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Datasheet for the decision of 31 January 2023

Case Number: T 0546/21 - 3.3.02

Application Number: 15181097.5

Publication Number: 2977372

IPC: C07D277/56, A61K31/425, A61P19/06

Language of the proceedings: EN

Title of invention:
POLYMORPHS OF FEBUXOSTAT

Patent Proprietor:
SANDOZ AG

Opponent:
Alfred E. Tiefenbacher (GmbH & Co. KG)

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(2)

Keyword:
Inventive step - try and see situation, bonus effect
Late-filed evidence - submitted shortly before oral proceedings

Decisions cited:
T 0595/90, T 0205/14, T 1667/15, T 1598/18, T 2604/18, T 2295/19

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Case Number: T 0546/21 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 31 January 2023

Appellant: (Opponent)	Alfred E. Tiefenbacher (GmbH & Co. KG) Van-der-Smissen-Straße 1 22767 Hamburg (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondent: (Patent Proprietor)	SANDOZ AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Prüfer & Partner mbB Patentanwälte · Rechtsanwälte Sohnckestraße 12 81479 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 9 March 2021 rejecting the opposition filed against European patent No. 2977372 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	L. Bühler

Summary of Facts and Submissions

I. This present decision concerns the appeal filed by the opponent (appellant) against the opposition division's decision (decision under appeal) to reject the opposition against European patent No. 2 977 372 (patent).

II. The following documents submitted before the opposition division are relevant to the present decision:

D2 US 7,361,676 B2
D6 Yu, L. X., Pharmaceutical Research 2003, vol. 20, No. 4, pages 531 to 536
D7 Brittain, H. G., "Polymorphism in Pharmaceutical Solids", New York: Marcel Dekker, Inc., 1999, pages 1 to 33 and 183 to 226
D10 Giron, D., Thermochimica Acta 1995, vol. 248, pages 1 to 59
D11 "Febuxostat - Preparative DSC & Temperature dependent XRPD studies" (8 pages)
D13 Threlfall, T. L., Analyst 1995, vol. 120, pages 2435 to 2460
D14 Burger, A., Pharmazie in unserer Zeit 1982, vol. 11, No. 6, pages 177 to 189
D15 "HW 20" (DSC of form A; one page)
D17 "Annex 2", comprising experiments 1 and 2 (2 pages)
D24 "DSC of form A of Febuxostat (aetFEB019EXP002) disclosed in HW 15" (1 page)
D25 DSC of form A at different heating rates and weights (one page)
D28 Neuenfeld, S., "Polymorphieuntersuchungen von Pharmawirkstoffen mittels Thermischer Analyse", Anwenderseminar Thermische Analyse: Würzburger

Tage 1998, 1st edn, 1999, pages 92 to 115

III. In preparation for the oral proceedings, arranged at the parties' request, the board issued a communication pursuant to Article 15(1) RPBA 2020.

IV. With its letter dated 25 January 2023, the patent proprietor (respondent) filed the following document:

A32 Kitamura, M., Crystal Growth & Design 2004, vol. 4, No. 6, pages 1153 to 1159

V. The oral proceedings before the board took place as a videoconference on 31 January 2023 in the presence of both parties. The board decided not to admit A32. At the end of the oral proceedings, the chair announced the order of the present decision.

VI. Summaries of the respondent's arguments relating to the admittance of A32 and to the allowability of the main request and auxiliary requests 1 to 3 are contained in the reasons for the decision.

VII. The appellant's arguments relating to the admittance of A32 and to the allowability of the main request and auxiliary requests 1 to 3 can be summarised as follows.

- Admittance of A32

A32 was a reaction to D15. At the latest, A32 should have been filed with the respondent's reply to the statement of grounds of appeal. However, it should not have been filed only very shortly before the oral proceedings before the board. Contrary to Article 13(2) RPBA 2020, there were no exceptional

circumstances that could justify the late filing of A32.

- Main request

D2 was the closest prior art and febuxostat form A disclosed therein was the most suitable starting point for the assessment of inventive step. The subject-matter of claim 1 differed from form A in that it related to three alternatives of a method for producing a pharmaceutical composition, and in that the pharmaceutical composition comprised form I instead of form A.

The higher solubility of form I compared to that of form A was only marginal and had no relevance for a therapeutic application. The respondent had also failed to show that the marginally higher solubility offered any advantage when form I was used in a wet granulation step. Therefore, these effects should not be taken into account for the objective technical problem.

The patent, in particular figure 8, could not provide any information about the intrinsic dissolution rates of forms I and A. This was because the patent did not contain any data relating to the surface area of the samples used for solubility testing.

There was no comparison of forms I and A in terms of hygroscopicity. Therefore, even if form I was non-hygroscopic, this should not be taken into account for the objective technical problem.

The board rightly considered that the question of whether form I could be reliably obtained in a stable, robust and repeatable manner did not relate to form I itself but to a process for its manufacture. This should, likewise, not be taken into account for the objective technical problem.

The respondent had not shown that form A prepared according to D2 inevitably contained methanol. This should not be taken into account for the objective technical problem.

The respondent had not provided any evidence that form I did not change its polymorphic state properties when stored under certain conditions, or any evidence of the storage stability of pharmaceutical compositions comprising form I.

The results in D17 could only show that form I had a higher stability than form A at higher temperatures. This should not to be taken into account, because the temperatures in question were far above those relevant for pharmaceutical compositions and their manufacture.

Hence, the objective technical problem was to provide a method for producing a pharmaceutical composition comprising a further crystalline form of febuxostat. Even if the objective technical problem had been formulated in more ambitious terms taking into account that, compared to form A, form I had: (i) a higher solubility and (ii) a higher stability at higher temperatures, the solution would have been obvious. This was because the relevant common general knowledge, more specifically the heat-of-transition rule, would

have urged the skilled person to look for forms resulting from form A by an endothermic phase transition at higher temperatures. The experimental evidence in the present case showed that, by proceeding in that way, the skilled person would have routinely found form I. Moreover, the solution to the objective technical problem would still have been obvious even if the non-hygroscopicity of form I had been taken into account. The fact that form I retained the non-hygroscopicity of form A was merely a bonus effect that the skilled person, who was primarily looking for a new crystalline solid form of febuxostat with higher solubility and higher stability at higher temperatures, would inevitably have achieved. Finally, the method steps recited in claim 1 did not involve an inventive step either. Thus, claim 1 of the main request was not based on an inventive step.

- Auxiliary requests 1 to 3

The reasoning for claim 1 of the main request also applied to claim 1 of each of auxiliary requests 1 and 3. As correctly pointed out by the board, the additional feature in claim 1 of auxiliary request 2 could not confer an inventive step either. Hence, the subject-matter of claim 1 of each of auxiliary requests 1 to 3 did not involve an inventive step.

VIII. The parties' final requests relevant to the present decision were as follows.

The appellant requested that the decision under appeal be set aside and the patent be revoked in its entirety. It also requested that A32 not be admitted.

The respondent requested that the appeal be dismissed, thereby implying that the patent should be maintained as granted (main request), in the alternative, that the patent be maintained in amended form based on one of the sets of claims of auxiliary requests 1 to 3, filed before the opposition division with a letter dated 19 June 2020.

Reasons for the Decision

Main request (patent as granted) - Inventive step (Article 56 EPC)

1. Claim 1 reads as follows (the numbering (i) to (iii) has been added by the board):

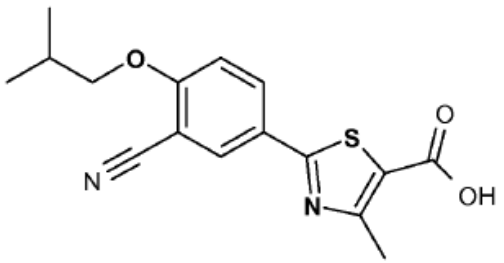
> "*Method for producing a pharmaceutical composition comprising a crystalline form of Febuxostat having an X-ray powder diffraction pattern as measured using CuK$\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm comprising peaks at 2-theta angles of 6.6 ± 0.2°, 12.8 ± 0.2°, 24.5 ± 0.2°, 25.8 ± 0.2°, 26.6 ± 0.2° and being characterized by an IR spectrum comprising absorption bands at wavenumbers of 2960 ± 2 cm^{-1}, 2874 ± 2 cm^{-1}, 2535 ± 2 cm^{-1}, 2229 ± 2 cm^{-1}, 1673 ± 2 cm^{-1}, 1605 ± 2 cm^{-1}, 1509 ± 2 cm^{-1}, 1422 ± 2 cm^{-1}, 1368 ± 2 cm^{-1}, 1323 ± 2 cm^{-1}, 1274 ± 2 cm^{-1}, 1166 ± 2 cm^{-1}, 1116 ± 2 cm^{-1}, 1045 ± 2 cm^{-1}, 1013 ± 2 cm^{-1}, 911 ± 2 cm^{-1}, 820 ± 2 cm^{-1}, 763 ± 2 cm^{-1} and 725 ± 2 cm^{-1} when measured using a diamond attenuated total reflection (ATR) cell, the method including:*

(i) mixing said crystalline form of Febuxostat with suitable excipients in a suitable mixer, and then directly compressing the mixture to tablets, or

(ii) employing a dry granulation step so as to produce granules suitable for tablet production, or

(iii) employing a wet granulation step."

2. The compound referred to in claim 1, febuxostat, is a medicament used in the treatment of hyperuricemia and gout. It has the following structure (patent, paragraph [0002]):



The crystalline form of febuxostat defined in claim 1 on the basis of 2-theta angles and wavenumbers is referred to in the patent as "form I" (patent, paragraphs [0015] and [0017]).

3. Thus, claim 1 relates to three alternatives of a method for producing a pharmaceutical composition comprising form I, each of these alternatives (i) to (iii) being characterised by different manufacturing steps for the pharmaceutical composition.

In the following paragraphs, only the last of the three alternatives mentioned in claim 1, namely alternative (iii), will be assessed. Given that this alternative is not based on an inventive step (see

below), there is no need to assess the other two alternatives (i) and (ii) mentioned in claim 1.

4. Closest prior art and starting point

4.1 It was common ground between the parties that D2 is the closest prior art. The board saw no reason to deviate from this unanimous view.

4.2 D2 relates to solid forms of febuxostat, referred to as crystalline forms A, B, C, D and G, and as amorphous form E.

Among the crystalline forms, form A has the highest intrinsic dissolution rate (D2, column 6, reference example 2). Only form A proved stable when tablets were produced by wet granulation, while the other forms that were tested partially converted to other solid forms (columns 7 and 8). Lastly, the dissolution profiles of tablets containing form A did not change significantly after storage for 6 months at 40 °C/75% relative humidity (column 9, example 3). Thus, it can be concluded that form A is clearly the preferred form among those tested in D2, a fact which - incidentally - is also reflected in the claims of D2 as they relate only to this form.

Against this background, form A of D2 is a realistic starting point for the assessment of inventive step.

4.3 The respondent argued that form A of D2 was not necessarily the closest prior art. The most common approach to screening and providing new solid forms was based on crystallisation from a solution. This approach, however, entailed the loss of the crystal structure of the initial solid form. Therefore, form A

was, objectively, not closer to a new solid form than any other form of febuxostat. This showed that starting from form A of D2 was based on hindsight.

As explained above, form A is singled out as clearly preferred among the solid forms of febuxostat disclosed in D2, in particular because it is the most suitable for the preparation of pharmaceutical formulations. This is the same context as that in which form I is also praised in the patent, namely as a solid form of febuxostat and in relation to its application for the preparation of pharmaceutical formulations. Contrary to the respondent’s argument, form A is therefore very much a possible starting point for assessing inventive step. In the board's view, the fact that the crystal structure of an initial solid form is lost when an attempt is made to crystallise it from a solution to thereby obtain a solid form with a different crystal structure is also not a sufficient reason not to start from a specific solid form within the framework of the problem-solution approach. If one were to follow the respondent's line of reasoning in this regard, any new solid form would ultimately also be inventive. The fact that the crystal structure of an initial solid form is lost in crystallisation attempts from a solution is, in any case, not relevant in the present case, since the relevant common general knowledge does not guide the skilled person to undertake such crystallisation attempts, but to search for a new solid form in a different way, namely by thermal treatment (see below).

5. Distinguishing features

Alternative (iii) of claim 1 is distinguished from form A of D2 in that

- it relates to a method for producing a pharmaceutical composition, the method employing a wet granulation step,
- the pharmaceutical composition comprises form I rather than form A.

6. Technical effects and objective technical problem

According to the respondent, form I was non-hygroscopic. It also had a higher solubility and a higher intrinsic dissolution rate than form A of D2. Unlike the latter, form I was free of methanol and could be obtained in a stable, robust and repeatable manner. Furthermore, form I had a higher thermal stability, and compositions comprising this form exhibited long-term storage stability.

All these effects relate to the properties of form I itself or its preparation. They do not relate to the wet granulation step as defined in alternative (iii) of claim 1 of the main request.

As regards this wet granulation step, the respondent argued that, on account of its higher solubility, form I offered a distinct advantage over form A when subjected to a wet granulation step and that the method of claim 1 had been improved compared to that disclosed in D2.

Therefore, at the oral proceedings before the board, the respondent formulated the objective technical problem as providing an improved method for producing a pharmaceutical composition containing an improved crystalline form of febuxostat.

The technical effects relied on by the respondent in this respect are assessed below.

6.1 Non-hygroscopicity

The patent shows that form I is virtually non-hygroscopic and is therefore very suitable for use in a wet granulation process for the production of pharmaceutical compositions comprising febuxostat (paragraph [0026], figure 3).

As set out above, form A is also stable during a wet granulation process. It can be concluded from this that form A is also virtually non-hygroscopic. Although the patent does not directly compare forms I and A in terms of hygroscopicity and does not therefore show that form I is any better than form A in this respect, this does not mean that the non-hygroscopicity of form I must - as argued by the appellant - simply be disregarded. Therefore, this effect is also taken into account.

6.2 Higher solubility

6.2.1 The patent (paragraphs [0024] and [0072], figure 8) compares forms I and A with regard to their solubility in MeOH/H_2O (1:1 v/v) at ambient temperature. The diagram in figure 8, in which the concentration (in mg/mL) is plotted against time (in min), shows that form I has a solubility at ambient temperature that is approximately 20% higher than that of form A in the state of equilibrium.

Without prejudice to the appellant's criticism of this data, the board assumed - for the sake of argument - in favour of the respondent that the effect of a higher

solubility could be considered when formulating the objective technical problem.

6.2.2 The respondent argued that the higher solubility of form I compared to form A offered an advantage when the method for producing the pharmaceutical composition included a wet granulation step. The reason for this was that the partial solubilisation of form I at the surface of the granules was greater than that of form A and this provided an advantage during compaction.

However, this alleged effect was not supported by any evidence. Therefore, it cannot be taken into account.

6.3 Higher intrinsic dissolution rate

According to the respondent, figure 8 of the patent allowed it to be concluded that form I had a higher intrinsic dissolution rate than form A. This was because the straight line connecting the origin and the first data point had a greater slope for form I than for form A.

The intrinsic dissolution rate measures the amount of substance that goes into solution per unit of area and time. It is given, for example, in the unit $mg/cm^2/min$ (see D2, reference example 2). However, the surface areas of forms A and I that were used in the solubility tests are not clear from the patent. For this reason alone, no intrinsic dissolution rates can be derived from the data given in the patent, either directly or indirectly, for example, from the diagram in figure 8.

The fact that there is no information on the intrinsic dissolution rates also distinguishes the present case from that underlying decision T 1667/15 (see point

3.1.8 of the Reasons), on which the respondent relied in support of inventive step. That case is therefore not relevant to the present case.

6.4 Absence of methanol

The respondent submitted that form A was prepared in D2 by crystallisation from a solvent system including, *inter alia*, methanol. Thus, inevitably, form A had to contain residual amounts of methanol. Due to its toxicity, however, methanol was an undesirable constituent for an active pharmaceutical ingredient. Form I must be free of methanol on account of the way it was prepared.

However, it cannot be assumed without further consideration that a solid form obtained from a solvent mixture by crystallisation will necessarily still contain residual amounts of a component of the solvent mixture used. In order to make this argument acceptable, the respondent would have had to provide appropriate evidence, which it did not do.

6.5 Effects related to the process of preparing form I

According to the respondent, the way in which form A was obtained in D2 was associated with a number of drawbacks. These included, e.g., the crystallisation conditions having to be carefully controlled in order to obtain polymorphically pure form A. In contrast, form I could be reliably obtained in a stable, robust and repeatable manner.

The advantages relied on by the respondent might be relevant to a process for making form I, but they are not relevant to form I as such (see T 205/14, point

5.6.4 of the Reasons for a similar case). This is because they are ultimately not based on a comparison of forms I and A but on a comparison of the processes for making those forms.

6.6 Stability

6.6.1 The patent (paragraph [0027]) discloses that form I does not change its polymorphic state properties when stored, e.g., at 40 °C for 3 months. According to the respondent, this showed that pharmaceutical compositions comprising form I exhibited long-term storage stability and that form I had a higher thermal stability than form A of D2.

However, apart from the mere assertion in the patent to this effect, the respondent did not provide any evidence that form I is polymorphically stable if stored under certain conditions for a certain period of time, let alone evidence of a direct comparison of forms I and A or pharmaceutical compositions comprising these forms.

6.6.2 In writing, the respondent had pointed to the results described in D17. D17 shows that form I has a higher melting point than form A (D17, experiment 1). Unlike form A, which converts to form I when subjected to thermal stress at 185 °C, form I does not convert to a different polymorph at this temperature (D17, experiment 2). According to the respondent, this constituted experimental evidence of a higher thermal stability of form I compared to form A, i.e. a higher stability at higher temperatures.

For the sake of argument, the board accepts - in favour of the respondent - that form I has a higher stability

than form A at higher temperatures. Since the board's final decision is in the appellant's favour, no reasoning needs to be given for taking this effect into account.

6.7 Since the effect allegedly resulting from the use of form I in a wet granulation step has not been demonstrated (see point 6.2.2 above), it cannot be said that this granulation step according to claim 1 constitutes an improvement over D2. The technical effects in the present case are therefore based solely on properties of form I as such, namely its non-hygroscopicity, higher solubility and higher stability at higher temperatures.

The objective technical problem - formulated by the respondent - of providing an improved method for producing a pharmaceutical composition containing an improved crystalline form of febuxostat must therefore be formulated less ambitiously as providing a method for producing a pharmaceutical composition containing a crystalline form of febuxostat which is non-hygroscopic and which is improved in terms of a higher solubility and a higher stability at higher temperatures.

7. Obviousness

7.1 With regard to the assessment of obviousness, the board considers it appropriate to first summarise the following aspects concerning polymorphs relevant to the present decision (for useful overviews: D6, page 532, right column, second paragraph; D7, chapter III on page 18 f. and table 4; D10, pages 11 ff.; D13, pages 2437 f. and 2446 to 2449; D14, pages 186 to 188; D28, pages 97 ff.). There was agreement between the parties that

these aspects belong to the skilled person's common general knowledge.

- The transition between two polymorphs can be categorised as either enantiotropic or monotropic.
- In a monotropic system, the higher-melting polymorph is always (thermodynamically) more stable than the lower-melting polymorph. The transition from the lower-melting to the higher-melting polymorph is thus irreversible.
- In an enantiotropic system, the transition from one polymorph into another, which occurs at a certain transition temperature, is reversible. Above the transition temperature, the higher-melting polymorph is (thermodynamically) more stable, whereas below the transition temperature it is the lower-melting polymorph that is more stable. As a lower (thermodynamic) stability goes hand in hand with a higher (thermodynamic) solubility, the higher-melting polymorph will have a higher solubility below the transition temperature than the lower-melting polymorph.
- The four thermodynamic rules developed by Burger and Ramberger can help decide whether two polymorphs are enantiotropes or monotropes. The most useful and applicable of these four rules are the heat-of-transition rule and the heat-of-fusion rule. The heat-of-transition rule states that, if an endothermic (exothermic) polymorphic transition is observed, the two forms are enantiotropes (monotropes). The heat-of-fusion rule states that, if the higher-melting polymorph has the lower (higher) heat of fusion, the two forms are enantiotropes (monotropes).

7.2 Against the background of this common general knowledge, the skilled person, faced with the problem of providing a crystalline form of febuxostat that has a higher solubility and a higher stability at higher temperatures than form A, will clearly be inclined to check whether form A undergoes an endothermic phase transition into a new higher-melting form at higher temperatures. This is because, according to the heat-of-transition rule, such a new solid form should then be an enantiotrope of form A which has a higher solubility than form A below the transition temperature (such as at ambient temperature in the present case - see point 6.2.1 above) and a higher stability than form A above the transition temperature.

Either such a form exists or it does not. The board concurs with the appellant that the skilled person would have been in a "try and see" situation.

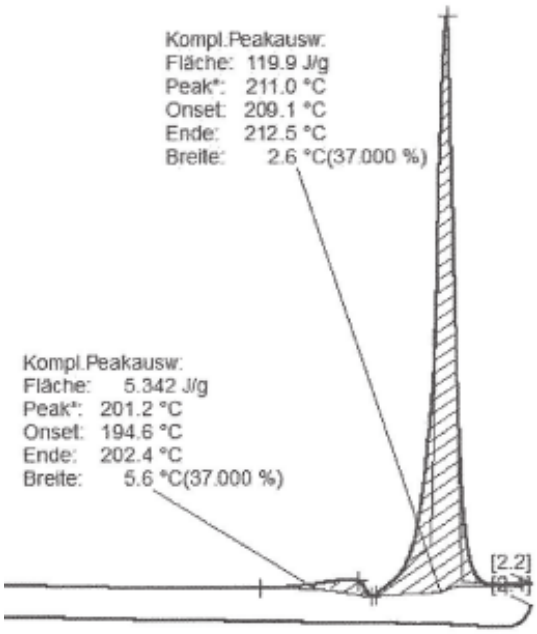
It may be true that the skilled person - as argued by the respondent - does not generally think of using DSC to find new solid forms. However, against the background of the common general knowledge summarised above and the objective technical problem, they would most certainly have done so - if only because DSC measures heat flow and is the method of choice for determining exo- and endothermic processes when heating a sample.

7.3 It was a matter of dispute between the parties whether the skilled person would have found that form A undergoes an endothermic phase transition to a new solid form during a DSC analysis. To this end, the appellant (D11, D15) and the respondent (D24, D25, A32) relied on various experimental data. The appellant requested that A32 not be admitted.

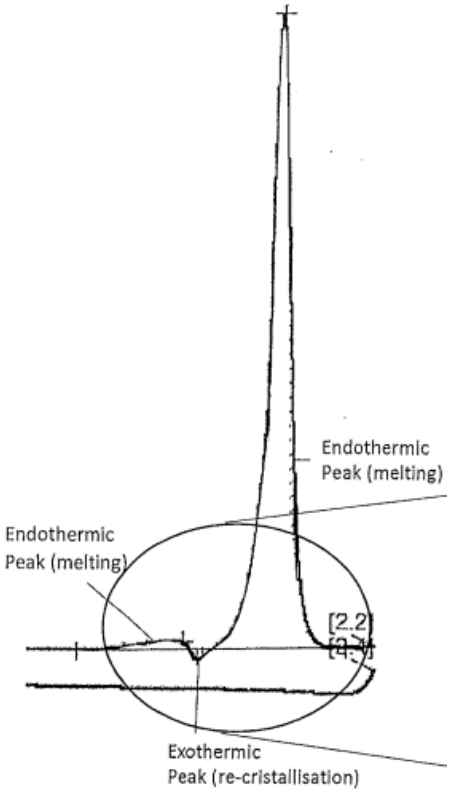
Therefore, before clarifying the question of what information the skilled person would have derived from a DSC analysis of form A, the question of admittance of A32 must first be answered.

7.4 Admittance of A32

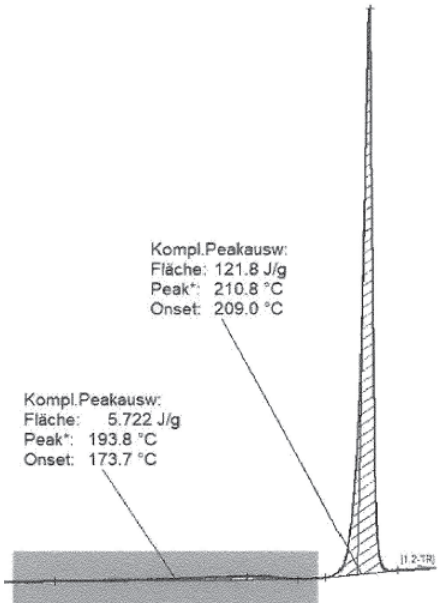
7.4.1 For the admittance of A32, the history of the case is relevant. It can be summarised as follows, with reference to the following DSC curves of form A in the various documents:

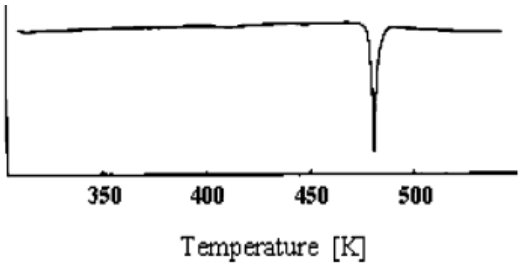


DSC of form A in D11



DSC of form A in D24





DSC of form A in D15 DSC of form A in A32

In the following paragraphs, peaks signifying an exo-/endothermic event in the DSC curve are referred to as exo-/endothermic peaks for the sake of simplicity. In the DSC curves in D11, D15 and D24, endothermic peaks point upwards, exothermic peaks downwards. In A32, it is the other way round. DSC peaks are counted in the direction of increasing temperature, i.e. from left to right.

- The appellant filed D11 with the notice of opposition. This document shows a DSC curve of form A at a heating rate of 10 °C/min. According to the appellant, this DSC curve had to be interpreted as showing two endothermic peaks, the first one corresponding to a transition of form A to a new form, the second one corresponding to the melting of the new form. Therefore, this DSC curve showed that form A and the new form were enantiotropes.
- The respondent filed D24 with its reply to the notice of opposition. It shows an enlargement of the DSC curve in D11 with a straight base line. The

respondent argued that the interpretation of the DSC curve of D11 had to be based on that straight base line. This showed an exothermic peak between two endothermic peaks. This peak sequence did not obviously show enantiotropy as it could also be due to a monotropic phase transition.

- With its notice of opposition, the appellant had in fact also filed D15. D15 shows a DSC curve of form A at a lower heating rate (5 °C/min) than that in D11 (10 °C/min). According to the appellant, reducing the heating rate made the exothermic peak - if it existed at all - disappear. This was explained in D13 and D14, and the DSC curve in D15 clearly showed an endothermic phase transition from from A to a new form.
- During the present appeal proceedings, and more specifically with its letter dated 25 January 2023, which was more than 3.5 years after the appellant's notice of opposition, the respondent filed A32. This document shows a DSC curve of form A at a heating rate of 5 °C/min. Unlike the DSC in D15, the one in A32 only shows one endothermic peak.

7.4.2 As regards the admittance of A32, the respondent essentially argued that this document showed an unbiased DSC analysis of form A. This DSC analysis was highly relevant. Although the heating rate was the same as in D15 (5 °C/min), the DSC curve showed only one endothermic peak. Thus, a normal DSC analysis would not have indicated, or hinted in any way at a thermal transition of form A to a new form. The interpretation of A32 did not pose any difficulties. A32 was also filed in response to the the board's communication pursuant to Article 15(1) RPBA 2020, which highlighted the importance of the experimental evidence in relation

to the DSC analyses submitted to that date. Hence, A32 should be admitted.

7.4.3 The board's position is as follows. The filing of A32 constitutes an amendment of the respondent's appeal case. It was filed with the respondent's letter dated 25 January 2023. This was after notification of the summons to oral proceedings. Pursuant to Article 13(2) RPBA 2020, A32 is not to be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the respondent. However, in the present case, there are no such exceptional circumstances. The late filing of A32 cannot be excused by it being filed in response to the board's communication under Article 15(1) RPBA 2020. This is because the board's communication was only based on the parties' earlier submissions and did not raise any new issues. Furthermore, even if one were to acknowledge that A32 is *prima facie* relevant, this would not constitute an exceptional circumstance within the meaning of Article 13(2) RPBA 2020.

The respondent argued that a merely formalistic approach to admittance, thereby disregarding the relevance of the submission, was not appropriate. However, the relevance of a submission cannot be the overriding consideration for admittance irrespective of the stage of that submission. Indeed, if late-filed submissions were admitted for their relevance no matter what stage the procedure had reached and whatever the reasons for late submission, this would not only reward negligence but would also invite tactical abuse. Moreover, the board did not adopt a merely formalistic approach, but did in fact consider whether the late submission of document A32 was detrimental to procedural economy or adversely affected the other

party (see decision T 1598/18, point 25.1 of the Reasons, T 2295/19, point 3.4.12 of the Reasons, T 2604/18, points 1.3 and 1.4 of the Reasons, holding that exceptional circumstances exist if the late submission does not negatively affect the other party and the efficient conduct of oral proceedings). In the present case, it is not readily apparent why two DSCs of the same solid form (form A) recorded at the same heating rate (5 °C/min) showed two different results, namely two endothermic peaks (D15) or only one (A32). The admittance of A32 would have made it necessary to find out the reason for this discrepancy. This would have required the discussion of complex questions only at the oral proceedings, e.g. the accuracy of the DSC method in general as well as in the specific context of D15/A32 in relation to form A. Such complex questions had not been discussed prior to the oral proceedings before the board. Thus, A32 actually raises new issues rather than being suitable for resolving existing issues. The filing of A32 was thus prejudicial to both procedural economy and the appellant's opportunity to duly reply to the new submission.

At the oral proceedings, therefore, the board decided not to admit A32 (Article 13(2) RPBA 2020).

7.5 In view of the experimental evidence in the proceedings (D11, D15, D17, D24 and D25), the board came to the following conclusion as regards obviousness.

7.5.1 Even if one were to agree with the respondent's interpretation of D11 in D24, namely that the DSC curve of form A in D11 is to be interpreted as a sequence of endo-, exo- and endothermic peaks and that this sequence is not unique to enantiotropic phase transitions insofar as it can also be observed in

certain monotropic phase transitions, the skilled person is well aware that an enantiotropic phase transition can underlie this peak sequence. In fact, it is common for a polymorph to show a transition to a higher-melting polymorph at the appropriate transition temperature if heated slowly, but to overshoot and melt at its own melting point under more rapid heating conditions. This is often followed immediately by re-solidification to the higher-melting polymorph, thereby giving a characteristic sequence of endo-,exo- and endothermic peaks (D13, page 2447, right column, second paragraph). In view of this, it is also clear to the skilled person that this "overshooting" may possibly be prevented by reducing the heating rate. This has been done in D15. D15 shows a DSC curve which is archetypical of an enantiotropic phase transition followed by melting of the higher-melting form, there being two endothermic peaks, the first signifying a much smaller heat transfer than the second (see, e.g., D14, page 188, figure 11). This reflects the fact that the energy difference between two solid forms of the same compound is generally much smaller than that between the solid state and the liquid (molten) state (D14, page 188, left column, penultimate paragraph).

7.5.2 In this context, the respondent referred to the DSC curves of form A in D25. They showed a sequence of endo-, exo- and endothermic peaks and were recorded at heating rates (10 and 20 °C/min) and sample weights (about 1.7 and 4.5 mg) typical for such measurements. Since the use of typical heating rates and sample weights yielded DSC curves with a peak sequence that did not allow a clear conclusion to be drawn as to whether it was an enantiotropic or monotropic phase transition, the skilled person could indeed have obtained the DSC curve shown in D15, but it could not

be said that they would necessarily have obtained it if confronted with the objective technical problem.

The board does not find this convincing, for the following reasons. As already stated above, against the background of their common general knowledge the skilled person would have reduced the heating rate if in doubt about the interpretation of the DSC curve in D11. The heating rate chosen by the appellant in D15 in this context (5 °C/min) is by no means unusual or unusually low. This is also illustrated by, e.g., D14, which uses heating rates as low as only 0.5 °C/min for similar investigations (figure 11). Against this background the results of D25 cannot be deemed to contradict the above conclusion - if only because they were obtained with heating rates of at least 10 °C/min, which is higher than that used in D15 (5 °C/min). To the extent that the respondent's argument implies that, in order to record the DSC curve in D15, the amount of form A only needed to be chosen low enough (i.e. lower than the typical amounts chosen by the respondent in D25) to make the exothermic peak in the DSC disappear, it did not provide any proof for this assertion. On the contrary, the peaks of the DSC curve in D25 measured with a lower sample weight are of lower intensity than those of the DSC curve measured with a higher sample weight, but both DSC curves still show the same qualitative sequence of endo-, exo- and endothermic peaks. Hence, the results of D25 do not contradict the above conclusion for this reason either.

7.5.3 Contrary to the above, the respondent still considered D15 as evidence that form A and the new form were monotropes. It argued that the first endothermic peak in D15 corresponded to the melting of the lower-melting form, the second endothermic peak to the melting of the

higher-melting form. Considering the heat-of-fusion rule (see above) and the fact that the heat of fusion of the higher-melting form was higher, it had to be concluded that both forms were monotropes.

This is not convincing already on account of the respondent's correlation of the first peak in the DSC curve of D15 with a melting event. As explained above, the energy difference between two solid forms of the same compound is generally much smaller than that between the solid and liquid states. Similarly, the heats of fusion of two solid forms of the same compound having melting points close to each other should not be as different as the DSC curve in D15 suggests. Furthermore, assuming that the first endothermic peak corresponds to the melting of the lower-melting form, the DSC curve should not actually show any further melting (as attributed to the second endothermic peak) - at least not without crystallisation being observed first, which is obviously not the case with the DSC curve of D15 due to the absence of an exothermic peak.

7.5.4 The appellant further showed by means of preparative DSC that heating form A up to 205 °C, i.e. to just below the melting temperature of the higher-melting form, resulted in the formation of form I (D11, pages 3 and 4). Similarly, the respondent showed in D17 (example 2) that a temperature of 185 °C is already sufficient for this transformation to occur. These results are consistent with the DSC in D15 showing that the first endothermic peak spans across a temperature range of approximately 175 to 200 °C.

7.6 Thus, by performing a DSC analysis of form A, the skilled person aiming at higher solubility and higher stability at higher temperatures would have identified

form I as being the desired form, i.e. a higher-melting form that results from form A by an endothermic phase transition at higher temperatures. In view of the heat-of-transition rule, they would have expected form I to be an enantiotrope of form A and form I to have a higher solubility than form A at temperatures below the transition temperature (somewhere between approx. 175 and 200 °C), i.e. at ambient temperature, and to have a higher stability at higher temperatures such as above the transition temperature. Further, the fact that form I merely retains the non-hygroscopicity of form A (in the absence of a comparison, one cannot speak, at any rate, of an improvement - see above) can be considered merely as a bonus effect that the skilled person inevitably achieves because they are primarily looking for a crystalline form of febuxostat with higher solubility and higher stability at higher temperatures.

The board cannot agree with the respondent's argument based on decision T 595/90 that form I contributed to inventive step of the claimed method already because no way of making form I had been found prior to the effective date of the patent. Decision T 595/90 (OJ EPO 1994, 695, point 5 of the Reasons) held that "*an otherwise obvious entity, may become nevertheless non-obvious and claimable as such, if there is no known way or applicable (analogy) method in the art to make it* ***and the*** *claimed* ***methods for its preparation are therefore the first to achieve this in an inventive manner***" (emphases added). However, the present case is different in that - as explained above - the skilled person would have obtained form I in an obvious manner, i.e. the process carried out until form I is obtained is also not based on an inventive step.

It follows from the above that the provision of form I as defined in the process of claim 1 of the main request does not involve any inventive step.

It remains to be examined whether the wet granulation step of alternative (iii) in claim 1 can establish an inventive step. With respect to that wet granulation step, the respondent relied only on the alleged advantage of wet granulation based on the higher solubility of form I. However, as already stated above, such an advantage was unproven and cannot therefore be taken into account. The respondent has not shown any other advantages or effects in connection with this step. For this reason alone, the wet granulation step cannot establish an inventive step. In addition, wet granulation is a routine method for producing a pharmaceutical composition. Also for this reason, an inventive step cannot be acknowledged. Notwithstanding this, wet granulation is also disclosed in D2 (claim 2) for producing a tablet, i.e. a pharmaceutical composition within the meaning of claim 1, and therefore an inventive step cannot be recognised for this reason either.

7.7 In summary, the subject-matter of claim 1 does not involve an inventive step and the main request is not allowable.

Auxiliary requests 1 and 3

8. Claim 1 of each of auxiliary requests 1 and 3 relates, *inter alia*, to the same alternative objected to above for claim 1 of the main request (alternative (iii)). Therefore, the above reasoning also applies to claim 1 of auxiliary request 1 and to claim 1 of auxiliary

request 3. Auxiliary requests 1 and 3 are not allowable.

Auxiliary request 2

9. Claim 1 of auxiliary request 2 differs from claim 1 of the main request as follows (emphasis and the number (iii) added by the board):

> "*Method for producing a pharmaceutical composition comprising [febuxostat form I], the method including: ...*
>
> *(iii) employing a wet granulation step* ***to produce granules suitable for tablet production, in which step water, ethanol and solutions containing binders can be used.***"

At the oral proceedings, the board pointed out that it could not see why the additional feature included in claim 1 of auxiliary request 2 supposedly contributed to an inventive step. The respondent conceded that the answer to the question of whether claim 1 of auxiliary request 2 was based on an inventive step depended solely on whether claim 1 of the main request was based on an inventive step. The additional feature (in bold above) had been included to overcome one of the appellant's objections under Article 123(2) EPC.

As claim 1 of the main request is not based on an inventive step, it must be concluded that the subject-matter of claim 1 of auxiliary request 2 is also not based on an inventive step. Accordingly, auxiliary request 2 is not allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated