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Datasheet for the decision of 27 February 2025

Case Number: T 0243/22 - 3.3.07

Application Number: 16183844.6

Publication Number: 3150610

IPC: C07D487/06, A61K31/55, A61P35/00, A61K45/06, C07C309/19, C07C57/145

Language of the proceedings: EN

Title of invention:

SALTS AND POLYMORPHS OF 8-FLUORO-2-{4-[(METHYLAMINO} METHYL]PHENYL}-1,3,4,5-TETRAHYDRO-6H-AZEPINO[5,4,3-CD]INDOL-6-ONE

Patent Proprietor:

Pfizer Inc.

Opponent:

Generics [UK] Ltd

Headword:

Rucaparib maleate/PFIZER

Relevant legal provisions:

EPC Art. 56

Keyword:
Inventive step - (yes)

Decisions cited:
T 1126/19, T 0970/00

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Case Number: T 0243/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 27 February 2025

Appellant: (Patent Proprietor)	Pfizer Inc. 235 East 42nd Street New York, NY 10017 (US)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Respondent: (Opponent)	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)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 15 December 2021 revoking European patent No. 3150610 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Molina de Alba
	S. Ruhwinkel

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision revoking European patent No. 3150610. The patent is derived from European patent application No. 16183844.6, which was filed as a divisional application of European patent application No. 11708094.5.

II. The decision was based on the claims of a main request and twelve auxiliary requests.

Auxiliary request 3 on which the decision was based contains two independent claims, namely claims 1 and 9. Claim 1 reads as follows:

"*1. A maleate salt of 8-fluoro-2-{4-[(methylamino) methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd] indol-6-one for use in a method of inhibiting poly(ADP-ribose)polymerase (PARP) activity in a mammal, the method comprising administering to the mammal a therapeutically effective amount of said salt, wherein the salt is crystalline.*"

Claim 9 corresponds to claim 1 reformulated in the Swiss-type format.

The compound cited in claim 1 is generally known as rucaparib.

III. The decision under appeal mentions, *inter alia*, the following documents:

D1 US 2006/0074073 A1
D3 Declaration of P. Basford dated 21 November 2017
D4 WO 2008/114114 A2
D6 Declaration of J.B. Etter dated 11 February 2014
D8 Declaration of J.B. Etter dated 10 February 2018
D10 S. Byrn et al., Pharmaceutical Research, 12(7), 1995, 945-54
D14 P.L Gould, International Journal of Pharmaceutics, 33, 1986, 201-17
D15 US 7,268,126 B2

IV. In the decision, the opposition division had concluded, among other things, that the subject-matter of the main request and auxiliary requests 1 and 2 was not novel over D1, and that the subject-matter of auxiliary requests 3 to 12 did not involve an inventive step starting from D1 as the closest prior art.

V. The patent proprietor (appellant) filed an appeal against the decision. With its statement of grounds of appeal, the appellant refiled the claims of the main request and auxiliary requests 1 to 12 on which the decision was based.

VI. In its reply to the statement of grounds of appeal, the opponent (respondent) requested that the appeal be dismissed.

VII. The board scheduled oral proceedings, in line with the parties' requests, and gave its preliminary opinion on the case.

VIII. In response to the board's preliminary opinion, the appellant withdrew its main request and auxiliary requests 1 and 2 filed with the statement of grounds of appeal. It made auxiliary requests 3 to 12 filed with the statement of grounds of appeal its main request and auxiliary requests 1 to 9, respectively.

On the same day, the respondent withdrew its request for oral proceedings and informed the board that it would not be represented at the oral proceedings.

IX. The board cancelled the oral proceedings and continued the proceedings in writing.

X. The appellant's arguments relevant to the present decision can be summarised as follows.

D1 was the closest prior art. The correct starting point within D1 was the list of pharmaceutically acceptable salts in paragraph [0043] rather than the maleate salt disclosed in that list. This was also the approach in T 1126/19, the decision on the patent deriving from the earlier application. Starting from the list as a whole reflected the technical information provided to the skilled person in a more realistic manner. An analysis starting from the maleate salt gave undue weight to a option that was neither preferred nor exemplified in D1.

The subject-matter of claim 1 of the main request differed from the closest prior art in the selection of the maleate salt, the specification that the salt was crystalline and the use of the salt for inhibiting PARP activity in a mammal.

The crystalline maleate salt of rucaparib had an unexpected combination of properties that made it particularly suitable for tablet development. As shown in the patent and confirmed by declarations D3 and D6, the polymorphism of crystalline rucaparib maleate was limited. Only two polymorphs were found, neither of them being a hydrate or a solvate. Each polymorph could be prepared separately using different preparation methods. The crystalline salt showed good physical and polymorphic stability, was non-hygroscopic as well as resistant to hydration and had a high melting point. Furthermore, it could be crystallised easily and provided good-quality crystalline material. These advantageous properties and the fact that they made the crystalline salt suitable for development into a solid dosage form were not contested by the respondent. On the contrary, the respondent had filed with the notice of opposition declarations D3 and D6, which confirmed this position.

Therefore, the objective technical problem was the provision of a form of rucaparib having a suitable combination of properties for development into a solid dosage form.

The solution proposed in claim 1 was not obvious. The skilled person had no reason to choose maleate from the list of multiple salts proposed in paragraph [0043] of D1, which explicitly stated that phosphate and gluconate salts were preferred. It was common general knowledge that finding a salt suitable for developing a solid formulation was a challenging process which involved extensive experimentation and had an uncertain outcome (D14, D1, D10). For instance, rucaparib phosphate, which was a preferred salt according to paragraph [0043] of D1, presented multiple polymorphic

forms, three of them being hydrates and showing polymorphic instability (D15). Therefore, the skilled person could not expect to find that, out of the many salts proposed in paragraph [0043] of D1, maleate would have the properties required for developing a solid dosage form.

XI. The respondent's arguments relevant to the present decision can be summarised as follows.

The closest prior art was D1, in particular the maleate salt disclosed in paragraph [0043]. The disclosure of rucaparib maleate in D1 was enabling. Therefore, there was no reason not to take it as the starting point for the assessment of inventive step. According to established case law, a specific embodiment could be taken as the closest prior art. This was not limited to examples.

The subject-matter of claim 1 differed from the closest prior art in the specification that the rucaparib maleate salt was in crystalline form. The appellant had submitted that crystalline rucaparib maleate had advantages over other salts. However, the alleged advantages could not be taken into account for the definition of the objective technical problem because the closest prior art was rucaparib maleate. Therefore, the objective technical problem was the provision of a particular form of rucaparib maleate.

The choice of a crystalline form instead of an amorphous form was an obvious selection with no associated unexpected technical effects. Therefore, it could not involve an inventive step.

XII. The parties' requests made during the written proceedings and relevant to the present decision are the following.

- The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request or one of auxiliary requests 1 to 9, filed as auxiliary requests 3 to 12 with the statement of grounds of appeal.

- The respondent requested that the appeal be dismissed and the patent be revoked in its entirety.

Reasons for the Decision

1. Cancellation of the scheduled oral proceedings - right to be heard (Article 113(1) EPC)

The decision is rendered in written proceedings in accordance with Article 12(8) RPBA and Articles 113 and 116 EPC.

One week before the scheduled oral proceedings, the respondent withdrew its request for oral proceedings and informed the board that it would not be represented at the oral proceedings. The appellant requested oral proceedings only in the event that its requests were rejected. The board then cancelled the oral proceedings.

The board considers that there is no need for oral proceedings (Article 116(1) EPC), since the case is suitable to be decided on the basis of the parties' written submissions and the other documents on file. The facts and evidence on which the present decision is based were known to the respondent from the written proceedings and the respondent had sufficient opportunity to present its comments. With regard to the appellant, the present decision is in its favour and fulfils its request for the patent to be maintained in amended form on the basis of the claims of the main request. Therefore, the right of each party to be heard (Article 113(1) EPC) was not compromised by the cancellation of the oral proceedings.

2. Inventive step (Article 56 EPC) - claim 1 of the main request (auxiliary request 3 filed with the statement of grounds of appeal)

2.1 The patent (paragraphs [0002], [0004], [0005] and [0007]) is concerned with polymorphic forms of rucaparib salts which have suitable properties for manufacture and formulation as solid dosage forms. Rucaparib is an inhibitor of poly(ADP-ribose) polymerase (PARP), an enzyme which induces DNA repair in the event of moderate DNA damage. Therefore, rucaparib is used in cancer treatment to potentiate the DNA damage caused in cancer cells by radiotherapy or cytotoxic drugs.

Claim 1 of the main request is directed to crystalline rucaparib maleate.

2.2 It was common ground between the parties that document D1 was the closest prior art. D1 (paragraphs [0002], [0003] and [0006]) is directed to rucaparib or

rucaparib salts for use as chemosensitisers: due to the ability of rucaparib to inhibit PARP, it can be combined with chemotherapeutic agents to potentiate the effect of the latter in the treatment of cancer. Paragraph [0043] of D1 discloses a list of about 60 pharmaceutically acceptable salts that can be used for the invention. The list includes maleate although the preferred salts are phosphate and gluconate. According to D1, the salts can be prepared by the method defined in paragraph [0051].

2.2.1 Although the parties agreed that D1 was the closest prior art, they disagreed on whether inventive step should be assessed starting from the whole list of salts in paragraph [0043] or the specific disclosure of the maleate salt in that list.

2.2.2 The board agrees with the appellant that the starting point should be the whole list rather than the specific option of the maleate salt. As explained by the board in decision T 1126/19 (Reasons 6.2.2), which deals with the patent deriving from the earlier application, the disclosure of the closest prior art must be considered on the basis of its technical information without the latter being distorted or misrepresented by the knowledge of the invention (see also T 970/00, Reasons 4.1.2).

In paragraph [0043] of D1, the maleate salt of rucaparib is not singled out. D1 neither illustrates nor presents rucaparib maleate as a standalone embodiment. Paragraph [0043] is merely a notional disclosure, in which maleate is one option in a long list of possible options, but is not among the preferred options. The isolation of one of the numerous non-preferred options from paragraph [0043] to use it

as the closest prior art would distort the teaching of D1, giving an inappropriate weight to that option.

2.2.3 The respondent argued that the starting point should be rucaparib maleate because D1 discloses it in an enabling manner. The skilled person would be able to prepare rucaparib maleate without undue burden, e.g. using the method proposed in paragraph [0051] of D1. Therefore, rucaparib maleate should be considered equivalent to an example and, in accordance with established case law, it could thus be taken as the starting point for assessing inventive step.

Irrespective of whether the skilled person could prepare rucaparib maleate without undue burden, the disclosure of rucaparib maleate in D1 is merely notional. Rucaparib maleate is recited as one possible option among many options of the same value. D1 does not single out rucaparib maleate nor does it disclose the preparation thereof. Therefore, rucaparib maleate does not have the disclosure status of an example, a standalone embodiment or even a preferred option. Using rucaparib maleate as the starting point for assessing inventive step would distort the teaching of D1 and jeopardise an objective assessment of the technical contribution of the invention.

2.3 Starting from the list of pharmaceutically acceptable salts in paragraph [0043] of D1, it was undisputed that the subject-matter of claim 1 differs in the selection of maleate as the rucaparib salt and the requirement for the salt to be in crystalline form.

Contrary to the appellant's view, the use of a rucaparib salt for inhibiting PARP activity in a mammal is not an additional distinguishing feature. The

therapeutic use of rucaparib or rucaparib salts based on their ability to inhibit PARP is at the core of the invention of D1 (see above point 2.2).

2.4 As to the technical effect brought about by the above-mentioned differences, the patent shows that crystalline rucaparib maleate is particularly suitable for the preparation of solid dosage forms (paragraph [0060]). The patent identifies and characterises two crystalline forms of rucaparib maleate, which were designated as Form A and Form B (paragraphs [0069] to [0081], [0168], [0169], [0173] and Figures 1 to 8). Form A can be prepared by the method disclosed in paragraph [0158] while Form B can be prepared by the methods in paragraphs [0159] and [0160]. As shown by the DSC thermograms in Figures 2 and 7, both Form A and Form B have a single endothermic transition peak at high temperature, indicating that both crystalline forms have a high melting point and are neither hydrated nor solvated. In addition, Form B is non-hygroscopic and remains highly stable even under conditions of high temperature and humidity (paragraphs [0079] and [0173], and Figure 8). These properties make crystalline rucaparib maleate particulary suitable for developing a solid formulation. This was confirmed by declarations D3 (paragraphs [0011] to [0014]) and D6 (point 5), the content of which has not been disputed by the respondent.

2.5 Based on this technical effect, the board agrees with the appellant that the objective technical problem is the provision of a rucaparib form which has a suitable combination of properties for development into a solid dosage form.

The respondent contended that the objective technical problem should be defined as the provision of a particular form of rucaparib maleate. However, such a definition necessitates starting from rucaparib maleate as the closest prior art, an approach that is not correct, as the board has explained in points 2.2.2 and 2.2.3 above.

2.6 With regard to the issue of obviousness, there is no indication in the cited prior art that crystalline rucaparib maleate could have properties suitable for preparing a solid dosage form.

D1 does not deal with the formulation of rucaparib. It contains no teaching on the issue of whether any of the salts in the long list in paragraph [0043] might possibly be suitable for preparing a solid dosage form. As the board acknowledged in decision T 1126/19 (Reasons 6.7), it is common general knowledge that finding a salt of an active compound which has a balanced combination of properties making it suitable for a solid formulation is generally a difficult, semi-empirical task, which requires non-routine experimentation and has an uncertain outcome. Thus, the skilled person would need to study each of the salts in paragraph [0043] of D1 to assess: first, whether it is solid; second, how many solid forms it may adopt; and third, whether there are forms with properties suitable for a solid formulation.

In this context, the appellant cited documents D14, D10 and D8. D14 (abstract) is a document setting out the reasoning behind salt selection for basic drugs. In Figure 5, it summarises the different properties that need to be investigated for a suitable salt and the possible actions that may need to be taken to modulate

those properties. D10 is a review article, which states on page 945 (first sentence of the paragraph bridging the columns) that "*solid drug substances display a wide and largely unpredictable variety of solid state properties*". D8 is a declaration from an expert which explains in paragraph [0008] that finding a salt that is suitable for the solid formulation of a drug requires extensive experimentation.

It is also worth noting that rucaparib phosphate, which is one of the two preferred salts according to D1, is not a suitable salt for solid dosage forms. As pointed out by the appellant, D15 identified six crystalline forms and one amorphous form of rucaparib phosphate (column 3, lines 43 to 46), some of which were hydrated and showed polymorphic instability (column 16, lines 19 to 22 and 51 to 55; column 17, lines 33 to 35 and 63 to 65). Similarly, the patent (page 10, lines 12 and 13) and declarations D6 (point 5) and D3(paragraphs [0015] and [0016]) acknowledged that rucaparib phosphate is prone to hydration and is thus unsuitable for preparing solid dosage forms.

Therefore, the board concludes that the subject-matter of claim 1 involves an inventive step.

3. *Inventive step (Article 56 EPC) - claim 9 of the main request*

Independent claim 9 is directed to the use of crystalline rucaparib maleate for the manufacture of a medicament. The fact that rucaparib maleate is particularly suitable for preparing a solid dosage form also renders the use of claim 9 inventive.

4. Alternative inventive-step objection (Article 56 EPC)

The respondent submitted that D4 could also be taken as the closest prior art and that the situation was essentially the same as starting from D1. The respondent did not provide any further substantiation or a separate reasoning for this alternative objection.

The board agrees that the situation starting from D4 is essentially the same as when starting from D1. The main difference between these two documents is that D1 focuses on the treatment of cancer while D4 focuses on the treatment of hyperproliferative ophthalmic conditions. Like D1, D4 relates to the therapeutic use of rucaparib as a PARP inhibitor (page 5, lines 1 to 11) and discloses a list of pharmaceutically acceptable salts (page 7, lines 14 to 29) equivalent to the list provided in paragraph [0043] of D1.

Therefore, for the same reasons as when starting from D1, the subject-matter of claims 1 and 9 involves an inventive step if D4 is taken as the closest prior art.

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 in amended form on the basis of the claims of the main request, filed as auxiliary request 3 with the statement of grounds of appeal, and, if necessary, a description and drawings to be adapted thereto.

The Registrar: The Chairman:

A. Vottner A. Usuelli

Decision electronically authenticated