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Datasheet for the decision of 13 March 2023

Case Number: T 1825/21 - 3.3.02

Application Number: 16167355.3

Publication Number: 3121171

IPC: C07D401/12, A61K31/506, A61P35/00

Language of the proceedings: EN

Title of invention:
CRYSTALLINE FORMS OF 5-CHLORO-N2-(2-ISOPROPOXY-5-METHYL-4-PIPERIDIN-4-YL-PHENYL)-N4[2-(PROPANE-2-SULFONYL)-PHENYL]-PYRIMIDINE-2,4-DIAMINE

Patent Proprietor:
NOVARTIS AG

Opponents:
Generics (UK) Ltd
Teva Pharmaceutical Industries Ltd

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step

Decisions cited:
G 0002/21, T 0777/08

Catchword:

Europäisches Patentamt
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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 1825/21 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 13 March 2023

Appellant: (Patent Proprietor)	NOVARTIS AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Aera A/S Niels Hemmingsens Gade 10, 5th Floor 1153 Copenhagen K (DK)
Respondent: (Opponent 1)	Generics (UK) Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent 2)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 26 July 2021 revoking European patent No. 3121171 pursuant to Article 101(2) and Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	M. Blasi

Summary of Facts and Submissions

I. The appeal of the patent proprietor (hereinafter appellant) lies from the decision of the opposition division according to which European patent 3 121 171 was revoked.

According to the contested decision, the ground for opposition under Article 100(a) EPC in combination with Article 56 EPC prejudiced the maintenance of the patent as granted. None of the auxiliary requests considered in the decision were allowable.

II. The following documents *inter alia* were cited in opposition proceedings:

D1: WO 2008/073687 A2
D14: Berge et al., Pharmaceutical Salts, Journal of Pharmaceutical Sciences, 1977, 66, 1, 1-19
D17: Remington: The Science and Practice of Pharmacy, 20th Edition, 2000, 704-707
D23: Declaration of Tove Tuntland dated 12 March 2019

III. In the statement of grounds of appeal the opposition division's finding of lack of inventive step was contested.

IV. Neither opponent 1 nor opponent 2 (respondents 1 and 2, respectively) made substantive submissions in appeal proceedings. Respondent 1 with the letter of 13 December 2021 stated that it endorsed the reasoning in the contested decision.

V. In preparation for oral proceedings, scheduled according to the appellant's request, the board issued a communication pursuant to Article 15(1) RPBA 2020 in which it provided the preliminary view that the claimed subject-matter lacked inventive step.

VI. Oral proceedings before the board took place as scheduled on 13 March 2023 in the presence of the appellant. Respondents 1 and 2 were absent, as announced with letters dated 13 December 2021 and 11 January 2023 respectively. The appeal proceedings were continued in the respondents' absence in accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020.

VII. Requests relevant to the present decision

The appellant requested that the contested decision be set aside, and that the patent be maintained as granted, implying rejection of the oppositions.

Respondent 1 requested dismissal of the appeal.

Respondent 2 did not submit any requests in appeal proceedings.

VIII. For the text of claim 1 of the patent as granted (main request), reference is made to the reasons for the decision, below.

IX. For the appellant's submissions relevant to the present decision, reference is made to the reasons for the decision provided below.

Reasons for the Decision

Main request (patent as granted)

Inventive step - Article 100(a) and Article 56 EPC

1. Closest prior art and distinguishing features

1.1 Claim 1 of the main request reads as follows:

"A crystalline form of 5-Chloro-N2-(2-isopropoxy-5-methyl-4-piperidin-4-yl-phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine."

This compound is in free base form (i.e. not in the form of a salt), and is also known as "ceritinib" (see contested decision, point 3 of the reasons).

1.2 According to the contested decision, the subject-matter of claim 1 of the main request lacked inventive step starting from D1 as the closest prior art. It was uncontested in appeal that patent document D1 represented the closest prior art.

1.3 D1 discloses kinase inhibitors, among which ceritinib is specifically disclosed as compound 66 in example 7 (pages 45 to 47). Although ceritinib is depicted structurally on page 45, example 7 as the free base, example 7 in fact discloses the preparation of the ceritinib hydrochloride salt (hereinafter ceritinib HCl) as a precipitate (D1, page 47, paragraph [0113]).

1.4 According to the contested decision, and also uncontested in appeal proceedings, the ceritinib HCl of example 7 of D1 is amorphous, and represents the

disclosure in D1 which is structurally closest to the claimed crystalline ceritinib. This amorphous ceritinib HCl represents the starting point for the assessment of inventive step of the claimed crystalline ceritinib.

1.5 In line with the appellant's submissions, the subject-matter of contested claim 1 is distinguished from this embodiment of D1 in that it concerns:

- ceritinib in free base form, rather than as its HCl salt,
- in crystalline, rather than in amorphous form.

2. Objective technical problem

2.1 According to the patent (paragraph [0006]), crystalline forms of ceritinib were discovered which exhibit new physical properties that may be exploited in order to obtain new pharmacological properties, and that may be utilised in the drug product development of ceritinib. The patent describes two crystalline forms of ceritinib, namely Form A (paragraphs [0017] to [0020] and examples 1, 3 and 4) and Form B (paragraphs [0021] to [0024] and example 2).

2.2 According to the contested decision (point 5.7), no technical effects associated with the claimed crystalline ceritinib free base over amorphous ceritinib HCl of D1 were disclosed in the opposed patent. In particular, the opposition division decided that certain post-published documents submitted by the appellant during opposition proceedings could not be taken into account on the grounds that the alleged effects were not credible from the data provided in the patent itself (decision, point 5.5).

2.3 While the board acknowledges that the patent - or the application as filed, respectively - does not comprise any data comparing the claimed crystalline ceritinib with the amorphous ceritinib HCl of D1, the board nevertheless concludes that the technical effects mentioned below may be accepted as being credible on the basis of the information in the patent and the common general knowledge of the skilled person.

2.4 As argued by the appellant, the effects of stability and ease of drying of the claimed crystalline ceritinib are credibly demonstrated in the patent. Specifically, both Form A and Form B were characterised by XRPD, TGA, DSC and IR analyses (Form A: paragraphs [0018] to [0020] and figures 1 to 3; Form B: paragraphs [0021] to [0024] and figures 4 to 6). The TGA and DSC tests (figure 2 and 3 for Form A; figure 5 and 6 for Form B) show that said forms are stable upon heating. Furthermore, Form A demonstrated a weight loss on drying at 200°C of only approximately 0.1%, while Form B demonstrated a weight loss of only 0.05% under the same conditions (figures 3 and 6), thus indicating that said forms may be prepared in dry form. Hence, it can be accepted that the claimed crystalline ceritinib possesses these properties.

2.5 As far as the comparative stability and drying properties of the amorphous ceritinib HCl of D1 are concerned, the following applies. In decision T 777/08, addressed in the contested decision (point 5.7), the relevant claim was directed to a specific crystalline form (Form IV) of atorvastatin. The known preparation of atorvastatin was experimentally demonstrated to yield an amorphous solid (point 4 of the reasons). The deciding board *inter alia* concluded that several disadvantages were generally expected for amorphous

forms over crystalline forms, namely with respect to chemical and physical stability (point 5.7 of the reasons, eighth paragraph). Furthermore, it was common general knowledge that crystalline products were generally the easiest to isolate, purify, dry, handle and formulate (point 5.2 of the reasons, ninth paragraph).

2.6 As indicated by the board in its communication pursuant to Article 15(1) RPBA 2020 (point 1.3.2, second paragraph), the advantages generally known to be associated with crystalline forms over amorphous forms mentioned in decision T 777/08 are not different from the effects of stability upon heating (chemical stability) and ease of drying demonstrated for the claimed crystalline ceritinib of the present patent. This view was not contested in appeal proceedings.

2.7 Hence, it is credible on the basis of this common general knowledge, which was known before the priority date of the claimed invention, that the effects of stability and ease of drying, demonstrated in the patent for crystalline ceritinib, represent improvements over the amorphous ceritinib HCl disclosed in D1. Therefore, an improvement over amorphous ceritinib HCl of D1 is acknowledged without taking the appellant's post-published evidence into account as proof of said improvement (supra). It follows also that case G 2/21, in which this issue is addressed, is not relevant to the present appeal case.

2.8 The objective technical problem starting from the amorphous hydrochloride salt of D1 is hence the provision of a form of ceritinib having improved stability and ease of drying.

3. Obviousness

3.1 The appellant argued that the skilled person attempting to obtain a form of ceritinib with improved stability and ease of drying would have tried to prepare the ceritinib HCl known from example 7 of D1 in crystalline form. However, as set out in point 5 of D23, a declaration of a technical expert, any attempt to prepare ceritinib HCl only resulted in amorphous (i.e. non-crystalline) precipitates having chloride levels inconsistent with a stoichiometric salt.

3.2 The board agrees. Having failed to solve the above problem in the most obvious way by providing a crystalline ceritinib HCl, there would have been no reason for the skilled person to turn to ceritinib free base in the expectation that it would provide a solution. As stated by the appellant, while the skilled person could have tested the free base for crystalline properties, there would have been no reason to do so, in particular in view of the fact that the preparation of a crystalline form of the known ceritinib hydrochloride salt had failed.

3.3 There is also no pointer to the claimed solution in D1, as submitted by the appellant. Specifically, D1 teaches generally that the free base compound may be employed as an alternative to pharmaceutically acceptable salts, (e.g. paragraph [0045]: "[*t*]*he compounds of the invention in free form or in pharmaceutically acceptable salt form ...*"; paragraph [0074]: "*only pharmaceutically acceptable salts or free compounds are employed*"; paragraph [0067]). The claims of D1 also include the free form (e.g. claim 1; ceritinib is specifically disclosed in claim 11 on page 171). D1 also discloses that the compounds disclosed therein may

be obtained in free form by treatment of the corresponding salt with suitable basic agents (paragraphs [0071] and [0079]). However, there is no teaching in D1 pointing towards a crystalline form of the free base of the disclosed compounds in D1 in general as a solution to the above-mentioned problem, let alone a specific teaching towards crystalline ceritinib free base.

3.4 Additionally, as submitted by the appellant, the skilled person starting from example 7 of D1 and trying to solve the above-mentioned problem, using common general knowledge, would have looked for crystalline ceritinib in salt rather than the free base form. Specifically, the review article D14 teaches that *inter alia* the physical characteristics of medicinal agents can often be optimised by conversion to a salt form (page 1, left hand column), while table I (page 2) indicates that hydrochloride salts account for 42.98% of FDA-approved commercially marketed salts. The text book D17 (page 706, left hand column, lines 7 to 10) states that salt selection is the first important API decision from the development perspective.

3.5 Consequently, the subject-matter of granted claim 1 involves an inventive step. The same applies *mutatis mutandis* to granted claims 2-4 which refer to the crystalline form of claim 1.

3.6 Hence, in view of the foregoing, the ground for opposition under Article 100(a) EPC in combination with Article 56 EPC does not prejudice the maintenance of the patent as granted.

3.7 Since there are no other issues to be dealt with by the board, the oppositions are to be rejected.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The oppositions are rejected.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated