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Datasheet for the decision of 10 December 2019

Case Number: T 0709/17 - 3.3.02

Application Number: 10737869.7

Publication Number: 2470529

IPC: C07D403/06, A61K31/506, A61P31/10

Language of the proceedings: EN

Title of invention:

A 1-(1H-1,2,4-TRIAZOL-1-YL)BUTAN-2-OL DERIVATIVE FOR PHARMACEUTICAL USE, AND THE USE OF A 1-(1H-1,2,4-TRIAZOL-1-YL)BUTAN-2-OL DERIVATE WITH SUBSTANTIALLY UNDEFINED CRYSTAL SHAPE FOR PREPARING SAID 1-(1H-1,2,4-TRIAZOL-1-YL)BUTAN-2-OL DERIVATIVE

Patent Proprietor:

Medichem, S.A.

Opponents:

Gillard, Richard Edward
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Actavis Group PTC ehf
FRKelly

Headword:

Relevant legal provisions:
EPC Art. 100(b), 54, 56

Keyword:
Insufficiency of disclosure
Novelty
Inventive step

Decisions cited:
T 0928/06

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0709/17 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 10 December 2019

Appellant: (Opponent 1)	Gillard, Richard Edward Thavies Inn House 3-4 Holborn Circus London EC1N 2HA (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Appellant: (Opponent 3) - appeal withdrawn -	Actavis Group PTC ehf Reykjavikurvegur 76-78 222 Hafnarfjordur (IS)
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Respondent: (Patent Proprietor)	Medichem, S.A. Fructuós Gelabert, 6-8 08970 Sant Joan Despi, Barcelona (ES)
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Party as of right: (Opponent 2)	isarpatent - Patentanwälte Behnisch Barth Charles Hassa Peckmann und Partner mbB Friedrichstrasse 31 80801 München (DE)
Representative:	Isarpatent, et al. Patent- und Rechtsanwälte Behnisch Barth Charles Hassa Peckmann & Partner mbB

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 17 February 2017 rejecting the opposition filed against European patent No. 2470529 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairman M. O. Müller
Members: A. Lenzen
M. Blasi

Summary of Facts and Submissions

I. Appeals were lodged by opponents 1 and 3 (appellants 1 and 3) against the decision of the opposition division (impugned decision) to reject the oppositions filed against European patent No. 2 470 529 (patent in suit).

II. The patent in suit had been opposed based on the grounds for opposition pursuant to Article 100(a) EPC (lack of novelty and lack of inventive step) and Article 100(b) EPC.

III. In its decision, the opposition division rejected the oppositions.

IV. The following documents, cited during the opposition proceedings, are relevant for the present decision:

D7 IP.com Journal, 31 May 2005, IPCOM000125373D

D12 "PHARMACEUTICAL DOSAGE FORMS - Tablets", second edition, revised and expanded, vol. 1, 1989, pages 1 to 12

D13 T 928/06

V. The board summoned the parties to oral proceedings in accordance with corresponding requests of the parties.

By letter dated 18 February 2019, appellant 3 withdrew both its opposition and its appeal, and ceased to be party to the appeal proceedings.

By letter dated 31 July 2019, opponent 2 who had not made any submissions in substance indicated that it would not be attending the oral proceedings.

By letter dated 19 September 2019, appellant 1 withdrew its request for oral proceedings and indicated that it would not be attending the oral proceedings.

VI. A communication pursuant to Article 15(1) RPBA was issued on 20 September 2019.

VII. Oral proceedings were held on 10 December 2019, with the patent proprietor (respondent) being the only party present.

VIII. Appellant 1 had requested in writing that the impugned decision be set aside and the patent in suit be revoked in its entirety.

The respondent requested

- that the patent in suit be maintained as granted, implying that the appeal of appellant 1 be dismissed,
- in the alternative, that the patent in suit be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 to 11, filed with its reply to the statements of grounds of appeal.

IX. Appellant 1's submissions, in so far as they are relevant to the present decision, can be summarised as follows:

The voriconazole of claim 1 was defined in terms of its average particle diameter D_{90}. This parametric definition led to an insufficiency of disclosure.

D7 was the closest prior art. Both (a) micronised voriconazole obtained from crystals having a plate-like habit, and (b) unmicronised voriconazole crystals having an undefined shape were equally suitable starting points for the assessment of inventive step. The subject-matter of claim 1 was distinguished from (a) in that the specific surface area was smaller. As clear from D12 and D13, however, this difference was merely the result of routine optimisation by the skilled person. The claimed subject-matter therefore did not involve an inventive step.

X. The respondent's submissions, in so far as they are relevant to the present decision, can be summarised as follows:

With regard to appellant 1's objection as to a lack of sufficiency of disclosure, the respondent agreed with the reasoning of the impugned decision and the board's communication pursuant to Article 15(1) RPBA.

D7 was the closest prior art. D7 clearly focused on (a) micronised voriconazole obtained from crystals having a plate-like habit. The skilled person would therefore not have considered (b) unmicronised voriconazole crystals having an undefined shape to be an equally suitable starting point for the assessment of inventive step. The experimental data in the patent in suit showed that, when compared with a product according to D7, the product of claim 1 was better in terms of flowability while at the same time a solubility rate which was comparable with that of the closest prior art was maintained. This was indicative of an inventive step.

XI. The independent claims of the main request (patent in suit as granted) read as follows:

Claim 1

"*Voriconazole suitable for pharmaceutical use, characterized by a specific surface area in the range of 0.5m^2/g to 2m^2/g and a D_{90} of less than 150 µm.*"

Claim 8

"*A process of preparing voriconazole according to any of claims 1 to 7, said process comprising: (a) providing voriconazole with substantially undefined shape and / or crystal habit; and (b) subjecting said voriconazole of step (a) to mechanical particle size reduction so as to at least modify the specific surface area, and D_{90} thereof, thereby providing voriconazole according to any of claims 1 to 7.*"

Claim 13

"*Use of voriconazole crystals with substantially undefined shape and/or crystal habit for preparing voriconazole according to any of claims 1 to 7.*"

Claim 14

"*A pharmaceutical composition comprising voriconazole according to any of claims 1 to 7, together with one or more pharmaceutically acceptable excipients.*"

Reasons for the Decision

Appellant 1's appeal is admissible. Appellant 1, having been duly summoned, had not attended the oral proceedings. In accordance with Rule 115(2) EPC the appeal proceedings were continued in appellant 1's absence and, in accordance with Article 15(3) RPBA, appellant 1 was treated as relying on its written case.

Main request (patent in suit as granted)

1. Sufficiency of disclosure (Article 100(b) EPC)

1.1 Claim 1 refers to voriconazole characterised, *inter alia*, by an average particle diameter D_{90} of less than 150 µm.

1.2 Appellant 1 argued that the average particle diameter D_{90} in claim 1 did not necessarily imply a limitation to "by volume". Claim 1 was broader and thus covered diameter values not based on a distribution by volume. Since the patent in suit did not teach how to measure these diameter values, there was a problem of sufficiency of disclosure.

This is not convincing. The patent in suit (paragraph [0070]) defines the notation D_x as being synonymous to D(v, 0.X), i.e. as representing diameter values derived from volume distributions. In line with this definition, the diameter values D_x are measured in the patent in suit via laser diffraction (paragraphs [0062] and [0067] to [0069]), i.e. a method that gives values based on a volume-weighted distribution. This method is well-established in the art. The skilled person reading the patent as a whole thus knows how to determine the average particle diameter D_{90}.

1.3 In conclusion, the ground for opposition under Article 100(b) EPC does not prejudice the maintenance of the patent as granted.

2. Inventive step (Article 56 EPC)

2.1 The parties agreed that D7 was the closest prior art document.

2.2 D7 (examples 1 and 2) discloses that voriconazole has the ability to crystallize in three different crystal habits, namely a plate-like crystal habit, a needle-like crystal habit and an undefined shape. Of the three different crystal habits, only voriconazole crystals with a plate-like crystal habit are micronised in D7 (example 3). Although the resulting product is not characterised, D7 points out in general terms that its micronisation products have a specific surface area of about 3 m^2/g to 5 m^2/g (page 4, lines 29 to 30), i.e. above the upper limit of the range defined in claim 1.

In its background section, D7 (page 1, line 25 to page 2 line 2) explicitly identifies a needle-like crystal habit as being undesirable and that consequently "[*a*]*lternative crystal habits, for example a plate-like crystal habit, are preferred*". On that basis, appellant 1 argued that the skilled person would have considered

(a) micronised voriconazole obtained from crystals having a plate-like habit, and
(b) unmicronised voriconazole crystals having an undefined shape

as equally suitable starting points for the assessment of inventive step.

This is not persuasive because the actual invention of D7 concerns voriconazole crystals in a plate-like crystal habit and the micronised product derived from them, i.e. (a) above. This can be concluded e.g. from page 2, lines 17 to 20 and the fact that it is only crystals with a plate-like habit which are micronised in D7, not the other crystal habits. The skilled person would therefore only have contemplated (a) micronised voriconazole obtained from crystals having a plate-like habit as a suitable starting point for the assessment of inventive step.

2.3 In its communication pursuant to Article 15(1) RPBA the board indicated that the subject-matter of claim 1 was distinguished from (a) micronised voriconazole obtained from crystals having a plate-like habit only on account of the specific surface area, with the specific surface area in claim 1 being lower than that disclosed in D7 ("*0.5 m^2/g to 2 m^2/g*" in claim 1 vs. "*about 3 m^2/g to 5 m^2/g*" in D7 (page 4, lines 29 to 30)). This was not contested by the parties.

2.4 Voriconazole crystals with an undefined shape are prepared in example 1 of the patent in suit, following D7, example 3. This product is micronised, *inter alia*, in examples 3 and 8 of the patent in suit to give voriconazole powders according to claim 1 with the following properties (see paragraphs [0088] and [0090]):

example 3: D_{90} = 56.2 µm
specific surface area = 1.0997 m^2/g

example 8: D_{90} = 29.9 µm
specific surface area = 1.5910 m^2/g

Voriconazole crystals with a plate-like crystal habit are prepared in comparative example 1 of the patent in suit, following D7, experiment 2. This product is micronised in comparative example 2. The resulting powder has a D_{90} value of less than 150 µm and a specific surface area of 2.94 m^2/g (impugned decision: page 12, paragraph 5), which is in agreement with the range disclosed for it in D7 (page 4, lines 29 to 30), i.e. about 3 m^2/g to 5 m^2/g. Thus, the powder of comparative example 2 is a fair representation of (a) micronised voriconazole obtained from crystals having a plate-like habit according to D7.

In examples 10 to 13 of the patent in suit, the powder of comparative example 2 is compared with those of examples 3 or 8 in terms of solubility rate (example 10, the results of which are shown in figure 4; example 13) and flowability (examples 11 and 12). Examples 11 and 12 show that the powder of example 8 has better flow properties than that of comparative example 2. Example 10 shows that the powder of example 3 has only a marginally lower solubility rate than that of comparative example 2, although the specific surface areas of both powders differ by a factor of almost three. Example 13 shows that the powder of example 8 dissolves faster in a given pharmaceutical solution than that of comparative example 2.

Based on the experimental data presented in the patent in suit it can be acknowledged that the distinguishing feature identified above is responsible for better flowability while at the same time a solubility rate

which is comparable with that of the closest prior art is maintained.

In this context, appellant 1 argued that the comparison in example 10/figure 4 was irrelevant because the products of both example 3 and comparative example 2 of the patent in suit, the solubility rates of which were tested in example 10, used different polymorphic forms. However, the XRD spectra of these products shown in figures 6 and 8 share the same characteristic peaks. This shows that the powders of example 3 and comparative example 2 of the patent in suit were derived from crystals having the same polymorphic form.

2.5 The objective technical problem is therefore providing voriconazole having better flowability while at the same time maintaining a solubility rate which is comparable with that of the closest prior art.

2.6 It is well-established in the art that the micronisation of a crystalline product leads to a reduction of its average particle size and to an increase of its specific surface area. The micronisation of a product thus generally leads to better solubility (D12: page 5, lines 6 to 9 under point IV; D13: page 10, paragraph 2). It is also well-known since before the effective date of the patent in suit that the degree of micronisation should not go too far because this would be detrimental to flowability (D12: page 5, lines 21 to 25 under point IV).

On that basis, appellant 1 argued that the skilled person would have tried to achieve an optimal balance between flowability and solubility by optimising the specific surface area/average particle size of the product (a) as disclosed in D7. The subject-matter of

claim 1 was therefore the result of routine experimentation.

This is not persuasive. As set out above, increasing the specific surface area leads to an increase in solubility. The skilled person would thus have expected that decreasing the surface area would reduce the solubility. Therefore, starting from D7 and faced with the problem of improving the flowability while maintaining solubility, the skilled person would not have decreased the specific surface area. The skilled person would thus not have arrived at the subject-matter of claim 1. The subject-matter of this claim therefore involves an inventive step.

2.7 The process and use in independent claims 8 and 13 (cf. point XI above) essentially result in voriconazole according to claim 1; the composition of independent claim 14 comprises this voriconazole.

The reasoning above thus also applies *mutatis mutandis* to independent claims 8, 13 and 14 as well as to dependent claims 2 to 7, 9 to 12 and 15 to 17.

Order

For these reasons it is decided that:

The appeal of the sole remaining appellant, appellant 1, is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos M. O. Müller

Decision electronically authenticated