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Datasheet for the decision of 21 October 2022

Case Number: T 0147/20 - 3.3.07

Application Number: 13730070.3

Publication Number: 2854768

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Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITIONS OF PEMETREXED

Patent Proprietor:
Fresenius Kabi Oncology Limited

Opponents:
Larsen & Birkeholm A/S
Generics (U.K.) Limited
Cooke, Richard

Headword:
Pemetrexed/FRESENIUS

Relevant legal provisions:
EPC Art. 123(2), 83, 87(1), 54, 56
RPBA 2020 Art. 12(2)

Keyword:

Amendments - allowable (yes)
Sufficiency of disclosure - (yes)
Priority - partial priority (no)
Novelty - main request- auxiliary requests 1-15 (no) - auxiliary request 16 (yes)
Inventive step - (yes)

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Case Number: T 0147/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 21 October 2022

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Appellant: (Opponent 3)	Cooke, Richard Elkington and Fife LLP Patents Department 3-4 Holborn Circus London EC1N 2HA (GB)
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Party as of right: (Opponent 2)	Generics (U.K.) Limited Station Close Potters Bar Hertfordshire EN6 1TL (GB)

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 29 November 2019 concerning maintenance of the European Patent No. 2854768 in amended form.**

Composition of the Board:

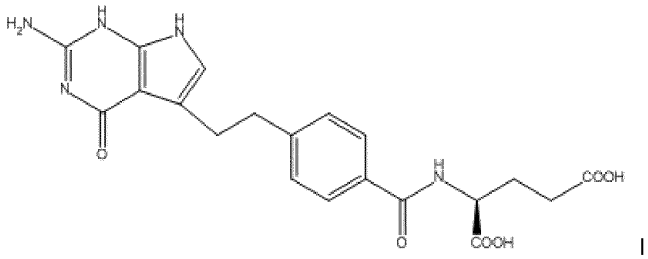
Chairman A. Usuelli
Members: M. Steendijk
P. Guntz

Summary of Facts and Submissions

I. European patent 2 854 768 ("the patent") was granted on the basis of ten claims.

Independent claim 1 as granted related to:

"A pharmaceutical composition comprising Pemetrexed represented by formula I,



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a pharmaceutically acceptable organic amine and optionally containing one or more pharmaceutically acceptable excipients, wherein the organic amine is tromethamine and wherein tromethamine is present in amounts of 40 to 90% by weight of Pemetrexed of formula I, wherein said pharmaceutical composition is produced by a method comprising mixing Pemetrexed according to formula I in a solvent with tromethamine and optionally one or more pharmaceutically acceptable excipients, wherein the solvent is purged with an inert gas before, during or after mixing."

Claim 2 as granted defined:

"A pharmaceutical composition according to claim 1, which is a liquid ready to use solution formulation or a lyophilized pharmaceutical composition for parenteral administration comprising an inert gas."

Claim 8 as granted defined:

"A process for preparing a ready to use solution formulation of claim 2 comprising the steps:
a) taking a suitable quantity of water for injection in vessel and adding a required quantity of tromethamine to the water for injection
b) adding organic solvent to the above mixture and mixing uniformly
c) adding Pemetrexed to the above mixture and dissolving and adjusting the pH to about 6-8
d) filtering the solution and filling in vials
e) stoppering and sealing the vials,
wherein the process comprises the step of purging inert gas into the solution to minimize the dissolved oxygen content."

II. Three oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed. The patent proprietor and opponents 01 and 03 filed appeals against the interlocutory decision of the opposition division that the patent as amended in accordance with auxiliary request 1 met the requirements of the EPC.

The decision was based on the main request relating to the patent as granted and auxiliary request 1 filed during the oral proceedings held on 28 October 2019.

In claim 1 of this auxiliary request 1 the definition of the process by which the composition is produced in claim 1 as granted was amended as follows:

"wherein said pharmaceutical composition is produced by a method comprising mixing Pemetrexed according to formula I in a solvent with tromethamine and optionally one or more pharmaceutically acceptable excipients, and adjusting the pH to 6-8, wherein the solvent is purged with an inert gas before, during or after mixing." [underlining by the Board]

The opposition division cited *inter alia* the following documents:

D4: WO 2010/030598
D8: Handbook of Pharmaceutical Salts (2002)
D29: WO 2014/167585
D30: IS 050051 (priority application for D29)
D34: Experimental report E3 (13 December 2016)

The opposition division arrived at the following conclusions:

(a) The patent did not define subject-matter extending beyond the content of the application as originally filed.

(b) The patent provided the skilled person in the claims, the general description and the examples sufficient guidance how to prepare the claimed compositions. The opponents had not provided evidence to the contrary.

(c) Documents D4 and D15 did not disclose the subject-matter of the claims as granted.

Document D29 described in its example 1 Formulations C and H, which fell under the scope of

claim 1 as granted. The patent did not validly claim priority for the subject-matter in question. Document D29 therefore represented prior art under Article 54(3) EPC. Claim 1 of the patent as granted therefore lacked novelty.

(d) Auxiliary request 1 complied with Articles 123(2), 84 and 83 EPC. The defined subject-matter was new over document D29, because the subject-matter in question was entitled to the claimed priority.

Document D4 represented the closest prior art. The most relevant specific compositions in document D4 were examples 4-5. The composition of claim 1 of auxiliary request 1 differed from these examples in the use of pemetrexed diacid instead of pemetrexed disodium and the addition of tromethamine in an amount of 40-90% by weight of pemetrexed. In view of the results reported in example 4 of the patent and tables 1-4 of document D34 the problem to be solved was the provision of further stable pemetrexed compositions. The claimed subject-matter was not obvious to the person skilled in the art as solution, because the prior art did not suggest that the defined compositions prepared from pemetrexed with tromethamine in the defined concentrations achieved the demonstrated stability.

III. With the statement of grounds of appeal the appellant-patent proprietor filed auxiliary request 1, which corresponds to auxiliary request 1 on which the decision under appeal was based.

With the reply to the appeals by opponents 01 and 03 the appellant-patent proprietor filed auxiliary requests 2-28.

Claim 1 of auxiliary request 2 corresponds to claim 1 as granted in which the composition is further defined as "free of the disodium salt of Pemetrexed". Claim 1 of auxiliary request 3 combines this amendment with the pH adjustment of auxiliary request 1.

Claim 1 of auxiliary request 4 corresponds to claim 1 of auxiliary request 2 further comprising a proviso aimed at excluding Formulation C of document D29. Claim 1 of auxiliary request 5 combines this amendment with the pH adjustment of auxiliary request 1.

Claim 1 of auxiliary request 6 corresponds to claim 1 of auxiliary request 2 further comprising a proviso aimed at excluding Formulations C and D of document D29. Claim 1 of auxiliary request 7 combines this amendment with the pH adjustment of auxiliary request 1.

Claim 1 of auxiliary request 8 corresponds to claim 1 of the main request further comprising a proviso aimed at excluding the composition of document D29 comprising *about* 0.5 mg tromethamine per mg pemetrexed. In claim 1 of auxiliary request 9 the term "about" is omitted.

In claim 1 of auxiliary requests 10 and 11 the provisos of auxiliary requests 8 and 9 are combined with the pH adjustment of auxiliary request 1.

In claim 1 of auxiliary requests 12 and 13 the provisos of auxiliary requests 8 and 9 are combined with the amendments of auxiliary request 6. In claim 1 of auxiliary requests 14 and 15 the amendments of auxiliary requests 12 and 13 are further combined with the pH adjustment of auxiliary request 1.

Auxiliary request 16 limits claim 1 to the lyophilized composition of claim 2 as granted and formulates in claim 4 a process for the preparation of a composition still defined in the terms of claim 1 as granted.

IV. In a communication pursuant to Article 15(1) RPBA issued on 17 December 2021 the Board expressed *inter alia* doubt whether the subject-matter of claim 1 of the main request was new in view of document D29.

V. With the consent of the parties oral proceedings were held on 21 October 2022 in the form of a videoconference. The oral proceedings were attended by the appellant-patent proprietor and appellant-opponent 01.

VI. The arguments of the appellant-patent proprietor relevant to the present decision are summarized as follows:

- The subject-matter of the patent as granted was limited to an originally disclosed preferred embodiment.

- The objection of lack of sufficient disclosure freshly raised by appellant-opponent 03 should not be admitted. Anyway, the objection of insufficient disclosure lacked substantiation.

- The patent enjoyed partial priority with respect to compositions comprising tromethamine in an amount of 60% by weight of pemetrexed.

  Document D29 did not disclose the selection of tromethamine in amounts of 0.50 and 0.60 mg

tromethamine per mg pemetrexed. Document D29 did further not describe the combination of this selected subject-matter with the feature of purging with an inert gas as defined in claim 1 as granted, its combination with the feature of pH adjustment as additionally defined in claim 1 of auxiliary request 1 nor its combination with the feature of a lyophilized formulation as additionally defined in claim 1 of auxiliary request 16.

- Document D4 merely mentioned tromethamine in a list of optional excipients without disclosure of any particular amount. Formulations C and H of example 1 in document D29 did not unambiguously disclose compositions with an amount of tromethamine as defined in claim 1 as granted.

- The defined amounts of tromethamine used with the pemetrexed diacid allowed for surprising stability of the defined pemetrexed formulations. The stabilizing effect was supported by the examples of the patent. Document D34 further demonstrated that the use of tromethamine resulted in lower impurity levels compared to the use of other salt-forming bases. No prior art suggested the stabilizing effect of the defined amounts of tromethamine in compositions prepared from pemetrexed diacid.

VII. The arguments of the appellant-opponents relevant to the present decision are summarized as follows:

- Claim 1 as granted resulted from multiple selections, including the selection of tromethamine as organic amine.

- The patent failed to teach how the defined composition comprising the acidic pemetrexed and the basic tromethamine can be prepared in the form of an aqueous solution, if at the same time the composition is characterized by the presence of pemetrexed as free acid.

- Document D29 validly claimed priority from document D30 and represented prior art under Article 54(3) EPC with respect to the patent, which did not enjoy the priority as claimed.

  Document D29 described in a general section of its disclosure preferred embodiments involving the use of tromethamine by itself as organic base for preparing pemetrexed compositions and mentioned in this context amounts of 0.50 and 0.60 mg tromethamine per mg pemetrexed. The product-by-process feature in claim 1 as granted concerning the purging of the solvent with an inert gas could not be considered to distinguish the resulting product. Document D29 therefore anticipated the subject-matter of claim 1 as granted.

  The additional feature of claim 1 of auxiliary request 1 concerning the pH adjustment lacked clarity and could as a product-by-process feature not be considered to distinguish the resulting product from the mentioned preferred embodiments described in document D29.

  Auxiliary requests 2-16 did not define any further distinguishing feature with respect to document D29, which also disclosed the lyophilisation of the described compositions.

- The subject-matter of the patent also lacked novelty in view of document D4, which disclosed tromethamine as an alkaline excipient in pemetrexed compositions taking into account that the required amount of tromethamine to fully deprotonate the pemetrexed diacid was 56.7%. Moreover, the subject-matter of the patent lacked novelty in view of the disclosure of Formulations C and H in example 1 of document D29.

- The subject-matter of the patent could only differ from the teaching of document D4 in the definition of the amounts of tromethamine. In accordance with the patent the water-soluble anionic form of premetrexed resulted from the combination of the diacid with tromethamine instead of the use of the disodium salt in examples 4 and 5 of document D4. Document D34 showed neither a surprising effect related to the defined amount of tromethamine nor any particular advantage over other alkalising agents. As no evidence of an effect with respect to the compositions of document D4 had been demonstrated, the patent merely provided for an alternative premetrexed composition. Tromethamine was well known as a suitable salt-forming agent for acidic drugs. Moreover, document D4 itself already referred to tromethamine as suitable alkalising agent for premetrexed compositions. The amount of tromethamine defined in claim 1 as granted evidently corresponded to the amount required for solubilisation of premetrexed by salt-formation. Accordingly the claimed subject-matter was obvious to the skilled person.

VIII. No substantive submissions were received from opponent 02 (party as of right pursuant to Article 107 EPC).

IX. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained as granted.

As an auxiliary measure, the appellant-patent proprietor requested that the patent be maintained on the basis of auxiliary request 1 as filed with its statement of grounds of appeal or on the basis of one of auxiliary requests 2-28 as filed with its reply to the appeals by opponents 01 and 03.

The appellant-patent proprietor further requested that an objection concerning the compliance of the patent with the requirement of sufficient disclosure raised by the appellant-opponent 03 for the first time in its statement of grounds of appeal be disregarded.

X. Appellant-opponent 01 and appellant-opponent 03, requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Reasons for the Decision

1. Main request

1.1 Basis in the application as filed

Claim 1 as granted relates to the embodiment of original claim 1 as defined in the original dependent claims 21 and 22 with specification of the amount of the organic amine corresponding to the originally described suitable amounts (see page 6 lines 14-15) and definition of tromethamine, which is described as the most preferred organic amine in the application as filed (see page 6 lines 12-13 and page 9 lines 11-13).

The Board therefore agrees with the decision under appeal that claim 1 as granted does not comprise subject-matter extending beyond the content of the application as filed.

1.2 Sufficiency

In its statement of grounds of appeal (see page 2, section 3) the appellant-opponent 03 argued that the patent failed to teach how an aqueous composition comprising pemetrexed as free acid could be prepared from combining pemetrexed diacid with tromethamine, which as a base should actually cause the deprotonation of the pemetrexed diacid.

The Board observes that appellant-opponent 03 thereby essentially maintained its objection of lack of sufficient disclosure as raised before the opposition division (see minutes of the oral proceedings of 28 October 2019 page 2 section 3; see also notice of opposition from opponent O3 paragraphs 08-12). Accordingly, this objection is part of the appeal proceedings under Article 12(1),(2) RPBA.

Regarding the merits of the argument the Board agrees with the decision under appeal (see pages 4-6, section 15, in particular 15.4) that a lack of sufficient disclosure has not been convincingly demonstrated. In this context the Board notes that the skilled person is well aware of the deprotonation of acids in aqueous solutions depending on the pH of the solution and the pKa of the acid and that the skilled person understands the claim accordingly.

1.3 Novelty in view of document D29

1.3.1 The application from which the patent derives was filed on 30 May 2013 claiming priority of 30 May 2012. Document D29 relates to an international patent application filed on 14 April 2014 and published on 16 October 2014 claiming priority of 12 April 2013 from document D30.
It was not in dispute that document D29 represents prior art under Article 54(3) EPC in as far as document D29 validly claims the priority from document D30 and in as far as the patent does at the same time not enjoy the priority as claimed.

1.3.2 The appellant-patent proprietor did not contest that the priority document relied upon for the patent does not specifically disclose the range for the relative amount of tromethamine of 40-90% as defined in claim 1 as granted. However, the appellant-patent proprietor maintained that the claimed subject-matter enjoyed partial priority for compositions comprising 60 wt% tromethamine relative to pemetrexed in view of examples 3-8 of the priority document. The relative amount of 60 wt% for the tromethamine described in these examples was not inextricably linked to the other features of the examples.

The Board observes that examples 3-8 of the priority document disclose pemetrexed compositions containing 60 wt% tromethamine relative to pemetrexed only in the context of specific compositions. These compositions consist of the ingredients listed in examples 3-8, including hydrochloric acid if needed for a pH of 6-8. In contrast, claim 1 of the patent as granted defines the compositions in an open-ended manner by use of the term "comprising". The appellant-patent proprietor has

not convincingly explained that the amount of 60 w% of tromethamine relative to pemetrexed in examples 3-8 of the priority document is not structurally or functionally linked to the further constitution of the exemplified compositions. To the contrary, it would seem evident to the skilled person that in the specific compositions of examples 3-8 of the priority document the amount of tromethamine relative to the pemetrexed affects the level of deprotonation of the pemetrexed and the amount of hydrochloric acid possibly needed to achieve the pH of 6-8. In line with the established jurisprudence regarding intermediate generalisations (see Case Law of the Boards of Appeal of the EPO, 10th Edition 2022, II.E.1.9) the board therefore considers that claim 1 as granted does not enjoy partial priority under Article 87(1) EPC for the claimed compositions comprising 60 w% of tromethamine relative to pemetrexed in general.

1.3.3 Document D29 discloses pharmaceutical formulations prepared from the diacid form of pemetrexed and an organic base selected from diethanolamine, tris(hydroxymethyl)aminomethane (*i.e.* tromethamine) and meglumine or a combination thereof, which form addition salts in solution (see D29, page 3, lines 24-30).

Document D29 further includes (see page 4, lines 31-34) the following passage:

"In certain preferred embodiments the organic base is tris(hydroxymethyl)aminomethane by itself, suitably in an amount as mentioned above, such as about 0.50 or 0.60 mg per mg of pemetrexed diacid, or about 1.0, 1.20, 1.22, 1.4, 1.48, or 1.5 mg per mg of pemetrexed diacid."[underlining by the Board]

The same information is presented in document D30 (see in particular page 4, lines 20-22). Accordingly, this information represents prior art under Article 54(3) EPC with respect to the claimed subject-matter which does not enjoy the priority as claimed.

1.3.4 The Board acknowledges that the cited passage from document D29 concerning tromethamine is part of a paragraph which presents further useful embodiments involving meglumina by itself and diethanolamine by itself (see D29 page 4 line 34 to page 5 line 2). However, the cited passage of document D29 highlights embodiments involving tromethamine by itself as preferred and specifically mentions in that context *inter alia* amounts of 0.50 or 0.60 mg tromethamine per mg of pemetrexed diacid. Accordingly, document D29 already anticipated the selection of tromethamine and specifically disclosed its use in amounts of 0.50 and 0.60 mg per mg of pemetrexed diacid in the preparation of a pharmaceutical composition as covered by the definition in claim 1 of the patent as granted.

Claim 1 as granted further defines that the composition is produced by a method comprising mixing pemetrexed in a solvent with tromethamine in which the solvent is purged with an inert gas before, during or after the mixing. In accordance with established jurisprudence (see Case Law of the Boards of Appeal, *supra*, I.C.5.2.7 and II.A.7.2) the process feature in such a product-by-process claim only contributes to the novelty of a product claim insofar as it is demonstrated to give rise to a distinct and identifiable characteristic of the product. Whilst the use of an inert gas during the preparation of the composition may contribute to the reduction of oxidative degradation, it has not been demonstrated that without any further measure, such as

subsequent containment, the mere purging of the solvent as defined in claim 1 as granted necessarily results in an identifiable characteristic of the product that distinguishes it from the product of the cited embodiment from document D29.

Accordingly, the Board concludes that claim 1 as granted lacks novelty in view of document D29.

2. Auxiliary request 1

Claim 1 of auxiliary request 1 additionally defines with respect to claim 1 of the main request the feature that the method for producing the composition comprises adjusting the pH to 6-8.

Due to the formulation in terms of a product-by-process using the term "comprises" this feature only requires that the composition is obtainable by a process including a step in which the pH is adjusted to 6-8. As further adjustment of the pH during potential subsequent steps is not excluded, claim 1 of auxiliary request 1 cannot be considered to define any further identifiable characteristic of the product that distinguishes it from the product of the preferred embodiment described in document D29. Contrary to the finding in the decision under appeal (see page 11, section 21) this interpretation of the claim is in line with the technical meaning of the used expressions, including the chosen formulation as a product-by-process feature, and does not involve any misreading of the claim.

The Board therefore concludes that claim 1 of auxiliary request 1 also lacks novelty in view of document D29.

3. Auxiliary requests 2-15

The amendments in accordance with auxiliary requests 2-15 do not exclude the compositions comprising tromethamine in amounts of 0.50 and 0.60 mg per mg of pemetrexed diacid as described in document D29.

These auxiliary requests do therefore not comply with the requirement of novelty in view of document D29 for the same reasons as set out above in sections 1.3 and 2 with respect to claim 1 as granted and claim 1 of auxiliary request 1.

4. Auxiliary request 16

4.1 Basis in the application as filed

Claim 1 of auxiliary request 16 additionally defines with respect to claim 1 as granted that the composition is a lyophilized pharmaceutical composition for parenteral administration comprising an inert gas in line with claim 2 of the application as originally filed. Claim 4 of auxiliary request corresponds to claim 8 as granted, which is merely re-drafted as an independent claim.

Auxiliary request 16 thus complies with Article 123(2) EPC.

4.2 Sufficiency

The amendments in accordance with auxiliary request 16 do not affect the Board's considerations regarding sufficiency of disclosure as set out above in section 1.2 with respect to the claims as granted.

Auxiliary request 16 thus complies with Article 83 EPC.

4.3 Novelty

4.3.1 Novelty in view of document D29

The passage of page 4 in document D29 discussed above in section 1.3.3 describes embodiments involving tromethamine as preferred, but does not disclose the amounts 0.50 or 0.60 mg tromethamine per mg of pemetrexed as particularly preferred and does not present a pointer towards any particular type of formulation for these embodiments.

Document D29 further teaches that the described pemetrexed formulations may be provided as liquids or lyophilized powders, but does not express a definite preference for the one or the other type of formulation (see page 2, lines 5-9; see also page 2 line 24 to page 3, line 6 and page 6, lines 23-24).

Accordingly, document D29 does not specifically link the compositions comprising tromethamine in amounts of 0.50 and 0.60 mg per mg of pemetrexed diacid discussed, for instance by a relevant pointer or preference, to the formulation in the form of a lyophilized composition. The Board therefore concludes that document D29 does not describe the compositions comprising tromethamine in amounts of 0.50 and 0.60 mg per mg of pemetrexed diacid in the form of a lyophilized composition as defined in claim 1 of auxiliary request 16.

Without prejudice to the question whether Formulations C and H of example 1 in document D29 unambiguously disclose compositions with an amount of tromethamine as

defined in claim 1 as granted the Board further observes that these Formulations C and H are presented in document D29 as liquid concentrates and not as lyophilized compositions as defined in claim 1 of auxiliary request 16.

4.3.2 Novelty in view of document D4

Document D4 merely mentions tromethamine in a list of optional excipients without disclosure of any particular amount to be used (see D4 page 18 lines 1-14). Document D4 does further not require an amount of an alkaline substance suitable for the complete salt-formation of the pemetrexed diacid, let alone the specific amount of 56.7% of tromethamine. The Board therefore considers that document D4 does not disclose the relative amount of the tromethamine as defined in claim 1 of auxiliary request 16.

4.3.3 Accordingly, the Board concludes that auxiliary request 16 complies with the requirement of novelty.

4.4 Inventive step

4.4.1 The appellant-opponents as well as the appellant-patent proprietor relied on document D4 as closest prior art.

Document D4 relates to pharmaceutical formulations with improved stability comprising pemetrexed or its salts or solvates in the form of ready-to-use solutions or in lyophilized forms (see D4 page 6 lines 3-6). The document provides a list of optional excipients for injectable formulations and mentions in this context tromethamine amongst a variety of other alkaline substances (see D4 page 18 lines 1-14). In examples 1 and 2 pemetrexed is dissolved in an aqueous mannitol

solution or in water and lyophilised. In examples 4 and 5 pemetrexed disodium is dissolved in an aqueous mannitol solution, subjected to lyophilisation and tested for stability.

4.4.2 The subject-matter defined in accordance with auxiliary request 16 differs from the teaching in document D1 in the defined amounts of tromethamine used to prepare the compositions. In this context the Board notes that the skilled person is well aware that the deprotonation of acids in an aqueous environment depends on the pH of the solution. As document D4 and the patent both aim at solutions with similar pH (see D4, page 19, lines 18-19; see patent paragraph [0031]), these solutions will comprise equal amounts of deprotonated pemetrexed.

4.4.3 Experiment 2 reported in document D34 involves a comparison between a composition prepared from premetrexed with tromethamine as defined in claim 1 of auxiliary request 16 and compositions prepared with sodium carbonate or sodium bicarbonate instead of tromethamine (see document D34, page 3, Table 3). The results of this experiment 2 show lower initial impurities after lyophilization in the thromethamine composition than in the comparative compositions prepared with sodium carbonate or sodium bicarbonate (see document D34, page 3, Table 4).

The appellant-opponents contest the relevance of these results because (i) document D34 does not provide a comparison with the mannitol comprising compositions exemplified in document D4, (ii) document D34 does not identify the bulking agents used in the experiment, (iii) the results of experiment 2 in document D34 only concern the initial impurities and not the stability over time, (iv) document D34 only provides data for

lyophilized compositions and (v) document D29 shows that in aqueous solutions the defined amounts of tromethamine result in lower stability than when higher amounts are used.

The Board does not consider the appellant-opponents' objections as to the relevance of the mentioned results convincing. Experiment 2 of document D34 compares a composition prepared from pemetrexed diacid with tromethamine as defined in claim 1 of the patent with compositions in which only the tromethamine is replaced with sodium salts as alkalising agents to show specifically the effect of the tromethamine. In line with the decision under appeal the Board therefore considers that the results of experiment 2 reported in document D34 support the assumption that the used tromethamine contributes in the claimed compositions to the stability of the pemetrexed.

Accordingly, the problem to be solved may be defined as the provision of a stabilized pemetrexed composition.

4.4.4 Document D4 itself only discloses examples of compositions prepared from the disodium salt and mentions tromethamine in a long list of optional excipients without suggestion of any stabilizing effect from its use. From for instance document D8 tromethamine was furhter well known as salt-forming agent for drugs with acidic groups (see D8, page 331, figure 2). However, no prior art suggests any stabilizing effect from the use of tromethamine in the preparation of compositions as defined in accordance with auxiliary request 16. The claimed subject-matter would therefore not seem obvious to the skilled person as solution to the defined technical problem.

4.4.5 Accordingly, the Board concludes that auxiliary request 16 also complies with the requirement of inventive step.

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 auxiliary request 16, submitted with the proprietor's reply to the opponents' statements of grounds of appeal, and a description to be adapted where necessary.

The Registrar: The Chairman:

L. Malécot-Grob A. Usuelli

Decision electronically authenticated