Internal distribution code:

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

Datasheet for the decision of 9 November 2021

Case Number: T 1667/15 - 3.3.02

Application Number: 10724664.7

Publication Number: 2398784

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

Language of the proceedings: EN

Title of invention:
CRYSTALLINE FORMS OF FEBUXOSTAT

Patent Proprietor:
Teva Pharmaceutical Industries Ltd.

Opponent:
Ahrens, Gabriele

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

Decisions cited:
T 0918/01, T 1396/06, T 0777/08

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1667/15 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 9 November 2021

Appellant: (Opponent)	Ahrens, Gabriele Jasperallee 1A 38102 Braunschweig (DE)
Representative:	Ahrens, Gabriele Patentanwälte Einsel & Kollegen Jasperallee 1A 38102 Braunschweig (DE)
Respondent: (Patent Proprietor)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. Tel Aviv 6944020 (IL)
Representative:	Greiner, Elisabeth df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstraße 16 80333 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 16 June 2015 rejecting the opposition filed against European patent No. 2398784 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	P. de Heij

Summary of Facts and Submissions

I. The appeal of the opponent (hereinafter appellant) lies from the decision of the opposition division to reject the opposition against European patent 2 398 784.

II. The patent was opposed under Article 100(a) EPC on the grounds that its subject-matter lacked novelty and inventive step.

III. Of the evidence cited in opposition proceedings, the following documents were invoked by the parties during appeal proceedings:

D1: WO 2008/067773 A
D2: EP 1 020 454 A1
D3: CN 101 412 700 A
D3A: English machine translation of D3
Dl1: Bavin, Chemistry & Industry, 1989, pages 527-529
D12: Byrn et al., Pharmaceutical Research, 12, 1995, pages 945-954
D13: Polymorphism in the Pharmaceutical Industry, R. Hilfiker (ed), Wiley 2006, pages 34-42 and 287-308
D15: Declaration of Prof. W. Schlocker dated 4 March 2015
Annex 4: Experimental report - dissolution studies of various polymorphic forms of febuxostat in 96% ethanol
Annex 5: Solubility tests - comparison of febuxostat form F10 and form A in ethanol
Annex 5a: Microscope images of crystals - comparison of febuxostat form F10 and form A

Annex 6: Solubility tests - comparison of febuxostat form F10 and form A in buffered aqueous solutions at pH 2 and 7
Annex 7a: Solubility tests - comparison of febuxostat form F10 and form A at pH 6.8
Annex 8: Stability of form CN700 compared to form F10 by XRPD analysis
Annex 9: Repetition experiments of crystalline forms described in D1 and D3;
Annex 10: Advantages of form F10 over forms J and form CN700

IV. With a communication pursuant to Article 15(1) RPBA, the board set out its preliminary opinion, and in particular expressed the view that D2 and D3 were suitable starting points for the assessment of inventive step with regard to the claimed subject-matter.

V. With the letter of 17 September 2021, the appellant stated that it would not be attending the scheduled oral proceedings.

VI. Oral proceedings by videoconference were held on 9 November 2021 in the appellant's absence.

Requests

VII. The appellant requested that the contested decision be set aside and the patent be revoked in its entirety.

VIII. The respondent (patent proprietor) requested that the appeal be dismissed, implying maintenance of the patent as granted. Alternatively, as an auxiliary measure, the respondent requested maintenance of the patent on the basis of the set of claims of the first auxiliary

request filed with the reply to the statement of grounds of appeal.

IX. Independent claims 1 and 6 of the main request (claims as granted) read as follows:

"*1. A crystalline form of Febuxostat, designated Form F10,* ***characterized by*** *data selected from:*

(a) an X-ray powder diffraction pattern having peaks at 6.7°, 7.7°, 12.8°, 13.3° and 20.0° ± 0.2° 2θ;
(b) a solid-state ^{13}C NMR spectrum with signals at 112.7, 125.7, 132.4 and 168.3 ± 0.2 ppm;
(c) a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of 11.7, 24.7, 31.4 and 67.3 ± 0.1 ppm;
and combinations thereof.

6. A crystalline form of Febuxostat, designated Form F2, ***characterized by*** *data selected from:*

(a) a powder XRD pattern with peaks at 3.0°, 5.9°, 8.8°, 11.8° and 12.5° ± 0.2° 2θ;
(b) a solid-state ^{13}C NMR spectrum with signals at 112.3, 163.9, 168.8 ± 0.2 ppm;
(c) a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of 11.5, 63.1 and 68.0 ± 0.1 ppm;
and combinations thereof."

X. The arguments of the appellant insofar as relevant to the present decision, may be summarised as follows:

Main request - Article 100(a) and 56 EPC

The closest prior art with respect to claims 1 and 6 was represented by crystalline Form A of febuxostat disclosed in D2 (hereinafter "Form A") or crystalline Form CN700 of febuxostat disclosed in D3 (hereinafter "Form CN700"; hereinafter reference is made to the English language translation D3A).

Claim 1 as granted - Form F10

The alleged effects of improved solubility of Form F10 over Form A of D2, and improved stability over Form CN700 of D3A, had not been achieved. Specifically, the appellant's tests in Annex 4 demonstrated that the solubility of Form F10 and Form A were similar. The respondent's tests in Annexes 5, 6 and 7a, in contrast to those of Annex 4, relied on an uncommon and unusual test method and therefore were unsuitable to demonstrate improved solubility. Even if accepted, the apparent improvements in dissolution rate allegedly demonstrated in the respondent's comparative tests may be explained by differences in particle sizes and/or particle shape of the samples used, and therefore did not reflect the intrinsic properties of Form F10 itself. Accordingly, the objective technical problem was the provision of an alternative crystalline form.

Even if it were accepted that Form F10 had improved solubility/dissolution rate over Form A, the solution set out in claim 1 would not have involved an inventive step, since the skilled person would have adopted a "try and see" attitude, and in carrying out routine

polymorphic screening, would have arrived at the subject-matter of claim 1.

The alleged effect of improved stability for Form F10 over Form CN700 of D3A was not to be accepted on the basis of the respondent's Annex 9 and 10, since the Form CN700 used as the basis for comparison therein was not the closest embodiment of D3A prepared according to example 2 thereof. The problem was therefore the provision of an alternative new polymorphic form. The solution was obvious in view of D3A as closest prior art.

Claim 6 as granted - Form F2

The general statements in D15 were not sufficient to acknowledge the effect of improved processability for the plate-like morphology of Form F2 compared to the needle-like morphology of inter alia Form A of the prior art, for which no evidence had been presented. This applied even more since document D9, which disclosed the formulation and processing of Form A, failed to disclose any handling or processing problems associated therewith. Furthermore, any improvement related to processability would be a process-related, not a product-related advantage, and would thereby not be suitable as an effect attributed to a product. Finally, there was typically always a trade-off between advantages and disadvantages of polymorphic forms. In the absence of evidence demonstrating that Form F2 had similar solubility and stability to Form CN700, these properties would outweigh the minor processability advantages associated with plate-like crystals. Inventive step for Form F2 vis à vis form A of D2 or form CN700 of D3 was therefore to be denied.

XI. The arguments of the respondent insofar as relevant to the present decision, may be summarised as follows:

Main request - Article 100(a) and 56 EPC

The closest prior art with respect to claims 1 and 6 were represented by Form A disclosed in D2 or Form CN700 disclosed in D3A.

Claim 1 as granted - Form F10

The results of the tests in Annexes 5, 6 and 7a were sufficient to acknowledge an improved dissolution rate associated with Form F10 compared to Form A of D2. Furthermore, the data in *inter alia* Annex 8 demonstrated that Form F10 possessed superior stability compared to Form CN700 of D3A. The methodology used by the appellant to generate the results reported in Annex 4 was not suitable for discerning differences in dissolution rate demonstrated in the respondent's data in Annexes 5, 6 and 7a. On the basis of these effects, inventive step was to be recognised for Form F10 over Form A and Form CN700 of the prior art.

Claim 6 as granted - Form F2

Crystals of Form F2 possessed plate-like morphology, while those of the prior art Form A and Form CN700 possessed needle-like morphology. As stated in expert declaration D15, it was common general knowledge that crystals with plate-like morphology offered handling and processability advantages compared to crystals in the form of needles. Since such effects were technically credible, there was no need for experimental proof that such an effect would apply specifically to the crystals of Form F2. There was also

no reason why such a process-related effect could not be taken into account for assessing whether a product claim involved an inventive step. Based on this effect, inventive step was to be recognised for Form F2 over Form A and Form CN700 of the prior art.

Reasons for the Decision

Main request - Inventive step, Article 100(a) EPC

1. The claims as granted comprise two independent claims directed to specific crystalline forms (i.e. polymorphs) of febuxostat. Claim 1 is directed to a crystalline form designated "Form F10", while claim 6 is directed to a crystalline form designated "Form F2".

2. Closest prior art

2.1 According to the contested decision, the disclosure in D2 represented the closest prior art. The appellant was of the view that either of D2 or D3A were suitable starting points for the skilled person. The respondent submitted that D2 was the closest prior, and that D3A was less suitable.

2.2 D2 discloses various polymorphic forms of febuxostat (paragraphs [0031] - [0036]), among which Form A is stated to be the preferred form in view of its "industrial superiority" (paragraph [0036]).

2.3 In view of this, as well as the statement of the respondent that Form A is the crystalline form present in the marketed drug product (page 5 of the reply,

footnote), the board is of the opinion that febuxostat form A of D2 represents a suitable starting point for the assessment of inventive step.

2.4 D3A discloses a further crystalline form of febuxostat. The aim of D3A is to prepare further crystal forms "*to ensure good stability .. and good dissolution degree..*" (page 1, "Background of the Invention"). Examples 1 and 2 describe the preparation of said crystalline form, denoted "Form CN700" by the parties to the present proceedings. In example 5 of D3A, the degree of dissolution and stability of Form CN700 compared to Form A is assessed.

2.5 The board is of the view that independently of which of documents D2 or D3A may be considered closest to the subject matter of the contested patent, D3A is certainly not so remote that the skilled person would never have considered it as a starting point.

2.6 Consequently, inventive step of the claimed subject-matter is to be assessed starting from the disclosures in both D2 and D3A.

3. Claim 1 as granted - Form F10

3.1 Distinguishing features & Problem solved

3.1.1 Claim 1 concerns Form F10 of febuxostat. It is undisputed that this form is different from Form A disclosed in D2 and Form CN700 disclosed in D3A.

According to the contested patent, Form F10 is said to have advantageous properties, and a list of such properties is provided. In particular it is stated that form F10 "*has better solubility in ethanol compared to*

other crystalline forms" (paragraph [0065]). The patent does not contain any working examples or experimental data demonstrating said solubility.

The appellant submitted solubility tests in Annex 4. The respondent submitted *inter alia* Annexes 5, 6 and 7a and argued that the data therein demonstrated that Form F10, compared to Form A of D2, possessed advantages in terms of its dissolution rate. The respondent also relied on improved stability in comparison to Form CN700 of D3A, referring to the data in *inter alia* Annex 8.

3.1.2 With regard to the respondent's data in terms of the dissolution rate of Form F10 compared to Form A, the board is of the following view. Annex 5 concerns tests wherein 100 mg of a sample of either Form A or Form F10 were added to 25 ml of 95% ethanol and shaken for 2 minutes. The mixture was filtered and the remaining solid was dried and weighed, allowing a calculation of the weight of material dissolved in ethanol. It was found that 850.3 ml of ethanol were required per gram of dissolved Form A, compared to 243.4 ml per gram of dissolved Form F10, thereby demonstrating that the dissolution rate of Form F10 is superior to that of Form A over a period of 2 minutes. Similarly, Annex 6 describes analogous tests carried out in an aqueous buffer solution at pH 2 and at pH 7. It was found that at pH 2, 748.5 ml of ethanol were required per gram of dissolved Form A, compared to 411.2 ml per gram of Form F10, while at pH 7 the corresponding figures were 3086.4 ml per gram of Form A, compared to 477.1 ml per gram of Form F10. These tests demonstrate that the results obtained in ethanol were also displayed in aqueous solution, both at pH 2 and pH 7. In Annex 7a, the time dependent solubility of Form A versus Form F10

in an aqueous buffer solution at pH 6.8 was measured and plotted. The plot clearly demonstrates that although after 200 minutes of stirring, the solubility of Form F10 and Form A approach similar levels (albeit Form F10 is still marginally more soluble after that time), Form F10 displays an initial dissolution rate that is clearly superior to that of Form F10.

3.1.3 The appellant noted, and the board agrees, that aqueous solubility is of primary importance to the skilled person undertaking polymorph screening (statement of grounds of appeal, 19.4). The data in aqueous solutions will be employed by the board in the formulation of the objective technical problem (infra). As set out above, the data in Annex 6 and 7a demonstrates that an improved dissolution rate in aqueous solution has been achieved for Form F10 compared to Form A.

3.1.4 The appellant's arguments to the contrary are not convincing, as set out in the following.

Annex 4 submitted by the appellant concerns tests which demonstrate that the solubility of *inter alia* Form F10 and Form A were similar. These results are not disputed by the respondent (reply, point 42; D15, point 21), and are not in contradiction with the data reported in the respondent's tests. Firstly, the tests in Annex 4 are carried out in ethanol, while the tests in Annexes 6 and 7a are performed in aqueous solution. Secondly, and more importantly, the test of Annex 4 is designed to measure equilibrium solubility, i.e. the maximum amount of the respective forms which can be dissolved at a particular temperature (Annex 4, figure on page 2). In contrast, the tests in Annexes 6 and 7a measure a different property, namely the dissolution rate, or the rate at which each respective form dissolves in an

aqueous solution over a specific period of time. The board agrees with the respondent (as set out in its reply to the statement of grounds of appeal, point 41) that the methodology used in Annex 4 is not suitable for discerning a technical effect related to an improved dissolution rate. This distinction was not addressed by the appellant. The distinction between equilibrium solubility and (intrinsic) dissolution rate is also acknowledged in D12 (page 947, line 4-8 under subheading "B"), cited by the appellant as evidence that solubility was important in polymorph screening. Consequently, the data in Annex 4 is irrelevant with regard to whether an improved dissolution rate is obtained with Form F10.

3.1.5 It was also argued by the appellant that the methodology used in inter alia Annexes 6 and 7a relied on an uncommon and unusual test method, while the results in Annex 4 were based on two different well established standardised and validated commercial measurement methods. However, as noted above, while the tests of Annex 4 may be well established, they are not suitable for assessing the dissolution rate of the respective forms. Furthermore, the board sees no reasons to doubt the validity of the results provided by the tests in Annex 6 and 7a, since the method employed is straightforward, easy to understand, and provides clear and unambiguous results. While in general a test designed to demonstrate a particular effect should be clear and credible, there is no general requirement that such a test must be well-established or validated.

3.1.6 Finally, the appellant submitted that the improvements in dissolution rate allegedly demonstrated in the respondent's comparative tests may be explained by

differences in the particle size and/or particle shape of the samples used, and therefore did not reflect the intrinsic properties of Form F10 itself. Specifically, Form F10 had a significantly greater particle size than Form A. Since it was known that dissolution rate was influenced by particle size and shape, it was likely that the observed improvements were attributable to these differences. Even if the respondent's original samples had been treated by grinding before the tests, it was likely that the respective particles still did not have similar sizes and shapes.

3.1.7 In the view of the board, even if it were to be accepted that in the tests of Annexes 6 and 7a, the Form F10 particles were larger than the tested Form A particles, this would not support the appellant's conclusion as set out above. While the board agrees with the appellant that particle size would affect dissolution rate, the skilled person would expect said effect to be one of a decreased dissolution rate for the larger Form F10 particles, since larger particles possess a lower surface area per unit of particle volume, and dissolution takes place at the surface. In view of the data in Annexes 6 and 7a demonstrating the opposite effect, it can only be concluded, under the assumption that the Form F10 particles were larger than the Form A particles, that the improved dissolution rate achieved is all the more convincingly linked to the intrinsic nature of Form F10. Furthermore, the appellant's additional argument that grinding of the larger F10 particles, if carried out prior to testing in Annexes 6 and 7a, would be unlikely to lead to similar particles, can only be seen as an unsubstantiated allegation, unsupported by evidence.

3.1.8 In view of the foregoing, the objective technical problem underlying the subject-matter of claim 1 vis à vis Form A of D2 is the provision of a crystalline form of febuxostat with an improved dissolution rate in aqueous solution.

3.1.9 With regard to the respondent's data concerning the stability of Form F10 compared to Form CN700 of D3A, the board is of the following view. Annex 8 concerns storage stability testing. Form CN700 was stored at 25°C and 60% relative humidity for 3 months. Form F10 was stored under the same conditions for 12 months. XRPD analysis demonstrated that Form CN700 converted at least partially into another form ("Form G") after 3 months, while Form F10 remained unchanged after 12 months.

3.1.10 The appellant stated that good stability results had also been obtained for Form CN700 in D3A. While this may be true, the stability results provided in D3A do not cast doubt on the effect demonstrated in Annex 8. Specifically, the conditions under which stability was tested in D3A were different (60°C for 14 days) to those employed in Annex 8, and the relative humidity was not provided. The data in Annex 8 therefore demonstrates that under storage conditions, Form F10 is more stable to polymorphic conversion than Form CN700. The effect of improved stability of Form F10 over Form CN700 has consequently been achieved. The board notes in this regard that while the appellant submitted that the effect of improved stability had not been demonstrated in view of the data in Annex 10 (statement of grounds, points 22 and 23), it was silent with regard to the relevance of the data in Annex 8 (see respondent's reply, point 69). In view of the board's conclusion concerning the data in Annex 8, there is no

need to assess whether the technical effect is supported by the respondent's Annex 10, submitted to demonstrate that Form F10 possessed improved stability under wet grinding conditions compared to Form CN700.

3.1.11 The appellant criticised the results in *inter alia* Annex 8 on the basis that the Form CN700 used therein, according to the respondent's Annex 9, was prepared according to example **1** of D3A. The stability data of D3A in contrast was based on Form CN700 prepared according to example **2**. Since examples 1 and 2 of D3A were not identical, and the melting points of the products differed (209-210°C for example 1 and 208-209°C for example 2), the respondent's tests did not involve the closest embodiment of D3A and for that reason could not be seen as a legitimate comparison with Form CN700 of D3A.

3.1.12 The board disagrees. Firstly, for the purposes of demonstrating improved stability, it is only required to compare Form F10 according to claim 1 with Form CN700 according to D3A. The specific method by which Form CN700 is prepared is irrelevant. D3A discloses a single crystalline form characterised by its XRPD spectrum (claim 1), namely the form herein denoted Form CN700. Examples 1 and 2 both concern methods for preparing "the" crystal form. The definite article "the" can only be understood to refer to said single form disclosed throughout D3A, characterised by its XRPD pattern. Only minor differences are observed in the respective examples in terms of the amount of ethyl acetate solvent used, and the temperature to which the mixture is heated to effect dissolution. Furthermore, the difference in measured melting point between the products of the respective examples is sufficiently narrow to fall within the bounds of experimental error

(1°C). There is therefore no reason to doubt that the crystalline form produced according to example 1 is anything other than the same form as that obtained according to example 2 of D3A, namely Form CN700. Consequently, the comparison drawn in Annex 8 must be regarded as valid.

3.1.13 In view of the foregoing, the objective technical problem underlying the subject-matter of claim 1 vis à vis Form CN700 of D3A is the provision of a crystalline form of febuxostat with improved stability to polymorphic conversion.

3.2 Obviousness

3.2.1 With regard to obviousness over Form A of D2, the appellant essentially submitted (citing *inter alia* D11-D14) that even if the objective technical problem were to be formulated as the provision of a form of febuxostat having improved solubility, the solution set out in claim 1 would not have involved an inventive step. Although the objective technical problem as set out above concerns an improved dissolution rate, the board considers that the appellant's arguments apply analogously thereto. Specifically, the appellant argued that it was incorrect to assume that in the field of polymorph screening, it would be entirely unexpected to find a polymorph with an improved dissolution rate compared to Form A. Rather, the skilled person was in a "try and see" situation in which absolute certainty was not needed (citing in particular decision T 1396/06). Accordingly, the skilled person, in addition to being motivated by the knowledge that Form A of D2 was known to be metastable, would have had a clear incentive to continue routine polymorph screening in order to prepare new crystalline forms having the desired

property, and thereby would have arrived at Form F10 of claim 1. Finally, the skilled person in view of the teachings of D6, D7 and D8 would have known anhydrates such as Form F10 to have better aqueous solubility compared to hydrates (citing D13).

3.2.2 The board is not convinced by these arguments. The situation in the present case is not the same as that underlying case T 1396/06 in which the deciding board concluded that a "try and see" attitude would have been adopted by the skilled person. In that case, the technical problem to be solved was closely related to the technical problem set out in the closest prior art, namely the provision of immunogenic peptides specifically binding to another HLA-allele (different from the HLA-A3.2 allele disclosed in the closest prior art; reasons 6). In contrast, in the present case, the technical problem of providing a crystalline form of febuxostat specifically having an improved dissolution rate, let alone a general problem related to improved solubility, is not addressed in D2 at all. Similarly, in T 918/01, cited in T 1396/06 (reason, 7), the closest prior art in combination with secondary documents provided a clear pointer as to the feasibility of a certain measure in order to solve the problem at hand (reasons, 8.3). Routine checks were all that was required to confirm that the proposed solution was effective (reasons, 9.1). In contrast, in the present case, there are no pointers in the prior art to the solution provided in claim 1. There is therefore no reasonable expectation of success that the specific problem as set out above could be solved at all, let alone solved by providing Form F10 of claim 1. Finally, while it can be accepted that solubility and dissolution rates are of importance in polymorph screening as set out by the appellant citing D11-D13,

or that better aqueous solubility is expected for anhydrates (D13, page 37, section 2.8), this does not change the above conclusions, since it remains the case that there was no reasonable expectation of success for the skilled person in desiring to solve the above-mentioned problem.

3.2.3 Rather, as noted by the respondent, the situation in the present case may be more appropriately contrasted with that underlying decision T 777/08 in which inventive step was denied. In that case, the problem was the provision of atorvastatin in a form having improved filterability and drying characteristics compared to the amorphous form (reasons, 5.1). The solution was the provision of a specific polymorphic form IV. The deciding board stated that polymorphism was commonplace and that it belonged to the routine tasks of the skilled person to screen for polymorphs early in the drug development process (reasons, 5.2, page 11, first paragraph). It was common general knowledge that "*crystalline products are generally the easiest to isolate, purify, dry ... handle and formulate*". Accordingly, the skilled person would have had a clear expectation that a crystalline form of atorvastatin would provide a solution to said problem. It was therefore obvious to try this avenue with reasonable expectation of success (reasons, 5.2, page 12, third paragraph). In contrast, in the present case, as stated above, there is no teaching in the prior art on the basis of which a crystalline form of febuxostat with an improved dissolution rate in aqueous solution could be expected to exist. Therefore, the skilled person would have had no reasonable expectation of success in attempting to provide a solution to the objective technical problem vis à vis Form A of D2 as set out above.

3.2.4 Therefore, inventive step must be acknowledged for the subject-matter of claim 1 vis à vis the disclosure of Form A in D2.

3.2.5 With regard to obviousness of claim 1 over Form CN700 of D3, the appellant's submissions are absent any line of argumentation according to which the subject-matter of claim 1 would lack inventive step if the objective technical problem were to be formulated as above, namely to include the provision of improved stability.

The board notes that the situation for Form F10 vis à vis Form CN700 of D3 is analogous to that set out above vis à vis Form A of D2. Specifically, there is no teaching in the prior art providing the skilled person with a reasonable expectation of success that a certain measure will provide a solution to the objective technical problem vis à vis Form CN700 of D3A as set out above, namely the provision of a crystalline form of febuxostat with improved stability to polymorphic conversion.

Therefore, inventive step must be acknowledged for the subject-matter of claim 1 vis à vis the disclosure of Form CN700 in D3A.

3.3 It follows from the foregoing that the subject-matter of claim 1 involves an inventive step.

4. Claim 6 as granted - Form F2

4.1 Distinguishing features & Problem solved

4.1.1 Claim 6 concerns a crystalline Form F2 of febuxostat. It is undisputed that this form is different from Form A disclosed in D2 and Form CN700 disclosed in D3A.

4.1.2 According to the contested patent, Form F2 is said to have advantageous properties, and a list of such properties is provided. In particular it is stated that *"while forms A, B and C ... are all needle shaped .. form F2 has plate morphology, and therefore has better technological properties, such as compactability, which may be better for e.g. tablet formulation"* (paragraph [0059]). The patent does not contain any working examples or experimental data demonstrating said properties. In D15, an expert declaration submitted by the respondent, it is stated that crystalline morphology is an important and pharmaceutically relevant property of crystalline drug compounds, and that it is generally known that different crystal morphologies result in differences with regard to handling and processing properties such as compactability, flowability and filterability (D15, points 8-11). In particular, it is stated that needle-like crystalline forms of a drug molecule typically exhibit worse flowability and compactability behaviour compared to more spherical particles such as those with the plate-like morphology of Form F2 (D15, point 12).

4.1.3 The board notes that the statements in the patent according to which the crystals of *inter alia* Form A of D2 are needle shaped and the crystals of Form F2 have plate morphology, as well as the respondent's statement that the crystals of Form CN700 of D3 crystallised in the form of elongated needles (reply, point 79) were not contested by the appellant. It is therefore accepted that the respective forms possess the morphology indicated.

4.1.4 The appellant challenged the general nature of the information provided in D15, stating that it had not been demonstrated that specifically Form F2 possessed advantages in terms of processability as compared to needle-like crystal forms. In the view of the board however, such concrete evidence is not necessary. Firstly, the information in D15 regarding said advantages in general was not disputed by the appellant. Secondly, that crystals having a plate-like morphology may be more easily processable than needle-like crystals makes sense from a technical perspective. Specifically, due to their shape, needle-like crystals would be expected to interfere more with each other while flowing, while plate-like crystals would be expected to slide over each other with more ease, thereby facilitating flow. Similarly, with regard to compactability, needle-like crystals would be expected to stack in a more random manner, and thereby create residual volume in between adjacent crystals. Plate-like crystals on the other hand would be expected to be more likely to lie on top of each other, thereby minimising residual space and facilitating compactability. For these reasons, it is technically reasonable and credible to assume that the general statements in D15 will apply to the crystals of Form F2, in particular in the absence of any evidence or credible technical argument to the contrary.

4.1.5 The appellant also submitted that the general statements in D15 would not apply since D9, which discloses the formulation and processing of Form A (e.g. D2, examples 1 and 2) failed to disclose any processing problems associated with Form A. This argument is not convincing because the absence of a reference to specific problems in D9 cannot be equated

with evidence that contrary to common general knowledge, processability would not be improved by providing a crystalline form having the plate-like morphology of Form F2.

4.1.6 Finally, the appellant essentially argued that any improvement related to processability would be a process-related, not a product-related advantage, and would thereby be unsuitable as an effect attributed to a product. The board disagrees. The appellant's argument is lacking any specific explanation as to why such a process-related effect would be unsuitable. The board sees no reason why a process-related technical effect cannot be based on an intrinsic feature of a product, namely in the present case the plate-like morphology of crystal Form F2, and therefore be invoked in the formulation of an objective technical problem concerning that product.

4.1.7 It follows that the effect of improved processability for Form F2 of claim 6 can be accepted. The objective technical problem underlying the subject-matter of claim 6 vis à vis Form A of D2 and Form CN700 of D3A is therefore the provision of a crystalline form of febuxostat with improved processability.

4.2 Obviousness

4.2.1 Similarly to the situation regarding the obviousness of Form F10 set out above, there is no teaching in the prior art providing the skilled person with a reasonable expectation of success that a certain measure will provide a solution to the objective technical problem vis à vis Form A of D2 or Form CN700 of D3 as set out above, namely the provision of a crystalline form of febuxostat with improved

processability. Therefore, it must be concluded that the subject-matter of claim 6 involves an inventive step.

4.2.2 The appellant submitted that in the field of polymorphs, the skilled person generally regarded potentially desirable properties as a matter of trade-off between advantages and disadvantages of polymorphic forms. Thus advantages such as good solubility and storage stability for example for Form CN700 of D3 could outweigh any advantage associated with plate-like morphology. In the absence of evidence demonstrating that Form F2 had similar solubility and stability to Form CN700, inventive step was therefore to be denied.

4.2.3 The board disagrees. It is for the appellant to support it's allegations with appropriate evidence. In the absence thereof, it is entirely speculative to state that the solubility and stability of Form F2 may be inferior to Form A and Form CN700. And even if this were the case, it does not detract from the improved processability. Consequently, this argument must fail.

It follows that the subject matter of claim 6 involves an inventive step.

4.3 In conclusion, the subject-matter of claims 1 and 6 involves an inventive step. The same conclusion applies by analogy to dependent claims 2-5, 7-9 and 11, composition claim 10, process claim 12 and medical use claims 13 and 14.

5. The main request is consequently allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated