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Datasheet for the decision of 12 October 2016

Case Number: T 2114/13 - 3.3.01

Application Number: 08005934.8

Publication Number: 1956015

IPC: C07D277/56, A61K31/426, A61P19/06

Language of the proceedings: EN

Title of invention:
Polymorph of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid and method of producing the same

Patent Proprietor:
Teijin Limited

Headword:
Stable polymorphic form of febuxostat/TEIJIN

Relevant legal provisions:
EPC Art. 115, 56

Keyword:
Observations by third parties - relevant (no)
Inventive step - unexpected improvement shown - reasonable expectation of success (no)

Decisions cited:
T 0777/08

Catchword:

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Case Number: T 2114/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 12 October 2016

Appellant: (Patent Proprietor)	Teijin Limited 6-7 Minamihommachi 1-chome Chuo-ku Osaka-shi, Osaka 541-0054 (JP)
Representative:	Hallybone, Huw George Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 23 July 2013 revoking European patent No. 1956015 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	G. Seufert
	L. Bühler

Summary of Facts and Submissions

I. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division revoking the European patent No. 1 956 015, which is based on the European patent application 08005934.8 filed as a divisional application of the European patent application 99957054.2 and claiming priority of 19 June 1998.

II. Independent claims 1 and 3 of the patent in suit as granted read as follows:

"1. A polymorph, Crystal C, of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, which shows a x-ray powder diffraction pattern having characteristic peaks at a reflection angle 2θ of 6.62, 10.82, 13.36, 15.52, 16.74, 17.40, 18.00, 18.70, 20.16, 20.62, 21.90, 23.50, 24.78, 25.18, 34.08, 36.72 and 38.04°."

"3. A method of producing crystal C according to claims 1 or 2 of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, which comprises heating 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid suspended in a mixed solvent of methanol and water in the presence of a small amount of crystal C of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid."

III. The present decision refers to the following documents:

(1) M. Hasegawa, Heterocycles, Vol. 47, No. 2, 1998, pages 857 to 864

(10) X-ray powder diffraction spectrum of mixture of crystalline Forms A and C, submitted by the

patentee with letter dated 16 April 2010

(11) Experimental evidence filed by the appellant with letter dated 26 June 2009

(13) S. Byrn *et al.*, Pharmaceutical Research, Vol. 12, No. 7, 1995, pages 945 to 954

(14) M. Bavin, Chemistry and Industry, 1989, 527 to 529

(15) Pharmaceutical Technology, Fundamental Pharmaceutics, E. L. Parrott, Burgess Publishing Company, Minneapolis, Minn. (US), 1970, pages iii, 86 to 89

(16) Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice, Ed. Yihong Qiu *et al.*, Elsevier, Amsterdam (NL), 2009, page 769

(17) Pharma Polymers, Leaflet of Röhm GmbH, 1996, one page

(20) Saishin Yakuzai Gaku, 1977, Hirokawa Publishing Company, Tokyo (JP), 1977, pages 149 to 151, and partial translation into English

IV. The patent was opposed by Quimica Sintética, S.A. (opponent) under Article 100(a) EPC for lack of novelty and inventive step, under Article 100(b) EPC for insufficiency of disclosure and under Article 100(c) EPC for added matter.

The opposition division decided that the main request (set of claims as granted) lacked novelty over the disclosure of document (1). The auxiliary request filed with letter dated 15 January 2013 was considered to comply with Articles 123(2) and (3), 76(1), 84 and 83 EPC. Its subject-matter was held to be novel, but not to involve an inventive step in view of document (1) and the skilled person's common general knowledge, illustrated in documents (13) and (14). In its

assessment of inventive step, the opposition division defined the technical problem as the provision of an alternative crystalline form of febuxostat for the treatment of hyperuricemia.

Claims 1 and 3 of the auxiliary request read as follows:

"1. A pharmaceutical composition comprising 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid consisting of crystal C, wherein the crystal C shows a x-ray powder diffraction pattern having characteristic peaks at a reflection angle 2θ of 6.62, 10.82, 13.36, 15.52, 16.74, 17.40, 18.00, 18.70, 20.16, 20.62, 21.90, 23.50, 24.78, 25.18, 34.08, 36.72 and 38.04°."

"3. A method of producing crystal C according to claims 1 or 2 of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, which comprises heating 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid suspended in a mixed solvent of methanol and water in the presence of a small amount of crystal C of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid."

V. With the statement of grounds of appeal, the appellant, maintained the set of claims as granted as main request and resubmitted the auxiliary request underlying the decision under appeal.

VI. Anonymous third party observations were filed on 24 June 2016.

VII. With letter dated 29 July 2016 the opponent withdrew its opposition with the effect that it ceased to be party to the appeal proceedings.

VIII. With letter dated 26 August 2016 third party observations with essentially identical content to those previously submitted (see point VI above) were filed by Mr Eberhard Becker, European representative, of Becker, Kurig, Straus, European patent attorneys.

IX. At the oral proceedings before the board, the appellant filed an amended main request, which was based on the auxiliary request underlying the decision under appeal.

Independent claims 1 and 2 of the main request read as follows:

"1. A pharmaceutical composition comprising 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid consisting of crystal C, wherein the crystal C shows a x-ray powder diffraction pattern having characteristic peaks at a reflection angle 2θ of 6.62, 10.82, 13.36, 15.52, 16.74, 17.40, 18.00, 18.70, 20.16, 20.62, 21.90, 23.50, 24.78, 25.18, 34.08, 36.72 and 38.04°, wherein the crystal C has characteristic absorptions, which can be distinguished from that of other polymorphs, at 1703 and 1219 cm^{-1} in infrared spectroscopic analysis."

"2. A method of producing crystal C according to claims 1 or 2 of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, which comprises heating 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid suspended in a mixed solvent of methanol and water in the presence of a small amount of

crystal C of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid."

The auxiliary request and the main request underlying the decision under appeal were maintained as auxiliary requests 1 and 2.

X. The arguments provided by the appellant, as far as they concern the decisive issues, can be summarised as follows:

The pharmaceutical composition according to claim 1 of the main request comprised a single specific crystalline form, that is Form C, defined by x-ray diffraction peaks and IR absorption bands. Document (1), which was a suitable starting point for the assessment of inventive step, disclosed a mixture of two crystalline forms, namely Form A and C, in a ratio of 80:20. As was apparent from the patent in suit (see paragraphs [0035] and [0036]) and from document (11) (see page 4, third and fourth paragraphs and table), the claimed crystalline form was the most stable form when stirred in solvents, such as methanol and acetone. Contact with solvents was commonly encountered in formulation technology, in which methanol and acetone were frequently used solvents (see for example documents (15) to (17) or (20)). Variability in the ratio of crystalline forms was undesirable from the point of view of a drug manufacturer. The problem to be solved was therefore the provision of a pharmaceutical composition of febuxostat with improved stability, quality and reliability during formulation. The opposition division erred in formulating the problem to be solved as the provision of merely an alternative crystalline form.

Document (1) did not address the technical problem and provided no pointer to the proposed solution. It did not mention the existence of polymorphs of febuxostat. Nor was their existence known in the prior art. The skilled person did not even know that the crystalline form of document (1) was a mixture. He therefore had no reason to expect to be able to obtain a different crystalline form, which would be more stable during formulation. Documents (13) and (14) were not helpful in this context. They did not describe or suggest a universal method for obtaining a specific desirable crystalline form. Furthermore, none of these documents, or any other document, described or suggested conditions necessary to generate crystalline Form C.

XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request filed during the oral proceedings of 12 October 2016, or, alternatively, on the basis of auxiliary request 1, filed as auxiliary request with the statement of grounds of appeal, or, alternatively, that the patent be maintained as granted (auxiliary request 2).

XII. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible

2. Observation by a third party (Article 115 EPC)

2.1 Third party observations were filed anonymously at a late stage in the appeal proceedings. Subsequently,

third party observations with essentially the same content were filed by a professional representative (see points VI and VIII above).

2.2 Observations by a party which pursuant to Article 115 EPC, second sentence, is not party to the proceedings can be taken into account at the boards' discretion. When exercising their discretion, the boards usually take criteria into account which they consider when deciding on the admission of late filed submissions by any party to the proceedings (cf. Articles 12(4), 13(1) and 13(3) RPBA). One of these criteria is the relevance of the submission filed.

In the present case, the board considers that the observations filed by the third party are not more relevant than what is already on file. Also, none of the parties to the proceedings adopted the arguments and documents provided by the third party as their own. In fact, the opponent withdrew its opposition (see point VII).

2.3 The board therefore decided not to admit the submissions by the third parties.

Main request

3. Amendments, clarity and sufficiency of disclosure (Articles 123(2), (3), 76(1), 84 and 83 EPC)

3.1 In the decision under appeal the opposition division held that the subject-matter of the auxiliary request, that is the pharmaceutical compositions consisting of crystalline Form C and their use in the treatment of hyperuricemia, complied with Articles 123(2) and (3) and 76(1) EPC (see decision under appeal, point 17.2 of

the reasons). The board has no reason to deviate from the opposition division's findings in this respect. The present main request differs from the request considered by the opposition division solely in that the crystalline form is further defined by IR data. This amendment finds a basis in claim 2 and page 5, lines 3 to 5 of the application as originally filed and page 5, lines 3 to 5 of the parent application. It does not give rise to an objection under Article 123(2) or 76(1) EPC.

3.2 The board also has no reason to deviate from the opposition division's findings with regard to Articles 84 and 83 EPC (see decision under appeal, points 17.3 and 17.4 of the reasons). The amendment in claim 1 of the main request is of no consequence as regards the opposition division's assessment of clarity and sufficiency of disclosure.

4. Novelty (Article 54 EPC)

4.1 Claim 1 is directed to a pharmaceutical composition comprising 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid (febuxostat) as active principle. This active principle consists of a single specific crystalline form (i.e. Form C) which is defined by a X-ray powder diffraction peaks and IR absorption bands.

Due to the word "comprising" the claimed pharmaceutical compositions may contain other ingredients (additives, excipients, coatings, etc.), but the presence of a crystalline form which is different from the crystalline form claimed is excluded.

4.2 Document (1) discloses a crystalline form, which lacks at least one of the characterising IR-absorption bands. X-ray powder diffraction peak are not disclosed in document (1). Moreover, it has been shown during the examination proceedings (see documents (10) and (11)) that the crystalline form obtained in document (1) is a mixture of two crystalline forms (Forms A and C).

4.3 In view of the above the board concludes that the claimed subject-matter is novel over document (1).

5. Inventive step (Article 56 EPC)

5.1 The board considers, in agreement with the opposition division and the appellant, that document (1) is the closest state of the art. It concerns a one-pot-synthesis of 4-alkoxy-1,3-benzenedicarbonitriles, which are key intermediates in the synthesis of 2-(4-alkoxy-3-cyanophenyl)-4-methylthiazole-5-carboxylic acid derivatives, including TEI-6729 (i.e. febuxostat). TEI-6720, which is described as a promising remedy for hyperuricemia and gouty arthritis (see page 857, lines 1 to 3), was synthesised and obtained in crystalline form, after crystallisation from the reaction mixture containing ethanol and THF and recrystallisation from acetone (see page 863, lines 5 to 20).

As mentioned in point 4.2 above, it has been shown by the appellant during the examination procedure that the crystalline form in document (1) is a mixture of two polymorphic forms, that is polymorphic Forms A and C, in an 80:20 ratio. This was not contested by the opposition division and, in the absence of any conclusive evidence to the contrary, is accepted by the board.

5.2 In the light of document (1), the appellant defined the problem to be solved as the provision of a pharmaceutical composition of febuxostat with improved quality and reliability, that is improved polymorphic stability, in particular during formulation. The proposed solution is the crystalline form of febuxostat with the X-ray diffraction peaks and IR absorption bands according to claim 1 of the main request.

5.3 In order to demonstrate that the aforementioned technical problem was plausibly solved, the appellant relied on experimental evidence provided in document (11) and the disclosure in the patent in suit, in particular paragraphs [0035] and [0036].

5.4 Document (11) describes on page 4 two experiments in which a slurry of the crystalline Form C according to the invention and a slurry of an 80:20 mixture of crystalline forms corresponding to "D4", which is document (1) in the present opposition appeal proceedings, was stirred with acetone water. Samples were taken after 2, 4 and 24 hours and analysed by X-ray diffraction in order to determine the crystalline form. The results are summarised in the table on page 4, which shows that the crystalline form according to the invention remained unchanged, while the mixture of crystalline forms according to document (1) converts into Form C.

Such solvent-mediated conversion is also disclosed in the patent in suit (cf. paragraph [0030]), according to which Form C is produced by solvent-mediated polymorphic transition. Furthermore, in paragraphs [0035] and [0036] it is stated that Form A, which is characterised as a metastable form in methanol, converts into the stable Form C.

5.5 In the decision under appeal, the opposition division did not accept the existence of an improvement, since the active principle of a drug was not stored in acetone and other standard tests were commonly applied for assessing long term stability of pharmaceuticals. Although these assertions are undoubtedly correct, it cannot be denied that polymorphic stability during formulation is also crucial for any drug manufacturer and that solvents, including acetone or alcohols, are frequently used in formulation technology (see for example document (15), page 87, second paragraph, page 88, fourth and last paragraph, page 89, fourth and fifth paragraphs; document (16), page 769, tables 33.6, 33.8. 33.9; document (17); document (20), English translation). The board notes that document (16) is a post-published text-book. However, it confirms the teaching of documents (15) or (17).

A formulation with a polymorphically stable crystalline form compared to a potentially unstable mixture represents an advantage, since it does not require particular efforts to monitor and control the presence of a different crystalline form (see also patent in suit paragraphs [0001], [0003] and [0010]). The board therefore accepts the formulation of the technical problem as defined in point 5.2 above.

5.6 In view of the above and in the absence of any evidence to the contrary, the board considers that the technical problem as formulated in point 5.2 above is plausibly solved.

5.7 It then remains to be decided whether or not the proposed solution was obvious in view of the prior art.

5.7.1 Document (1) neither mentions polymorphs of febuxostat or their potential existence, nor does it address the problem of providing a pharmaceutical composition with improved polymorphic stability. Without knowledge of the invention the skilled person would not even have been aware of the fact that the crystalline form in document (1) is a mixture of crystalline forms with a potential for conversion into a different crystalline form. This document therefore cannot provide the skilled person with any useful information pointing to the presently claimed crystalline form or an incentive to modify the crystalline form according to document (1).

5.7.2 Documents (13) and (14) also cannot help in this respect.

These documents demonstrate that the occurrence of different solid states (polymorphs, hydrates, amorphous forms) is a widespread phenomenon in solid drug substances and that screening for polymorphic forms is advisable and even a regulatory requirement (see document (13), page 945, left-hand column, line 1 to right-hand column, line 15; document (14), page 527, left-hand column, third and fourth paragraphs; page 528, left-hand column, first paragraph). Methods for screening for polymorph are also disclosed (see document (13), page 946, right-hand column, last paragraph; document (14), page 528, left-hand column, first paragraph).

5.7.3 The board notes that the opposition division considered the problem to be solved as the provision of a mere alternative crystalline form, which means any form likely to be found in routine screening methods solves this problem. The board, based on the available

evidence, accepts that the problem to be solved is the provision of a polymorphically stable pharmaceutical composition of febuxostat. No guidance can be found in any of the documents (13) or (14) as to how a particular crystalline form with desirable properties can be obtained in a targeted manner.

5.7.4 The board would also like to point out that the facts of the present case differ from those leading to decision T 777/08 (OJ EPO 2011, 633) relied on by both parties during the opposition proceedings (see minutes page 2, penultimate paragraph). In that decision, the specific polymorph claimed was found to be an arbitrary choice from equally suitable candidates, in view of the skilled person's clear expectation that a crystalline form would have improved filterability and drying properties compared to the known amorphous form (see Headnote, point 2). In the present case, the board has no doubt that not all crystalline forms of febuxostat are equally suitable candidates to solve the problem of providing a crystalline form with improved polymorphic stability. Indeed, the patent in suit also mentions crystalline forms, which are not polymorphically stable (see paragraphs [0037] to [0038]).

5.7.5 With regard to the method claim 2 of the main request, the board observes the following:

Starting from document (1), the problem to be solved can be seen in the provision of a consistent and reliable method for the preparation of the crystalline form according to claim 1. The proposed solution was the crystallisation in methanol and water in the presence of seed crystals. The board has no doubt that this problem is solved by the claimed method.

Neither document (1) nor any of the other documents on file provides any guidance that the aforementioned technical problem can be solved by replacing the solvents (THF/ethanol or acetone) used in document (1) with methanol and water. The addition of seed crystals is not essential; it merely helps to accelerate the crystallisation and to improve the reproducibility on an industrial level.

5.8 In view of the above considerations, the board concludes that the subject-matter of the main request involves an inventive step.

6. Having decided that the main request complied with the requirements of the EPC, the board does not need to decide on auxiliary requests 1 and 2.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent with the following claims and a description to be adapted thereto:

   claims 1 to 3 filed as main request during the oral proceedings of 12 October 2016.

The Registrar: The Chairman:

M. Patin A. Lindner

Decision electronically authenticated