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Datasheet for the decision of 8 April 2025

Case Number: T 2424/22 - 3.3.07

Application Number: 11849974.8

Publication Number: 2654736

IPC: A61K9/28, A61K9/20, A61K31/519, A61P35/00

Language of the proceedings: EN

Title of invention:
NOVEL PHARMACEUTICAL COMPOSITION

Patent Proprietor:
Novartis AG

Opponents:
Generics [UK] Limited
Teva Pharmaceutical Industries Ltd.

Headword:
Novel Pharmaceutical Composition/NOVARTIS

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 12(2), 12(3), 12(4)

Keyword:
Inventive step - main request and auxiliary requests 1 to 4 (no)
Amendment to case - argument (no)

Decisions cited:
G 0002/21

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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

Case Number: T 2424/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 8 April 2025

Appellant: (Opponent 1)	Generics [UK] Limited Building 4, Trident Place Mosquito Way Hatfield Hertfordshire AL10 9UL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Appellant: (Opponent 2)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. Tel Aviv 6944020 (IL)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Respondent: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Aera A/S Niels Hemmingsens Gade 10, 5th Floor 1153 Copenhagen K (DK)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 5 October 2022 concerning maintenance of the European Patent No. 2654736 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	A. Jimenez

Summary of Facts and Submissions

I. European patent 2 654 736 (hereinafter "the patent") was granted on the basis of 15 claims.

II. An opposition was filed against the patent on the grounds that its subject-matter lacked inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. The opposition division took the interlocutory decision that, on the basis of the amended main request filed on 30 August 2021, the patent met the requirements of the EPC.

IV. The decision of the opposition division, posted on 5 October 2022, cited *inter alia* the following documents:

D2: WO 2011/038380 A2
D7: Biopharmaceutics and Clinical Pharmacokinetics, Milo Gibaldi, 4th Edition, 1991, page 51
D8: Pharmaceutical Dosage Forms: Tablets, Volume 1, 2nd Edition, ed. by Herbert A. Lieberman, Leon Lachman and Joseph B. Schwartz, 1989, pages 1-24, 34-37 and 54
D18: Polymorphism in Pharmaceutical solids, 2nd Edition, ed. by Harry G. Brittain, 2009, pages 436-437
D19: Polymorphism in the Pharmaceutical Industry, ed. by Rolf Hilfiker, 2006, pages 224, 227, 228 and 333 to 336
D23: Infante JR et al., J Clin Oncol, 28, no. 15, 15 May 2010, suppl 2503
D27: Product development report for trametinib DMSO solvate, GSK, July 2012, pages 1, 8 and 29 to 35

D30: Polymorphism in Pharmaceutical Solids, ed. by Harry G. Brittain, 1999, Chapter 8 "Effects of Pharmaceutical Processing on Drug Polymorphs and Solvates", pages 338 to 343
D31: Pharmaceutical Dosage Forms: Tablets, vol 1, 2nd Edition, ed. by Lieberman, Lachman and Schwartz, 1989, pages 195 to 198
D32: Modern Pharmaceutics, Volume 1, Basic Principles and Systems, ed. by Alexander T. Florence and Juergen Siepmann, 2010, pages 265 to 266
D33: Abe *et al.*, ACS Med Chem Lett, 2011, 2, 320-324

V. The opposition division decided in particular as follows:

(a) The main request fulfilled the requirements of Articles 123(2), 123(3), 84 and 83 EPC.

(b) The claimed tablets were not directly and unambiguously disclosed in the priority document, so that the claimed priority was not valid.

(c) The main request met the requirements of Article 56 EPC starting from D2 as closest prior art.

VI. Opponents 1 and 2 (appellants 1 and 2) lodged an appeal against the above decision of the opposition division.

VII. With their reply to the appellants' statements setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the amended main request filed during opposition proceedings on 30 August 2021 (main request), and on the basis of auxiliary requests 1 to 4 filed therewith. Auxiliary request 1 and 3 were newly filed and auxiliary requests 2 and 4 corresponded to auxiliary

requests 1 and 2 field during the opposition proceedings on 30 August 2021.

VIII. The content of the claims upon which the present decision is based can be illustrated as follows:

Claim 1 of the main request read as follows:

"1. A pharmaceutical tablet comprising:
a) a drug which is N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide solvate in an amount selected from: 0.5 mg, 1 mg, and 2 mg, by weight of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide;
wherein,
b) the tablet contains from 25% to 89% by weight of one or more excipients, where the excipients contain about 5% by weight or less of water; and
c) the amount of unsolvated drug does not exceed about 20%; and
d) the drug particles are micronized; and
e) the tablet is prepared by direct compression or dry granulation"

Claim 1 of auxiliary request 1 was identical to claim 1 of the main request.

Claim 1 of auxiliary request 2 corresponded to claim 1 of the main request wherein feature e) was limited to "e) the tablet is prepared by direct compression".

Claim 1 of auxiliary request 3 was identical to claim 1 of auxiliary request 2.

Auxiliary request 4 contained a single claim corresponding to claim 15 of the patent which read as follows:

"15. A process for preparing pharmaceutical tablets containing a drug which is N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide dimethyl sulfoxide solvate in an amount selected from: 0.5 mg, 1 mg, and 2 mg by weight of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl} acetamide, which process comprises the steps of:

admixing:

N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl} acetamide dimethyl sulfoxide solvate,
one or more excipients, where the excipients contain about 5% by weight or less of water, and further excipients,
to form a mixture; and
compressing the mixture into tablets;

provided:

each tablet contains N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}

acetamide dimethyl sulfoxide solvate in an amount selected from:

0,5 mg, 1 mg, and 2 mg by weight of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6, 7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide; each tablet contains from 25% to 89% by weight of one or more excipients, where the excipients contain about 5% by weight or less of water; and the amount of unsolvated drug does not exceed about 20%; and the drug particles are micronized."

IX. Oral proceedings were held before the Board on 8 April 2025.

X. The appellants 1 and 2 requested that the decision under appeal be set aside and the patent be revoked.

XI. The respondent requested that the appeal be dismissed, *i.e.* that the patent be maintained as amended during first instance proceedings (main request), or that the patent be maintained on the basis of one of the auxiliary requests 1 to 4 submitted with the reply to the statements setting out the grounds of appeal.

The respondent further requested that the objection of appellant 2 based on the absence of a technical effect be held inadmissible.

XII. The arguments of the appellants, as far as relevant for the present decision, can be summarised as follows:

(a) The main request did not comply with Article 56 EPC. The subject-matter of claim 1 of the main request differed from the closest prior art D2

(example 5) in the amount trametinib, the amount of water in the excipients, the drug particles being micronized, and the preparation method (direct compression or dry granulation versus wet granulation).

Appellant 2 disputed that a faster dissolution had been demonstrated as resulting from the preparation method. Appellant 2 argued that this argument was to be admitted into the appeal proceedings. According to appellant 2, the present composition was an obvious solution to the objective technical problem of providing an alternative composition of trametinib solvate.

Appellant 1 based its argument on the technical effect of the preparation method alleged by the respondent.

Both appellants considered that the present composition represented an obvious solution to the more ambitious problem of providing a solid dosage form of trametinib DMSO solvate with improved dissolution properties.

The amount of trametinib, the amount of water in the excipients, and the micronization of the drug particles were not linked to any technical effect and were obvious from the prior art (see D23, abstract; D8 page 54; D7 page 51 and D8 page 5). Regarding the preparation method, the skilled person would have known from D33 and common general knowledge that maintenance of trametinib in its DMSO solvate form was required for bioavailability and good dissolution. The skilled person, who would have routinely monitored the stability of

trametinib DMSO solvate, would consequently have identified the issue of desolvation under humid atmosphere linked to the step of wet granulation. The replacement of wet granulation by a method avoiding humid conditions such as dry granulation or direct compression was therefore obvious.

(b) Auxiliary requests 1 to 4 did not involve an inventive step for the same reasons as the main request.

XIII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) The main request met the requirement of Article 56 EPC. The subject-matter of claim 1 of the main request differed from the closest prior art D2 (example 5) in the amount trametinib, the amount of water in the excipients, the drug particles being micronized, and the preparation method (direct compression or dry granulation versus wet granulation).

The data provided in the patent and D27 substantiated that the preparation method used provided a faster dissolution. The argument of appellant 2 regarding the absence of a technical effect should not be admitted into the appeal proceedings.

The objective technical problem resided therefore in the provision of a solid dosage form of trametinib DMSO solvate with improved dissolution properties.

None of the cited documents provided an indication that wet granulation used in D2 would lead to stability issues and hence slower dissolution of trametinib DMSO. D33 did not represent common general knowledge. Moreover D33 only stated that the DMSO solvate was preferred but did not provide any indication regarding stability or dissolution. The further prior art documents cited by the appellants in support of common general knowledge made only conditional statements. The skilled person would therefore not have been motivated to perform stability measurements as argued by the appellants. Accordingly, the skilled person would have had no reasonable expectation of success of improving the dissolution properties of the composition by modifying the preparation method of D2.

(d) Auxiliary requests 1 to 4 involved an inventive step for at least the same reasons as the main request.

Reasons for the Decision

Main request

1. Inventive step - independent claim 1

1.1 Closest prior art and distinguishing features

1.1.1 The main request relates to a pharmaceutical tablet comprising trametinib DMSO solvate ("compound A"), said tablet for use in the treatment of cancer and a process for the preparation of a pharmaceutical tablet comprising trametinib DMSO solvate. The main purpose of the patent is the provision of a solid oral

pharmaceutical dosage form of trametinib DMSO solvate with desirable pharmacodynamic profile (see paragraph [0006] of the patent).

1.1.2 In agreement with all parties, the Board considers D2 as closest prior art document and example 5 thereof as closest starting point. In this context, it was undisputed that, since the claimed priority was not valid, D2 belongs to the prior art relevant under Article 54(2) EPC.

1.1.3 D2 relates to a method of treating cancer using a combination comprising trametinib or a solvate thereof (see claim 1, structure (I) and page 1 lines 4-12 of D2). Example 5 of D2 discloses tablets comprising 5 mg trametinib DMSO solvate and excipients, prepared by wet granulation.

1.1.4 It was also undisputed amongst the parties that the tablet of claim 1 of the main request differs from the one of example 5 of D2 in the following features:
(i) the amount trametinib (0.5, 1, 2 mg in claim 1; 5mg of solvate in D2 corresponding to around 4.4 mg of trametinib),
(ii) the amount of water in the excipients (25% - 89% by weight of excipients containing 5% by weight or less of water in claim 1; D2 is silent on the amount of water in the excipients),
(iii) the drug particles being micronized (D2 is silent on micronization), and
(iv) the preparation method (direct compression or dry granulation in claim 1; wet granulation in D2).

1.2 Technical effects

1.2.1 No technical effect was brought forward by the respondent for features (i) to (iii). A faster dissolution resulting from feature (iv) was relied upon by the respondent and acknowledged in the impugned decision based on the results of the patent (see paragraph [0084] and table 12) and of D27.

1.2.2 The Board observes that the fact that D27 could be taken into account in accordance with G 2/21 was not disputed.

1.2.3 Appellant 2 contested that the data provided in D27 would show that this effect was directly linked to the method of preparation. According to appellant 2, the comparative compositions prepared by wet granulation in said document (WG-A to WG-E in table 8) contain excipients which are not present in the compositions prepared by direct compression (DC-A to DC-E in table 9) nor in example 5 of D2. It could therefore not be excluded that the effect observed would be linked to the nature of the excipients instead of feature (iv), *i.e.* the method of preparation.

1.2.4 In this context, the respondent requested that the argument of appellant 2 based on the lack of substantiation of the technical effect not be admitted into the appeal proceedings. According to the respondent, appellant 2 merely repeated in their statement of the grounds of appeal (see paragraphs 6.4 and 6.5) their arguments already provided in the opposition proceedings and would hence not have substantiated why the decision of the opposition division in this respect was wrong. Furthermore, the remaining part of the argumentation of appellant 2 was

based on the formulation of the objective technical problem chosen by the opposition division (see paragraph 6.3 of the statement of the grounds of appeal of appellant 2), so that appellant 2 admitted *de facto* the presence of the alleged technical effect.

As stated by appellant 2, their statement of the grounds of appeal (see paragraphs 6.3 to 6.5) addressed the impugned decision by (i) explaining that the formulation of the objective technical problem chosen by the opposition division was wrong and then (ii) still addressing the reasoning of the opposition division based on the objective technical problem as formulated in the decision. As argued by appellant 2, it was therefore clear why they considered that the decision of the opposition division was wrong, including in acknowledging the alleged technical effect. Accordingly, the statement of the grounds of appeal of appellant 2 met in this respect the requirement of Article 12(3) RPBA. Moreover, the arguments provided by appellant in this context had already been submitted in the opposition proceedings, as acknowledged by the respondent themselves. They did therefore not represent an amendment to the case of appellant 2 (Article 12(2) and 12(4) RPBA).

Accordingly, the Board considers that the argument of appellant 2 regarding the absence of a technical effect forms part of the appeal proceedings.

1.2.5 The Board observes that the data provided in Table 12 of the patent as well as under point 4.3.1 of D27 indeed substantiate that in an humid environment such as during wet granulation, desolvation of trametinib DMSO solvate occurs. Since, as explained in paragraph [0084] of the patent, trametinib is known as being

significantly less soluble than trametinib DMSO solvate, depending on the degree of desolvation an associated reduced dissolution is expected.

1.2.6 Regarding the difference in excipients used between the compositions WG-A to WG-E on the one hand and the compositions DC-A to DC-E on the other hand (D27), the respondent argued in line with the impugned decision that the different preparation methods (wet granulation *versus* direct compression) would require different classes of excipients.

Furthermore, the respondent explained during oral proceedings that the difference in excipients in the compositions of D27 could not be considered to induce the faster dissolution observed for the compositions according to the main request (DC-A to DC-E), for the following reasons:

- Both types of compositions (prepared by direct compression or wet granulation) contained sodium lauryl sulfate (SLS), croscarmellose and magnesium stearate in identical amounts (when present; see Tables 8 and 9 of D27). These excipients did hence not differ between both types of compositions.

- The composition WG-E differed from the composition WG-A merely in that it did not contain MCC (see Table 8 of D27). Figure 8 of D27 revealed a faster dissolution rate for WG-E (about 75% at 20 minutes, Figure 8) than for WG-A (about 62% at 20 minutes, Figure 8). Hence MCC actually negatively impacted the dissolution rate of the compositions. Since the DC-compositions (according to the main request) contained more MCC than the corresponding WG-compositions, the improved dissolution rate

observed for the DC-compositions (compare *e.g.* DC-A re WG-A, DC-D re WG-D or DC-E re WG-F in Figures 8 and 9) could not be attributed to the amount of MCC.

- The composition WG-E differed from the composition DC-A in that it contained HPMC (5% w/w) while DC-A contained MCC (30% w/w). The significantly faster dissolution rate observed for DC-A (around 82% at 20 minutes, Figure 9) compared to WG-E (around 75% at 20 minutes, Figure 8) despite the absence of MCC in WG-E could not be explained by the sole presence of HPMC. It followed that the improvement in dissolution rate observed for the DC-compositions (compare *e.g.* DC-A re WG-A, DC-D re WG-D or DC-E re WG-F in Figures 8 and 9) could also not be attributed to the sole presence of HPMC.

1.2.7 The Board agrees with these conclusions and considers that the improved dissolution rate observed in D27 can be attributed to the preparation methods of the compositions according to the invention avoiding any humid environment (direct compression or dry granulation re wet granulation).

1.3 Objective technical problem

The objective technical problem resides therefore in the provision of a solid dosage form of trametinib DMSO solvate with improved dissolution properties.

1.4 Obviousness

1.4.1 The lack of inventiveness of features (i) to (iii) was not questioned. The Board agrees with the appellants that they are not linked to any technical effect and

are obvious from the prior art (see D23, abstract; D8 page 54; D7 page 51 and D8 page 5).

1.4.2 Regarding feature (iv), as argued by the appellants, the skilled person willing to improve the dissolution profile of the tablets of example 5 of D2 would have acquired knowledge about trametinib and its DMSO solvate form.

1.4.3 The skilled person would have learned from D33 that the most stable polymorphic form of trametinib (compound 8b in D33) had poor bioavailability (see "poor oral exposure", page 322, right hand column, 2nd paragraph) and that the DMSO solvate form restored the bioavailability.

In this context the respondent argued that D33 was not representative of common general knowledge (regular research article) and did thus not form part of the mental baggage of the skilled person. The Board considers that, even if D33 does indeed not represent common general knowledge, it is a scientific article from a renown journal investigating several inhibitors of MEK activity, in particular trametinib DMSO solvate stated therein as having been "selected for development" (see page 322, right hand column, 2nd paragraph, last sentence). A skilled person working in the field of inhibitors of MEK activity and willing to improve a composition containing trametinib DMSO would have consulted D33.

Bioavailability and dissolution were commonly known as interrelated (see *e.g.* D18 pages 436 and 437). Furthermore, it was also common general knowledge that solvates are usually more soluble than unsolvated or hydrated forms (see D32, page 266, 2nd paragraph, third

sentence). The skilled person would consequently have recognised that the DMSO solvate of trametinib had improved dissolution properties compared to the unsolvated form. The skilled person would therefore have known from D33 and common general knowledge that maintenance of trametinib in its DMSO solvate form was required for bioavailability and good dissolution.

1.4.4 As further brought forward by the appellants, the skilled person would have been aware from its common general knowledge of the reduced stability of solvates due to the risk of desolvation under humid atmosphere including during wet granulation (see *inter alia* D32, pages 265-266, in particular page 266, 2nd paragraph; D19, page 228, 1st full paragraph; and D30, pages 339-340).

1.4.5 It follows that, the skilled person would have routinely monitored the stability of trametinib DMSO solvate during the preparation according to example 5 of D2. By doing so, the skilled person would have observed desolvation upon wet granulation and understood from common general knowledge (see above 1.4.4) that it was linked to the presence of water. In consequence, the skilled person willing to maintain the solvate form of trametinib, would have replaced wet granulation by dry granulation or in particular direct compression, known from common general knowledge to avoid humid conditions and drying cycles (see D31, page 198, 2nd full paragraph).

1.4.6 Contrary to the respondent's opinion, the skilled person would therefore have had a reasonable expectation to avoid desolvation and hence improve the dissolution profile by replacing wet granulation by dry granulation or direct compression in example 5 of D2.

1.5 Consequently, claim 1 of the main request does not comply with the requirement of Article 56 EPC.

Auxiliary requests 1 to 4

2. Inventive step

2.1 Claim 1 of auxiliary request 1 is identical to claim 1 of the main request, so that it does not comply with the requirement of Article 56 EPC for the same reasons.

2.2 Claim 1 of auxiliary request 2 and claim 1 of auxiliary request 3 correspond to claim 1 of the main request which has been limited to a preparation by direct compression. The same reasoning as developed for the main request applies therefore *mutatis mutandis* and auxiliary requests 2 and 3 do not meet the requirement of Article 56 EPC.

2.3 Auxiliary request 4 has been limited to the process claim of the main request (claim 15 of the main request and of the patent). Claim 1 of auxiliary request 4 is directed to the preparation of a tablet defined by the features a) to d) of claim 1 of the main request comprising the steps of admixing the components of the tablet to form a mixture and compressing the mixture into tablets. These process steps are standard in the preparation of tablets, in particular by dry granulation or direct compression. The respondent did not provide any arguments in support of an inventive step of these specific process steps and relied on the same arguments as provided for claim 1 of the main request. It follows that claim 1 of auxiliary request 4 relates to the preparation of an obvious product (see reasons provided for claim 1 of the main request) by

standard commonly known process steps. As a result, auxiliary request 4 does not fulfil the requirement of Article 56 EPC.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

A. Vottner A. Usuelli

Decision electronically authenticated