Internal distribution code:

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

Datasheet for the decision of 21 July 2023

Case Number: T 1126/19 - 3.3.07

Application Number: 11708094.5

Publication Number: 2534153

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

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.

Opponents:
Hamm&Wittkopp Patentanwälte PartmbB
Hexal AG

Headword:
Rucaparib camsylate/PFIZER

Relevant legal provisions:
EPC Art. 54, 56

Keyword:

Novelty - implicit disclosure (no)
Inventive step - non-obvious solution

Decisions cited:

T 0041/17, T 1555/12, T 0777/08, T 0970/00

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 1126/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 21 July 2023

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)
Appellant: (Opponent 2)	Hexal AG Industriestraße 25 83607 Holzkirchen (DE)
Representative:	Altmann Stößel Dick Patentanwälte PartG mbB Isartorplatz 1 80331 München (DE)
Party as of right: (Opponent 1)	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 4 February 2019 concerning maintenance of the European Patent No. 2534153 in amended form**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Molina de Alba
	M. Blasi

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's interlocutory decision rejecting the patent proprietor's main request (patent as granted) and finding that European patent No. 2534153 as amended in the form of auxiliary request 1 met the requirements of the EPC.

II. The amended version of the patent held allowable by the opposition division contained four independent claims, namely claims 1, 9, 10 and 13. They read as follows:

"*1. A camsylate salt of 8-fluoro-2-{4-[(methylamino) methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd] indol-6-one, wherein the salt is crystalline and has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) 12.2±0.2, 14.8±0.2 and 22.4±0.2, wherein said powder X-ray diffraction pattern is obtained using copper K-alpha$_1$ X-rays at a wavelength of 1.5406 Ångstroms.*"

"*9. A pharmaceutical composition comprising the salt of any of claims 1-8.*"

"*10. The salt of any of claims 1-8 or the pharmaceutical composition of claim 9 for use in a method of treating a mammalian disease condition mediated by poly(ADP-ribose) polymerase activity, the method comprising administering to a mammal in need thereof a therapeutically effective amount of said salt or said pharmaceutical composition.*"

"*13. A process for the preparation of a salt of any one of claims 1-8.*"

The heterocyclic component of the camsylate salt in claim 1 is also known as "rucaparib". Thus, claim 1 is directed to a crystalline rucaparib camsylate salt.

III. In the decision under appeal, the opposition division considered, among other things, that the subject-matter claimed by the patent as granted was not novel. In contrast, the subject-matter claimed by auxiliary request 1 was novel and inventive.

IV. The following documents are referred to in the present decision:

D1 US 2006/0074073 A1

D3 R. Liu, Water-Insoluble Drug Formation, Interpharm Press, 2000, 525 and 557-61

D4 P.H. Stahl et al., Handbook of Pharmaceutical Salts, Verlag Helvetica Chimica Acta, 2002, 167-8, 170-3 and 216-7

D5 R.J. Bastin et al., Organic Process Research & Development, 4, 2000, 427-35

D6 P.L. Gould, International Journal of Pharmaceutics, 33, 1986, 201-17

D7 J. Swarbrick et al., Encyclopedia of Pharmaceutical Technology, vol. 13, CRC Press, 1995, 453

D19 S.L. Morissette et al., Advanced Drug Delivery Reviews, 56, 2004, 275-300

D20 S.M. Berge et al., Journal of Pharmaceutical Sciences, 66(1), 1977, 1-20

D30 Declaration of J.B. Etter dated 16 November 2017

D33 Declaration of J.B. Etter dated 10 February 2018

D35 Y. Qiu et al., Solid Oral Dosage Forms: Pharmaceutical Theory and Practice, Elsevier, 2009, 75-86

D36 Experimental report by U. Griesser dated 8 June 2019

D37 K.B. Wiberg, Laboratory Technique in Organic Chemistry, Mc Graw Hill, 1960, v-vii and 104-6

D38 Declaration of G. Coquerel dated 30 November 2019

D39 R.C. Rowe et al., Handbook of Pharmaceutical Excipients, Pharmaceutical Press, 2009, 663-6, 685-94

D40 K. Kachrimanis et al., European Journal of Pharmaceutics and Biopharmaceutics, 64, 2006, 307-15

D41 P.M. Young et al., Pharmaceutical Development and Technology, 10, 2005, 249-59

V. The patent proprietor (appellant-patent proprietor) and opponent 2 (appellant-opponent) each filed an appeal against the opposition division's decision.

Opponent 1 is party as of right in these appeal proceedings.

VI. In its statement of grounds of appeal, the appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained as granted.

VII. With its statement of grounds of appeal, the appellant-opponent filed experimental report D36 to support its novelty and inventive-step objections based on D1.

VIII. With its reply to the appellant-opponent's statement of grounds of appeal, the appellant-patent proprietor

filed eight sets of claims as auxiliary requests and documents D37 and D38. Auxiliary request 1 was the set of claims allowed by the opposition division.

IX. The board scheduled oral proceedings in line with the appellants' requests. In a communication pursuant to Article 15(1) RPBA, the board gave its preliminary opinion on the case.

X. In response to the board's preliminary opinion, the appellant-patent proprietor withdrew its request that the patent be maintained as granted and made the request allowed by the opposition division its main request.

XI. The appellant-opponent then filed documents D39 to D41 to support an alleged lack of technical effect across the whole breadth of claim 9 of the new main request. It also argued that the PXRD pattern in Figure 18 of the patent showed that Form C of rucaparib camsylate exhibited the three peaks recited in claim 1 and therefore Form C was encompassed by the claim.

XII. Oral proceedings were held before the board. The party as of right was absent, as previously notified. At the end of the oral proceedings, the board announced its decision.

XIII. The appellant-opponent's arguments relevant to this decision can be summarised as follows.

Admittance issues

D36 should be admitted. Its filing was a direct reaction to the decision under appeal in which the opposition division decided that the salt claimed by

the request held allowable was not inevitably obtained by the method disclosed in paragraph [0051] of D1.

Documents D39 to D41 and the inventive-step objection against claim 9 based on these documents should be admitted. The documents represented common general knowledge and the objection derived from the interpretation of claim 1. Therefore, they could be filed at any time.

The argument that Form C of rucaparib camsylate exhibited the PXRD peaks of claim 1 should be admitted as a matter of claim interpretation. It was a direct reaction to the appellant-patent proprietor's allegation of the contrary.

Novelty

The salt of claim 1 was not novel. In paragraph [0043], D1 disclosed rucaparib camsylate as one of the salts of the invention. The salt could be prepared by the method disclosed in paragraph [0051]. D36 demonstrated that the preparation of rucaparib camsylate by the method in paragraph [0051] of D1 inevitably gave the salt of claim 1.

Interpretation of claim 1

Claim 1 did not define a pure polymorphic form. It encompassed mixtures of different solid forms, including amorphous forms, as taught in paragraph [0053] of the patent. The only limitation in claim 1 was that the three recited peaks were present in the PXRD pattern of the mixture. Therefore, claim 1 covered mixtures of polymorphic Forms A, B and/or C and mixtures containing amorphous forms. This

interpretation was technically sensible since a crystalline solid could contain impurities of other solid forms, including amorphous forms. This was confirmed by dependent claim 8, which was directed to a substantially pure polymorph, and by paragraph [0070], which referred to different degrees of crystallinity and purity in a sample.

Inventive step

The closest prior art was the disclosure of rucaparib camsylate in paragraph [0043] of D1 as an individualised embodiment.

If novel, the subject-matter of claim 1 differed from D1 in that the latter did not explicitly disclose the crystalline form of rucaparib camsylate having the three PXRD peaks recited in claim 1.

This difference did not result in any technical effect. The advantageous properties alleged by the appellant-patent proprietor could not be acknowledged because they were associated only with crystalline Form A of rucaparib S-camsylate. But claim 1 was not limited to that solid form. Amorphous forms or crystalline Form C containing impurities of Form A would also fall within the scope of claim 1. In addition, the hygroscopicity and stability of Form A had been shown for S-camsylate but not for R-camsylate. Therefore, the objective technical problem was the provision of an alternative solid form of rucaparib camsylate.

Even if all the salts falling within the scope of claim 1 were assumed to have low hygroscopicity and high stability, this effect would not be surprising. It was common general knowledge (D3, page 557) that

crystalline forms are generally less hygroscopic and more stable than amorphous ones. Therefore, starting from rucaparib camsylate in paragraph [0043] of D1, it was obvious to try and find crystalline forms that are less hygroscopic and more stable. The skilled person would have screened the salts in paragraph [0043] as an essential part of the development of solid oral dosage forms (D35, page 83, Figure 4.7). In particular, the skilled person would have tested the camsylate salt since camsylate was known to be suitable for solid drug formulation (D4, page 217, point 8.3.4; D5, page 433, left-hand column, first paragraph). As noted in T 777/08 (Headnote), a prejudice or an unexpected property was required for a polymorph to be patentable.

XIV. The appellant-patent proprietor's arguments relevant to this decision can be summarised as follows.

Admittance issues

Document D36 should not be admitted. A novelty objection against claim 1 of the request held allowable by the opposition division was raised for the first time at the oral proceedings before that division, and was not substantiated.

D39 to D41 and the related inventive-step objection against claim 9 should not be admitted. A claim equivalent to claim 9 was in the granted claims. Furthermore, claims 1 and 9 of the request allowed by the opposition division had been on file since December 2017. The documents and the objection could and should have been filed during the opposition proceedings.

The appellant-opponent's allegation that Form C of rucaparib camsylate exhibited the three peaks recited by claim 1 should not be admitted. The allegation was based on a technically flawed reinterpretation of Figure 18 of the patent at a late stage of the appeal proceedings.

Novelty

D1 did not anticipate the salt of claim 1. Rucaparib camsylate was one of the salts listed in paragraph [0043], but had not been prepared. There was no evidence on file that the preparation of rucaparib camsylate by the method in paragraph [0051] of D1 necessarily gave a crystalline solid, let alone one exhibiting the PXRD peaks required by claim 1. D36 did not provide evidence. Its experiments did not reproduce the method of paragraph [0051]: instead of the salt being prepared by acid-base neutralisation, an existing amorphous salt was recrystallised.

Interpretation of claim 1

Claim 1 had to be read in a technically sensible manner taking the description into account and noting that the description and the claims as granted were broader than claim 1. The patent was directed to crystalline polymorphic forms of rucaparib camsylate. Although the patent included mixtures of polymorphic forms (paragraph [0053]), claim 1 referred to "a" salt which was crystalline and "the" salt had a PXRD pattern comprising peaks at 12.2±0.2, 14.8±0.2 and 22.4±0.2. Therefore, claim 1 covered only salts that exhibited the three peaks or mixtures of salts each of which exhibited the three peaks. These conditions were only met by Forms A and B of rucaparib camsylate, which

could be S-camsylate, R-camsylate or a mixture of both; claim 1 did not encompass mixtures containing amorphous forms or Form C.

Inventive step

The closest prior art was the list of pharmaceutically acceptable salts in paragraph [0043] of D1. Singling out the camsylate salt from the list would distort the teaching of D1 (T 970/00, Reasons 4.1.2).

The subject-matter of claim 1 differed from that closest prior art in that the camsylate salt was selected and in that it was crystalline and showed the three PXRD peaks recited in claim 1. The technical effect produced by this difference was derivable from the patent and had been confirmed by declarations D30 and D33: the claimed salt was non-hygroscopic, anhydrous, soluble, unexpectedly stable, could be prepared in very pure form and had a good dissolution rate. These properties made it particularly suitable for formulating an oral dosage form.

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

Finding a salt with the balance of properties of the salt of claim 1 was not obvious. It was common general knowledge that the selection of a salt with the desired combination of properties was a difficult semi-empirical choice (see e.g. D6, D7, D19 and D20). Its finding required non-routine experimentation involving multiple options and choices. The salt of claim 1 had been approved and was commercially available as Rubraca®, a tablet based on Form A of rucaparib S-

camsylate. Documents D4 and D5 did not make the salt obvious either: camsylate salts were rare in approved pharmaceuticals.

XV. The parties' final requests relevant to this decision were as follows.

- The appellant-patent proprietor requested that the appellant-opponent's appeal be dismissed and that the decision under appeal be upheld (main request).

  It also requested that the following elements filed with the appellant-opponent's statement of grounds of appeal not be admitted into the proceedings:
    - document D36
    - the novelty objection based on D36
    - the new interpretation of claim 1 of the main request that it was not limited to a single camsylate salt having the three listed PXRD peaks.

  The appellant-patent proprietor further requested that documents D39, D40 and D41 and the new objections filed with the letter dated 24 January 2023 not be admitted into the appeal proceedings.

- The appellant-opponent requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

  It also requested that document D36 be admitted into the appeal proceedings, as well as the submissions on claim interpretation contained in the appellant-opponent's letters.

The party as of right did not make any request in these appeal proceedings.

Reasons for the Decision

1. *Admittance of D36 and the novelty objection based on it (Article 12(4) RPBA 2007)*

D36 was filed by the appellant-opponent with its statement of grounds of appeal, allegedly in reaction to the decision under appeal. D36 was intended to demonstrate that the salt of claim 1 allowed by the opposition division (claim 1 of the main request at hand) was inevitably obtained when using the method disclosed in paragraph [0051] of D1 for preparing the camsylate salt of paragraph [0043]. Therefore, the subject-matter of claim 1 as allowed by the opposition division lacked novelty over D1.

The board accepted the appellant-opponent's argument that D36 had been filed in response to the decision under appeal and therefore decided to admit it into the proceedings. As in the end D36 was not considered relevant for the assessment of novelty (point 4.3 below), the board sees no need to give more details on the reasons for admitting D36 and the novelty objection based on it under Article 12(4) RPBA 2007.

2. *Admittance of D39 to D41 and the appellant-opponent's change of case based on them (Article 13(2) RPBA 2020)*

With a letter dated 24 January 2023, the appellant-opponent filed documents D39 to D41 to support a new

inventive-step objection against claim 9 of the main request. The appellant-opponent argued (page 6, second full paragraph to page 7, fourth paragraph) that the composition of claim 9 did not exhibit the required low hygroscopicity across the whole breadth of the claim because claim 9 was open to including highly hygroscopic ingredients.

At the oral proceedings before the board, the appellant-opponent justified the filing of the new submissions as being based on the interpretation of claim 1 according to common general knowledge, represented by D39 to D41. Therefore, the objection and the documents were admissible at any stage of the proceedings.

This argument fails. Claim 9 had an equivalent claim in the patent as granted, namely claim 22. Furthermore, the sets of claims filed as auxiliary request 3 in December 2017 and as auxiliary request 1 in October 2018 contained the same claims 1 and 9 as the main request at hand. Therefore, an objection based on an alleged lack of effect across the whole breadth of the claim and the supporting documents D39 to D41 could and should have been filed during the opposition proceedings. The fact that the objection was based on claim interpretation and common general knowledge does not change this situation. No exceptional circumstances for the late submission were apparent. For these reasons, the board decided not to admit the inventive-step objection against claim 9 and documents D39 to D41 under Article 13(2) RPBA 2020 (applicable pursuant to Article 24 and Article 25(3) RPBA 2020).

3. Admittance of the appellant-opponent's amendment to its appeal case in view of the allegation that Form C exhibits the three PXRD peaks of claim 1 (Article 13(2) RPBA 2020)

With a letter dated 24 January 2023 (pages 4 and 5), the appellant-opponent submitted for the first time that Form C of rucaparib camsylate exhibited the three PXRD peaks of claim 1 of the main request. This submission was based on a new interpretation of the PXRD pattern of Form C in Figure 18 of the patent.

The appellant-opponent argued (letter of 24 January 2023, page 4, third paragraph) that its new submission was a reaction to the appellant-patent proprietor's allegation in its letter of 25 October 2022 that the peaks of claim 1 did not characterise amorphous forms or crystalline Form C.

The appellant-opponent's argument is not convincing. Claim 1 of the main request corresponds to claim 6 as granted. It had been filed as claim 1 of auxiliary request 3 in December 2017 and as claim 1 of auxiliary request 1 in October 2018. The decision under appeal was based on the latter claim request. The patent discloses in Table 15 (page 26) the list of PXRD peaks which characterise Form C of rucaparib camsylate. The list, which is based on the PXRD pattern in Figure 18, does not contain any peak at 22.4±0.2. This fact was never disputed in the appeal proceedings. The reinterpretation of Figure 18 of the patent to contest the correctness of the list in Table 15 was an amendment to the appellant-opponent's appeal case. However, there were no exceptional circumstances justified by cogent reasons for such an amendment of

case at a late stage of the appeal proceedings. Therefore, the board decided not to admit the amendment under Article 13(2) RPBA 2020 (applicable pursuant to Article 24 and Article 25(3) RPBA 2020).

4. Novelty (Article 54 EPC) - claim 1 of the main request

4.1 The appellant-opponent argued that the salt of claim 1 was not novel over D1. D1 (paragraph [0002]) was directed to rucaparib or rucaparib salts and their use as chemosensitisers. Paragraph [0043] of D1 disclosed pharmaceutically acceptable salts that could be used for the invention. They included camsylate. The salts could be prepared by the method defined in paragraph [0051]. According to the appellant-opponent, the preparation of rucaparib camsylate by the method of paragraph [0051] necessarily resulted in the salt of claim 1. This was allegedly evidenced by D36, an experimental report in which rucaparib camsylate had been prepared by the method of paragraph [0051] of D1.

4.2 The board cannot subscribe to the appellant-opponent's position.

Paragraph [0051] of D1 discloses the preparation of rucaparib salts by treating the basic form of rucaparib with an equivalent amount of an acid in an aqueous or organic solvent, e.g. methanol or ethanol. The solid salt can be obtained by evaporation of the solvent. As an alternative, paragraph [0051] proposes precipitating the salt from a solution of the free base of rucaparib in an organic solvent by adding an acid.

Thus, paragraph [0051] describes a method for preparing solid salts by acid-base neutralisation with subsequent or concomitant precipitation. The method could be used

for preparing each of the pharmaceutically acceptable salts recited in paragraph [0043] of D1, including camsylate. However, D1 does not illustrate the preparation of any of those salts - the preferred salts, phosphate and gluconate, were used but their preparation was not disclosed either. Even less does D1 characterise the solid structure of the precipitates that would be obtained by the method of paragraph [0051]. Therefore, the board agrees with the appellant-patent proprietor that it cannot be concluded from D1 that the preparation of rucaparib camsylate by the method of paragraph [0051] necessarily results in a solid crystalline form, even less one that exhibits the PXRD peaks recited in claim 1.

4.3 The appellant-opponent filed experimental report D36 to demonstrate that the preparation of rucaparib camsylate by the method in paragraph [0051] of D1 did indeed lead to the salt of claim 1. The relevant experiments were disclosed in section 3.3 (pages 7 and 8) of D36. However, as noted by the appellant-patent proprietor, the experiments in section 3.3 of D36 do not reproduce the method of paragraph [0051]. Instead of preparing rucaparib camsylate by acid-base neutralisation and characterising the resulting precipitate, the experiments in D36 recrystallise an existing amorphous form of rucaparib camsylate. For this reason alone, D36 cannot prove that the preparation of rucaparib camsylate by the method of D1 necessarily results in the salt of claim 1.

Documents D37 and D38 were filed by the appellant-patent proprietor in reaction to the filing of D36 by the appellant-opponent. The three documents were admitted at the oral proceedings before the board (minutes, page 3). Nevertheless, considering the

outcome of the analysis of D36 in the paragraph above, the board does not need to discuss the admittance and the content of D37 and D38 in this decision.

4.4 Therefore, the subject-matter of claim 1 is novel and claim 1 meets the requirements of Article 54 EPC.

5. Interpretation of claim 1 of the main request

5.1 Claim 1 is directed to a camsylate salt of rucaparib which is crystalline and has a PXRD pattern comprising the characterising peaks 12.2±0.2, 14.8±0.2 and 22.4±0.2.

The appellants interpreted claim 1 in different ways. According to the appellant-patent proprietor, the salt of claim 1 encompasses only a pure polymorphic form characterised by the three peaks, or a mixture of polymorphic forms in which each polymorphic form is characterised by the three peaks. In contrast, the appellant-opponent maintained that claim 1 covers any mixture of solid forms, provided that the three characterising peaks can be identified in the PXRD pattern of the mixture. This includes mixtures containing forms that are not characterised by the three peaks, in particular Form C and amorphous forms of rucaparib camsylate.

5.2 As set out at the oral proceedings (minutes, page 2, second paragraph), the board does not agree with either of the two interpretations.

On the one hand, claim 1 is directed to a crystalline salt of rucaparib camsylate. Such a wording is not open to the addition of further components. Therefore, contrary to the appellant-opponent's interpretation,

the salt of claim 1 does not contain substantial amounts of amorphous forms. This interpretation is not precluded by the broader disclosure in paragraph [0053] of the patent. As noted by the appellant-patent proprietor, the description and the claims as granted are broader than claim 1 of the main request.

On the other hand, claim 1 is directed to a crystalline salt. It is not limited to a pure polymorphic form of a crystalline salt characterised by the three peaks or to mixtures of polymorphic forms in which each form is characterised by the three peaks. The crystalline salt of claim 1 may be composed of a mixture of any crystalline forms of rucaparib camsylate, provided that the PXRD pattern of the mixture exhibits the peaks 12.2±0.2, 14.8±0.2 and 22.4±0.2. This view is also in line with dependent claim 8, in which it is specified that the salt is a substantially pure polymorph of S-camsylate Form A, and with paragraph [0053] of the description, which teaches that solid forms may contain more than one polymorphic form or may exist in a substantially pure form of a single polymorph. Therefore, contrary to the appellant-patent proprietor's interpretation, although the salt must exhibit the three peaks, this is not required for each of the crystalline polymorphic forms present in the salt. It suffices that one of the polymorphs exhibits the three peaks, and that it is present in an amount sufficient for the three peaks to be identifiable in the PXRD pattern of the salt.

In this connection, the board notes that the patent identified and characterised three crystalline polymorphs of rucaparib camsylate, Forms A, B and C. It was undisputed that Forms A and B of both the S- and R-camsylate exhibit the peaks required by claim 1 (see

patent: Table 9 and Figure 10; Table 27 and Figure 23; Figure 15). In contrast, Form C does not exhibit a peak at 22.4±0.2 (Table 15 and Figure 18). Therefore, the board concludes that the salt of claim 1 contains Forms A and/or B and, additionally, it may contain Form C. This conclusion is in line with the sentence in paragraph [0053] of the patent according to which where a solid form comprises two or more polymorphs, the X-ray diffraction pattern will typically have peaks characteristic of each of the individual polymorphs. For each form, the camsylate salt may have R-, S- or both configurations, as illustrated in Examples 17 to 20 of the patent.

6. Inventive step (Article 56 EPC) - claim 1 of the main request

6.1 The patent (paragraphs [0001] to [0005]) is directed to new polymorphic forms of rucaparib salts. Rucaparib is an inhibitor of PARP, an enzyme which induces DNA repair in the event of moderate DNA damage. Therefore, rucaparib is used in cancer therapy to potentiate the effect of radiotherapy or cytotoxic drugs which cause DNA damage.

The invention is based on the finding that crystalline rucaparib camsylate is particularly suitable for the preparation of solid dosage forms due to its physical stability and low hygroscopicity (paragraph [0045]). The patent identified three crystalline forms of rucaparib camsylate, which were designated as Forms A, B and C (paragraph [0054]). Form A could be prepared by the methods disclosed in paragraphs [0146], [0147] or [0165]. This form appeared to be non-hygroscopic and highly stable (paragraphs [0073] and [0158]). Form C could be prepared from Form A (paragraph [0160]). With

regard to Form B, the patent showed its PXRD pattern in Figure 15.

6.2 It was common ground between the parties that document D1 was the closest prior art. As set out in point 4.1 above, D1 relates to the use of rucaparib as a chemosensitiser: it is combined with chemotherapeutic agents for potentiating the effect of the latter in the treatment of cancer. In paragraph [0043], D1 discloses a list of about 60 pharmaceutically acceptable salts of rucaparib that can be used in therapy. The list includes camsylate, although the preferred salts are phosphate and gluconate.

6.2.1 The parties agreed that D1 was the closest prior art but disagreed on whether inventive step should be assessed starting from the whole list in paragraph [0043] or the specific disclosure of the camsylate salt in that paragraph.

6.2.2 The board agrees with the appellant-patent proprietor (reply to the appellant-opponent's statement of grounds of appeal, point 7.2) that the starting point should be the whole list rather than the specific option of the camsylate salt. As explained in decision T 970/00 (Reasons 4.1.2), cited by the appellant-patent proprietor, the disclosure of the closest prior art must be considered on the basis of its technical information, without distorting or misrepresenting it by the knowledge of the invention.

In paragraph [0043] of D1, the camsylate salt of rucaparib is not singled out. D1 neither illustrates the camsylate salt of rucaparib nor presents it as a standalone embodiment. Paragraph [0043] is merely a notional disclosure in which camsylate is one among a

long list of possible options, but not among the preferred ones. The isolation of one of the non-preferred options from paragraph [0043] would distort the teaching of D1, putting an inappropriate weight on that option.

6.3 Starting from the list of pharmaceutically acceptable salts in paragraph [0043] of D1, the subject-matter of claim 1 differs in the selection of camsylate as the rucaparib salt and the additional requirements that the salt be crystalline and show three specific PXRD peaks.

6.4 As to the technical effect brought about by these differences, the board set out in point 5.2 above (last paragraph) that claim 1 defines a rucaparib salt that contains Forms A and/or B, and that, additionally, it may contain Form C.

6.4.1 The patent shows in paragraphs [0073] and [0158] (application as filed, page 36, lines 15 to 18 and page 86, lines 16 to 20) that Form A of rucaparib camsylate is non-hygroscopic and highly stable even under conditions of high temperature and humidity. These properties were confirmed in declarations D30 and D33, the content of which was not disputed by the appellant-opponent.

According to D30 (paragraph [0004]), rucaparib camsylate can be prepared as R- or S-camsylate and both stereoisomers have an equivalent crystalline Form A. Therefore, the physico-chemical properties of the R- and S-camsylate salts should be identical. D30 (paragraphs [0007], [0008], [0010] and [0011]) confirmed that rucaparib S-camsylate Form A is highly stable and soluble. Similar statements can be found in D33 (paragraphs [0013] to [0021]).

On the relationship between Form A and the other two polymorphs of rucaparib camsylate identified in the patent, D30 (paragraphs [0003] and [0005]) states that Form A is thermodynamically the most stable of the three forms and that it is preferentially formed during crystallisation. Therefore, Form A can be easily crystallised to provide highly crystalline material in a controlled manner and a very pure form, preventing the formation of Form C. Form A is also highly soluble and dissolves rapidly (D30, paragraphs [0010] and [0011]).

Form C is an anhydrous polymorph which converts to Form A in solvent-mediated systems (D30, paragraph [0003]). Therefore, the presence of Form C can easily be avoided but, if present, Form C would not impair the anhydrous properties of crystalline rucaparib camsylate for solid oral formulations.

As to Form B, D30 states that Form A and Form B repeatedly and reversibly convert into each other by heating within the range 128 to 140°C (D30, paragraph [0003]). In other words, Form B exists only at high temperatures incompatible with storage or therapeutic conditions; at temperatures lower than 128°C, Form B converts into Form A.

The low number of crystalline polymorphs of rucaparib camsylate, and the relationship between these polymorphs and the physical properties of Forms A and C, the only existing forms in use, make crystalline rucaparib camsylate particularly suitable for the formulation of a solid dosage form.

6.4.2 The appellant-opponent argued that because claim 1 encompasses salt mixtures that could contain only low amounts of Form A, the advantageous properties shown for Form A would not arise across the whole breadth of claim 1. Therefore, a technical effect could not be considered for the formulation of the objective technical problem. This was the situation in the case on which decision T 1555/12 (Reasons 5.2 and 7.3) is based.

However, as explained above, Form B does not exist at in-use temperatures. The only possible components in the salt of claim 1 when present in a solid formulation are Forms A and C. Contrary to the case on which T 1555/12 is based, the less-stable form of crystalline rucaparib camsylate, i.e. Form C, also confers advantageous properties on the formulation since it is anhydrous. Furthermore, the only polymorph to which Form C can evolve is Form A. The evolution of Form C to the most advantageous Form A can only improve the properties of the formulation even further. Therefore, the crystalline rucaparib camsylate according to claim 1 is particularly suitable for the formulation of oral dosage forms of rucaparib.

The appellant-opponent also argued that the advantageous effects of Form A had only been shown for the S-camsylate. Nevertheless, as stated in D30 (paragraph [0004]), the S- and R-camsylates have equivalent Forms A and are expected to have the same physical properties.

6.5 Consequently, the board agrees with the objective technical problem proposed by the appellant-patent proprietor, i.e. the provision of a solid form of

rucaparib having a suitable combination of properties for development into a solid dosage form.

6.6 The board is satisfied that the subject-mater of claim 1 solves this problem, as explained above in the context of the technical effect achieved by the difference from the closest prior art.

6.7 On the issue of obviousness, D1 does not deal with the formulation of solid forms of rucaparib. It contains no teaching on whether any of the salts in the long list of paragraph [0043] might possibly be suitable for preparing an oral solid formulation. The skilled person would have needed to study each of the salts for assessing: first, whether they are solid; second, how many solid forms they may adopt; and third, whether there are forms with properties suitable for a solid formulation.

As noted by the appellant-patent proprietor, it is common general knowledge that finding a salt of an active compound which has a balance of properties making it suitable for an oral solid formulation is generally a difficult semi-empirical task which requires non-routine experimentation and has an uncertain outcome. This is confirmed for instance by the encyclopaedia excerpt D7 (page 453, introduction) or review articles D20 (page 1, paragraph bridging the two columns, and page 16, conclusions), D19 (page 277, left-hand column, first paragraph and page 286, left-hand column, first paragraph) and D6 (page 201, introduction, and page 213, conclusion). Therefore, the salt of claim 1 was not obvious from D1.

6.8 The board does not find a pointer to the salt of claim 1 in any of the combination documents cited by

the appellant-opponent either. The appellant-opponent's arguments were mainly based on the assumption that the closest prior art was the camsylate salt rather than the whole list of paragraph [0043] of D1. As set out in point 6.2.2 above, this assumption was wrong.

The appellant-opponent cited D3 and D35 to show that it was common general knowledge that crystalline forms are less hygroscopic and more stable than amorphous forms (D3, page 557), and that searching for stable solid forms is part of the development of solid oral dosage forms (D35, page 83, Figure 4.7). This can be accepted by the board. However, starting from the list of salts in paragraph [0043], it goes beyond routine work to find whether any of the listed salts, if at all, exhibit the set of properties required for solid oral dosage forms.

The appellant-opponent also cited D4 (page 217, point 8.3.4) and D5 (page 433, left-hand column, first paragraph) to show that camsylate was known to be a salt that could be used for the formulation of drugs. This can also be accepted by the board. But the teaching that camsylate can be used for the formulation of drugs is nothing more than the teaching of paragraph [0043] of D1, which lists salts that are pharmaceutically acceptable. It has already been explained that this paragraph does not render the salt of claim 1 obvious.

The appellant-opponent also referred to the headnote of decision T 777/08. In that decision, in particular in point 2 of the headnote, the competent board dealt with the situation in which the starting point for assessing inventive step was the amorphous form of a drug, and the skilled person was seeking a solid form with

improved filterability and drying characteristics. That is clearly not the situation at hand, in which the skilled person does not start from the amorphous form of the salt but has a long list of possible salts to investigate.

The appellant-opponent cited T 41/17 (Reasons 1.2 to 1.4) too. In this decision the competent board held that finding the most stable crystalline form of sorafenib tosylate was a matter of routine screening. In that case, the skilled person started from a known crystalline form of sorafenib tosylate and sought a more stable form. Such a situation is again not comparable with the one at hand, in which the skilled person has to start from a long list of possible salts.

6.9 Therefore, the salt of claim 1 involves an inventive step and claim 1 meets the requirements of Article 56 EPC.

7. Independent claims 9, 10 and 13 are directed to a pharmaceutical composition comprising the salt of claim 1, a use of the salt of claim 1, or a process for the preparation of the salt of claim 1, respectively. As the salt of claim 1 is novel and inventive, the subject-matter of claims 9, 10 and 13 is also considered to be novel and inventive. As a consequence, the board agrees with the conclusion reached by the opposition division that the main request in these appeal proceedings is allowable.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated