalline dichloromethane solvate form and a crystalline THF solvate form of macitentan. Table

1 shows that the crystalline form I of macitentan has a better stability than the crystalline forms II and III, when tested at 40°C and 75% relative humidity during 4 weeks.

In D13, tablets were packaged in polyethylene bags, a material having a high water vapour transmission rate as claimed and stored at 30°C/65% r.h. for 50 days. Other tablets were filled in aluminium bags, a packaging material having a very low vapour transmission rate, i.e lower than the claimed vapour transmission rate, and stored in the same way. The polymorphic Forms I-IV of macitentan were compared. The results show that the tablets comprising form I have a higher stability. Moreover, when comparing differently packed tablets (aluminium and polyethylene bags) comprising macitentan form I, marginal differences were observed, which, according to D13, confirm the teaching of the patent that packaging material having a relatively high water vapour transmission rate can be used to store tablets comprising macitentan in its form I.

In view of these experiments, it appears credible that the storage stability is the best with the form I of macitentan, and that these properties are not altered with a packaging material as claimed.

1.4.3 The appellant argued that there is a lack of technical effect for the claimed subject-matter over the whole scope of the claims. The appellant argues first that the packaging material does not appear to contribute to the solution of the technical problem. Moreover, claim 1 does not include any quantitative limitations on the amount of form I present, or the exclusion of other forms of macitentan, as illustrated by dependent claim

2 which includes the possibility to have at most 5% by weight of amorphous macitentan. Consequently, the increased stability cannot be obtained over the whole scope of the claims in view of the term "comprising" in claim 1. Finally, claim 1 relates to a composition and not to a compound as such, and it is not possible to extrapolate the stability properties of the form I of macitentan to any composition comprising it.

The Board agrees with the appellant with regard to the contribution of the packaging material to a possible technical effect on the stability of the claimed oral dosage form. D13 shows indeed clearly that the packaging material has only a marginal effect on the stability of tablets comprising the form I of macitentan. This shows also that packaging materials having a relatively high water vapour transmission rate as claimed can be used for form I based tablets, and that it was not necessary to select a packaging having a low water vapour transmission rate. The Board notes furthermore that no other advantage regarding the claimed packaging material was provided by the respondent.

With regard to the absence of quantitative amounts of the form I of macitentan in claim 1, the Board agrees with the conclusion reached by the opposition division in its decision. It appears indeed reasonable to consider that any oral dosage form as claimed comprising any amounts of the form I of macitentan will still be more stable than the same dosage form comprising partially another form of macitentan. The same conclusion applies with regard to the presence of unspecified excipients in the claimed oral dosage form, since some excipients might have either a favourable or unfavourable effect on the stability of the dosage from

comprising the form I of macitentan. There is however no evidence on file that some excipients have a specific and exclusive effect on the stability of the dosage form comprising form I of macitentan, and this is furthermore contradicted by the experiments shown in D13.

1.4.4 Consequently, the problem is as defined by the opposition division or the respondent, namely the provision of an oral solid dosage form comprising macitentan with improved storage stability in conditions of elevated temperature and high humidity.

1.5 It remains to determine whether the claimed solution is obvious. On this point, documents D7, D9 and D6 were particularly mentioned by the parties.

1.5.1 As mentioned above (see point 1.2.1) the closest prior art D7 indicates that morphological forms of macitentan can be included in the pharmaceutical compositions disclosed therein. The skilled person would consider this information as a clear incentive for the selection of a known polymorphic form of macitentan.

1.5.2 The contested patent makes a reference to D9 in paragraph [0089], said passage mentioning that the crystalline Form I of macitentan of the claimed invention was prepared according to the method given in D9.

D9 discloses the process for the preparation of macitentan and its purification, in particular its obtention by recrystallization of the compound 17 of D9 from methanol; D9 (see page 7851, left column, last sentence of the first paragraph) mentions that "in general, the target compounds could be purified easily

by recrystallization from methanol". As accepted by the respondent, this compound has been identified in D9a as being the polymorphic form I of macitentan. D9a (see page 26, second paragraph, lines 9-10) mentions indeed that "a second X-ray structure analysis was performed with crystals obtained from methanol" on compound 17.

Several compounds were tested orally as shown in Tables 5 and 6 of D9. Compound 17 was found to be promising for further studies as particularly interesting for the inhibition of ETA with a significant affinity for the ETB receptor (see Abstract, Table 6; page 7854, last paragraph; page 7856, left-hand column, last paragraph).

D9 identifies on page 7856 (see Table 7) an oral composition comprising the form I of macitentan in either 7.5% aqueous modified gelatin or a PEG 400 solution and mentions further on page 7856 in the "Conclusions" that compound 17 had successfully completed a phase III clinical trial for pulmonary arterial hypertension. A phase IIIb clinical trial for digital ulcers and a phase I/Ib for recurrent glioblastoma were currently ongoing.

In view of the disclosure of D9, it appears clear that not only the polymorphic form I of macitentan was known at the filing date of the contested patent, but also that this form was the preferred form which was selected for clinical trials. Hence, the skilled person would have been encouraged to select form I of macitentan and to incorporate it in an oral dosage form as disclosed in D7. Furthermore, at the priority date the only known crystalline form of macitentan free base was that disclosed in D9/D9a. Thus, starting from D7, the obvious morphological form to use was the one

disclosed in D9/D9a, alone for the reason that there were no others.

1.5.3 D6 is a common general knowledge book relating to pharmaceutical technology. It discloses on page 407 and Table 21.3 a list of all polymers useful as packaging material for pharmaceutical products, with their physicochemical properties, *inter alia* with their water vapour transmission rate. It follows from this disclosure that all of the known polymers have a water vapour transmission rate as claimed in claim 1 of the main request. Consequently, the claimed packaging material is a conventional and commonly used packaging material, and its choice, in particular in the absence of any particular effect linked therewith, is also obvious.

1.5.4 Consequently, the claimed solution is obvious in view of D7 combined with the teachings of D9 and D6. The main request lacks therefore inventive step.

2. Auxiliary request 1 - Admittance into the appeal proceedings

2.1 This request has been filed by the respondent with letter dated 27 May 2024, after the Board issued its preliminary opinion. Claim 1 of this request has been amended by incorporating the subject-matter of dependent claims 2 and 3, i.e. the features "the oral dosage form comprising at most 5% by weight of amorphous free base and wherein the solid dosage form is a tablet".

According the respondent, this request was in response to the preliminary opinion of the Board which envisaged the possibility to take D9 as closest prior art.

2.2 In the present case, Article 13(2) RPBA as in force from 1 January 2024 is relevant with regard to the new submission. That provision indicates that: "Any amendment to a party's appeal case made...after notification of a communication under Article 15, paragraph 1 shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned".

This request represents an amendment to the appellant's case filed at a very late stage of the appeal proceedings, since it does not correspond to any request previously on file. Hence, the Board needs to decide whether there are exceptional circumstances, justified by cogent reasons, why the submission is to be taken into account.

First, the new auxiliary request 1 cannot be seen as a response to the preliminary opinion of the Board, which did not raise any new point in its communication. The argument put forward by the respondent with regard to the citation of D9 as alternative possible closest prior art by the Board in its preliminary opinion does not hold. The suitability of D9 as possible closest prior art was already discussed by the opposition division in its decision (see point 2.1), and D9 was presented again as possible alternative to D7 as closest prior art by the appellant in the statement of grounds of appeal. Moreover, the respondent mentioned in its response to the grounds of appeal that "the above-provided observations apply in the same way and the same conclusions must also be drawn when starting from D9 (instead of D7 as closest prior art)" (see page 17 of the respondent's letter dated 1 July 2022).

Consequently, the eventuality to use D9 as starting point for the assessment of inventive mentioned by the Board in its preliminary opinion cannot constitute a surprise to the respondent and the preliminary opinion does not raise a new point.

In the Board's view, there are thus no exceptional circumstances justifying the admittance of the new auxiliary request 1 into the appeal proceedings.

Consequently, the Board decides not to admit the new auxiliary request 1 into the proceedings (Article 13(2) RPBA).

3. Auxiliary request 2 - Inventive step

Claim 1 of this request has been amended by the incorporation of the subject-matter of the granted dependent claim 6, namely the feature "**wherein the crystalline macitentan free base has a particle size distribution having a D98% of at most 680 pm, a D50% of from 3 µm to 250 µm and a D5% of at least 0.5 µm**".

The appellant cites paragraph [0046] of the contested patent in support of a surprising technical effect linked with the specific particle size distribution: "*These particle size distributions strike a beneficial balance between processability during formulation - crystals which are too small may stick to the plunger in a tableting machine - on the one hand and dissolution rate on the other - if the crystals are too large this may gradually compromise the bioavailability of macitentan*.".

However, there is no evidence to support any effect arising from the particle size distribution; the passage cited by the respondent is a general statement which is not translated in any concrete effect in the contested patent. As argued by the appellant, D7 shows furthermore on page 35 and Figure 1 the dissolution profile of the tablets disclosed in D7, and there was no evidence that the new feature provides some surprising technical effect compared to the particulate products of D7 . Thus, the new feature appears to be an arbitrary limitation. Accordingly, the claimed subject-matter is not inventive over D7 in combination with D9 and D6, as concluded above for the main request.

Consequently, auxiliary request 2 does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated