Internal distribution code:

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

Datasheet for the decision of 26 February 2024

Case Number: T 0461/22 - 3.3.02

Application Number: 12791764.9

Publication Number: 2785702

IPC: C07D309/10, A61K31/351, A61P3/10

Language of the proceedings: EN

Title of invention:
CRYSTALLINE DAPAGLIFLOZIN HYDRATE

Patent Proprietor:
Sandoz AG

Opponent:
Generics [UK] Limited (trading as Mylan)

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step

Decisions cited:
G 0003/14

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 0461/22 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 26 February 2024

Appellant: (Opponent)	Generics [UK] Limited (trading as Mylan) Building 4 Trident Place Mosquito Way Hatfield Hertfordshire AL10 9UL (GB)
Representative:	Gill Jennings & Every LLP The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
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 14 December 2021 rejecting the opposition filed against European patent No. 2785702 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	B. Burm-Herregodts

Summary of Facts and Submissions

I. This 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. 2 785 702 (patent).

II. Reference is made in the present decision to the following document filed with the opposition division:

D1 WO 2008/002824 A1

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

IV. The oral proceedings before the board were held by videoconference on 26 February 2024 in the presence of the appellant and the patent proprietor (respondent). At the end of the oral proceedings, the chair announced the order of the present decision.

V. For the parties' submissions of relevance to the present decision, reference is made to the reasons for the decision provided below.

VI. The parties' final requests at the end of the oral proceedings of relevance 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 the respondent's submission not be admitted that the addition of a polyol in step b) of claim 4 was responsible for the fact that the obtained

product was a pure hydrate in contrast to what was obtained by the process of examples 4 and 5 of D1.

The respondent requested that the appeal be dismissed, implying maintenance of the patent as granted (main request).

Reasons for the Decision

Main request (patent as granted) - Inventive step

1. The independent claims of the main request read as follows:

1.1 Claim 1

> "*Crystalline dapagliflozin hydrate, characterized in that it has the XRPD pattern shown in figure 1, wherein a hydrate designates a crystalline form of a molecular compound, whereby the only further molecules incorporated into the crystal lattice are water molecules.*"

The crystalline dapagliflozin hydrate of claim 1 is referred to in the patent as form A (paragraphs [0019], [0045], [0046] and figure 1). Form A is a dihydrate (patent, paragraph [0048]).

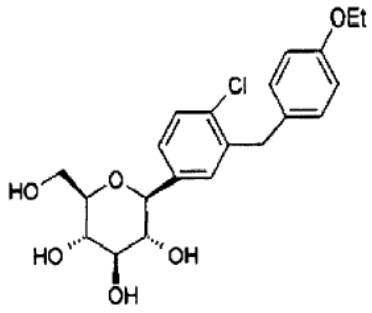
1.2 Claim 3

> "*The crystalline dapagliflozin hydrate according to at least one of the claims 1 to 2 for use in the treatment of type II diabetes (NIDDM - non-insulin-dependent diabetes mellitus).*"

1.3 Claim 4

"*A process for obtaining the crystalline form according to at least one of the claims 1 to 2 comprising the steps of:*

a) providing a compound of formula 1, Dapagliflozin,



formula 1

in a suitable solvent or a mixture of solvents;
b) adding a polyol to the mixture of step a);
c) concentrating the composition of step b);
d) crystallizing;
e) equilibrating the obtained suspension of step d), whereby the composition containing crystalline material is stirred until a thermodynamically [sic] *equilibrium between solid and liquid phase is obtained; and*
f) isolating the obtained precipitate

wherein the polyol of step b) is a sugar alcohol selected from the group consisting of arabitol, xylitol, mannitol and mixtures thereof and/or in step d) and/or e) seed crystals are added."

1.4 Claim 8

"*A pharmaceutical composition comprising crystalline dapagliflozin hydrate according to at*

least one of the claims 1 to 2 and optionally one or more pharmaceutically acceptable excipients."

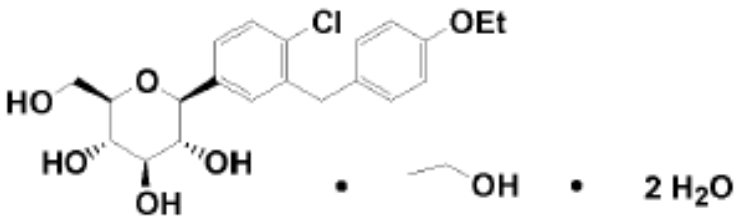
1.5 Claim 9

"*The pharmaceutical composition of claim 8 for use in the treatment of type II diabetes (NIDDM - non-insulin-dependent diabetes mellitus).*"

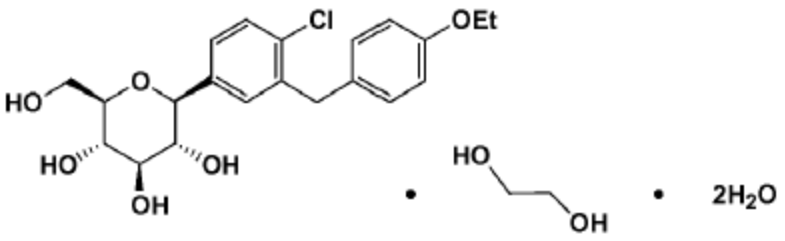
2. There was agreement between both parties that D1 is the prior art closest to the claimed subject-matter of the main request.

3. D1 relates to, *inter alia*, crystalline solvates of dapagliflozin and their preparation. In particular, it discloses the following three crystalline dapagliflozin solvates and their preparation (examples 3 to 5):

- the dapagliflozin ethanol dihydrate **SA-1** with the following general structure:



- the two dapagliflozin ethylene glycol dihydrates **SB-1** and **SB-2** with the following general structure:



The three dapagliflozin solvates of D1 above contain, per molecule of dapagliflozin, two molecules of water and an organic solvent molecule, namely ethanol (SA-1) or ethylene glycol (SB-1, SB-2).

4. There was agreement between the parties that each of the three dapagliflozin solvates and, if applicable, the preparation thereof, is a suitable starting point for the assessment of inventive step.

Claim 1

5. Distinguishing feature

The appellant submitted that the subject-matter of claim 1 differs from each of the three dapagliflozin solvates SA-1, SB-1 and SB-2 only in that it contains no organic solvent molecules. This is accepted below.

6. Technical effect and objective technical problem

6.1 The respondent argued

- that form A of claim 1 allowed the preparation of amorphous dapagliflozin by vitrification (i.e. melting and subsequent quenching) without the latter containing any organic solvents or residues thereof
- that, in contrast, amorphous dapagliflozin prepared from one of the three dapagliflozin hydrates SA-1, SB-1 or SB-2 of D1 still had to contain the organic solvents ethanol/ethylene glycol or at least residual amounts thereof, and that the presence of such organic solvents in the amorphous form was undesirable from a regulatory point of view because

amorphous dapagliflozin was used as the active pharmaceutical ingredient in the drug sold

6.2 The board does not see any reason to doubt that forming an amorphous material by vitrification from a material without solvent molecules will lead to an amorphous material without solvent molecules and conversely, vitrification of a material with solvent molecules will lead to an amorphous material with solvent molecules.

6.3 The board does not in this respect see any reason why, as argued by the appellant, the preparation of amorphous dapagliflozin from one of the three dapagliflozin hydrates SA-1, SB-1 or SB-2 of D1 could be carried out with complete loss of the organic solvent molecules during vitrification, and no reasons were provided by the appellant. Moreover, even if the appellant's argument were to be accepted, this approach would still involve the disadvantage, as pointed out by the respondent, that the absence of these solvents would have to be verified for regulatory reasons, a step which is not necessary when starting from form A of claim 1. The appellant's argument cannot, therefore, call into question the objective technical problem formulated below.

6.4 In view of this, the board accepts the objective technical problem formulated by the respondent which is to provide an improved crystalline form of dapagliflozin.

7. Obviousness

7.1 The appellant argued that the skilled person starting from SA-1, SB-1 or SB-2 would have obtained the claimed

hydrate without solvent molecules by way of routine experimentation.

7.2 The board does not agree.

In example 12 of the patent, 101 mg of amorphous dapagliflozin was suspended in 2.0 mL water. The mixture was stirred at room temperature for about one week, after which no crystallisation had taken place.

The board agrees with the respondent that this example reflects what the skilled person would realistically have done when attempting to prepare a crystalline dapagliflozin hydrate. It thus corresponds to the routine experimentation referred to by the appellant.

Nevertheless, no crystallisation had taken place in this example after one week. This shows that form A of claim 1 is not the result of a mere routine screening for dapagliflozin hydrates.

7.3 The appellant submitted that the approach taken in example 12 of the patent was unusual. The amount of amorphous dapagliflozin in relation to the amount of water was very high. Furthermore, the suspension of dapagliflozin in water was not heated above room temperature. Therefore, it could not be concluded that form A of claim 1 was not the result of a mere routine screening.

However, since in example 12 an approximately 20-fold excess by weight of water was used compared to dapagliflozin, the board sees no reason why the amount of dapagliflozin compared to that of water should have been too high to allow crystallization of a dapagliflozin hydrate. It is true that the suspension

of amorphous dapagliflozin in water was not heated above room temperature in example 12. However, in the absence of any evidence to the contrary, it must be assumed that the lack of heating is compensated for by stirring the suspension over a very long period of about one week.

7.4 The appellant also argued that D1 (paragraph [00115]) disclosed that stable forms of dapagliflozin could be crystallised as solvates, e.g. hydrates, confirming that the claimed hydrate could be obtained by routine experimentation.

The board does not agree with this argument either. The reference to hydrates in the cited passage of D1 can only be a reference to the hydrates as further specified in D1, i.e. hydrates with organic solvent molecules. Hence, D1 by no means suggests that hydrates as claimed, i.e. without organic solvent molecules, can be obtained by routine experimentation.

7.5 Lastly, the appellant pointed out that D1 (paragraph [00103]) disclosed non-crystalline, i.e. amorphous, dapagliflozin in substantially pure form. Therefore, D1 had already found a solution to the problem of providing amorphous dapagliflozin without any organic solvent molecules.

However, the mere fact that a document discloses a solution to a certain problem does not necessarily render another solution to the same problem obvious. Irrespective of this, the claimed form is crystalline, such that paragraph [00103] of D1, directed to amorphous dapagliflozin, is not relevant.

7.6 D1 thus in no way suggests preparing a compound as claimed. Even less does it suggest doing so in order to solve the objective technical problem as defined above. It must therefore be concluded that the subject-matter of claim 1 involves an inventive step.

Claim 4

8. Claim 4 relates to a process for obtaining form A of claim 1. The reasoning given above for claim 1 therefore also applies *mutatis mutandis* to the subject-matter of claim 4.

9. The appellant submitted that D1 (examples 3 to 5) disclosed process steps a) to f) as required by claim 4. The subject-matter of claim 4 was distinguished from D1 solely on the basis of a result to be achieved, i.e. form A. Nevertheless, form A was not obtained in D1 but instead hydrates which further comprised either ethanol or ethylene glycol. Therefore, the subject-matter of claim 4 was too broad and did not involve an inventive step over its entire breadth. The reason for this was that claim 4 lacked three essential features which were actually responsible for form A being obtained.

10. This is not convincing, not least because the precondition for the appellant's argument is not fulfilled. As pointed out by the respondent, at very least D1 does not disclose process step b), i.e. the addition of a polyol to the mixture of dapagliflozin and solvent(s) prepared in step a):

- Example 3 of D1 discloses the preparation of form SA-1. Dapagliflozin tetraacetate is dissolved in ethanol, heated and diluted with water. The

resulting solution, which is a solution of dapagliflozin in aqueous ethanol, is provided with an additional amount of ethanol. Ethanol, however, is a mono-alcohol and not a polyol as required by claim 4.

- Examples 4 and 5 disclose the preparation of forms SB-1 and SB-2, respectively. They start out from a solution of dapagliflozin tetraacetate in aqueous ethylene glycol but no other solvent, let alone a polyol as required by claim 4, is added during the further course of the preparation of forms SB-1 and SB-2.

11. To reach the above conclusion, all that is relevant is that the addition of a polyol, i.e. step b) of claim 4, is not disclosed in D1.

However, it is irrelevant whether the addition of a polyol is actually responsible for obtaining a dapagliflozin hydrate which is free from organic solvent molecules, as submitted by the respondent. Therefore, there was no need to decide at the oral proceedings on the appellant's request not to admit this submission from the respondent.

12. In addition to the above, the product of the process of claim 4 is defined in structural terms by means of an XRPD pattern and the presence of only dapagliflozin and water molecules in the crystal lattice. It is clearly not defined in terms of a result to be achieved. Form A is a technical feature of claim 4. This means that the subject-matter of claim 4 only covers processes which actually produce form A. Since, as set out above, form A is inventive, the more restricted claim 4 directed to the process of preparing it must be inventive as well.

As already stated in the board's communication under Article 15(1) RPBA and not contested by the appellant during the oral proceedings, the allegation that essential features are missing from claim 4 is an objection under Article 84 EPC. However, such an objection is not admissible in the present case since claim 4 is a claim as granted (G 3/14).

Claims 3 and 8

13. Claim 3 relates to a second medical use of form A, and claim 8 to a pharmaceutical composition comprising form A.

As pointed out by the board at the oral proceedings and not disputed by the appellant, the reasoning for the subject-matter of claim 1 also applies *mutatis mutandis* to the subject-matter of claims 3 and 8.

Claim 9

14. Claim 9 defines the same second medical use as claim 3 with the only difference that it does not relate to form A but to a pharmaceutical composition according to claim 8, i.e. a pharmaceutical composition comprising form A.

At the oral proceedings before the board, the appellant did not specifically address claim 9. In the statement of grounds of appeal, the appellant submitted that "*[c]laim 9 lacks inventive step for analogous reasons to claim 3.*"

However, since the subject-matter of claim 3 does involve an inventive step (see above), the same

conclusion must be drawn for the subject-matter of claim 9.

Dependent claims

15. The reasoning for the subject-matter of claims 1 and 4 also applies *mutatis mutandis* to the subject-matter of their dependent claims 2 and 5 to 7, respectively.

Conclusion

16. The main request is allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

C. Rodríguez Rodríguez M. O. Müller

Decision electronically authenticated