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Datasheet for the decision of 29 February 2024

Case Number: T 1503/21 - 3.3.07

Application Number: 10782116.7

Publication Number: 2498759

IPC: A61K9/20, A61K31/155, A61K31/351, A61K45/06

Language of the proceedings: EN

Title of invention:
IMMEDIATE RELEASE TABLET FORMULATIONS

Patent Proprietor:
AstraZeneca AB
AstraZeneca UK Limited

Opponents:
Hoefer & Partner Patentanwälte mbB
STADA Arzneimittel AG
Generics (U.K.) Limited
Galenicum Health S.L.U.

Headword:
Combination Tablet/ASTRAZENECA

Relevant legal provisions:
EPC Art. 56, 123(2), 84, 83
RPBA 2020 Art. 12(4), 12(6), 13(1), 13(2)

Keyword:

Inventive step - main request, auxiliary requests 1c, 2-6, 11b, 11c, 12-16 (no) - auxiliary request 17 (yes)
Amendments - auxiliary requests 7-9 - allowable (no) - auxiliary request 17 - allowable (yes)
Claims - clarity - auxiliary request 17 (yes)
Sufficiency of disclosure - auxiliary reqeust 17 (yes)
Amendment to case - exercise of discretion

Decisions cited:

T 1287/14

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1503/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 29 February 2024

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(Opponent 4)

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Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office posted on 30 June 2021 concerning maintenance of the European Patent No. 2498759 in amended form.

Composition of the Board:

Chairman A. Usuelli
Members: M. Steendijk
A. Jimenez

Summary of Facts and Submissions

I. European patent 2 498 759 ("the patent") was granted on the basis of thirty-six claims.

Claim 1 as granted defined:

"An immediate release pharmaceutical formulation in the form of a tablet, stock granulation, or capsule comprising: (1) an SGLT2 inhibitor selected from dapagliflozin and dapagliflozin (S) propylene glycol hydrate; (2) metformin hydrochloride; hydroxypropyl cellulose as a binder; microcrystalline cellulose as a filler; sodium starch glycolate or hydroxypropyl cellulose, low substituted as a disintegrant; and magnesium stearate as a lubricant."

"SGLT2 inhibitor" stands for sodium glucose cotransporter 2 inhibitor, which designates a relatively new type of anti-diabetic agent.

Claim 24 as granted defined:

"A method of preparing an immediate release pharmaceutical formulation comprising : (1) an SGLT2 inhibitor selected from dapagliflozin and dapagliflozin (S)-propylene glycol hydrate; (2) metformin or a pharmaceutically acceptable salt or solvate thereof; and (3) optionally a coating;
the method comprising:
(a) dissolving a binder in water;
(b) adding the SGLT2 inhibitor to the binder and the water to obtain an SGLT2 inhibitor-binder-water solution or a suspension of SGLT2 inhibitor-binder-water;

(c) spraying the SGLT2 inhibitor-binder-water solution or suspension on metformin in a fluidised bed, thereby performing a fluid bed granulation to obtain granules;
(d) milling the granules;
(e) mixing the granules with a filler and a disintegrant;
(f) further mixing with a lubricant to obtain a final mixture;
(g) compressing the final mixture into tablets; and
(h) optionally coating the tablets."

Dependent claims 9, 14, 33 and 34 as granted defined the formulation in the form of a tablet with a coating comprising specific components.

II. Four oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed.

III. The patent proprietors and opponents 1, 2 and 3 filed appeals against the interlocutory decision of the opposition division that the patent as amended in accordance with auxiliary request 1 met the requirements of the EPC.

The decision was based on the patent as granted (main request) and auxiliary request 1 filed on 7 April 2021.

Claim 1 of auxiliary request 1 defined:

"An immediate release pharmaceutical formulation in the form of an optionally coated tablet comprising: (1) an SGLT2 inhibitor selected from dapagliflozin and

dapagliflozin (S) propylene glycol hydrate; (2) metformin hydrochloride; hydroxypropyl cellulose as a binder; microcrystalline cellulose as a filler; sodium starch glycolate or hydroxypropyl cellulose, low substituted as a disintegrant; and magnesium stearate as a lubricant." [underlining by the Board to identify the amendments with respect to claim 1 as granted]

Claim 19 of auxiliary request 1 defined:

"A method of preparing an immediate release pharmaceutical formulation according to claim 1; the method comprising:
(a) dissolving a binder in water;
(b) adding the SGLT2 inhibitor to the binder and the water to obtain an SGLT2 inhibitor-binder-water solution or a suspension of SGLT2 inhibitor-binder-water;
(c) spraying the SGLT2 inhibitor-binder-water solution or suspension on metformin in a fluidised bed, thereby performing a fluid bed granulation to obtain granules;
(d) milling the granules;
(e) mixing the granules with a filler and a disintegrant;
(f) further mixing with a lubricant to obtain a final mixture;
(g) compressing the final mixture into tablets; and
(h) optionally coating the tablets." [underlining by the Board to identify the amendments with respect to claim 24 as granted]

Claims 9, 14, 33 and 34 as granted were deleted in auxiliary request 1.

In its decision the opposition division cited *inter alia* the following documents:

D1: ClinicalTrials.gov archive, History of Changes for Study: NCT01002807, latest version 14 October 2016
D2: WO 2008/116179 A1
D9: WO 2009/121945 A2
D14: WO 2010/045656 A2
D22: Diabetes, Obesity and Metabolism (2009), 11, 527-533
D25: FORMULATION AND ANALYTICAL DEVELOPMENT FOR LOW-DOSE ORAL DRUG PRODUCTS, edited by Jack Zheng, John Wiley & Sons, Inc., 2009, pages 63, 77, 78, 86, 87, 108, 109, 112, 114
D34: Diabctologia (2009), 52:[Suppl1] S76, abstract 169 of Oral Presentation 29: Novel therapies for type 2 diabetes mellitus, 45th EASD Annual Meeting of the European Association for the Study of Diabetes, Vienna, Austria, 30 September - 2 October 2009
D37: WO 2007/131930 A1.
D38: Handbook of Pharmaceutical Granulation Technology, edited by Dilip M. Parikh, second edition, 2005, Process-related variables, pages 274-277
D58: Drug Development and Industrial Pharmacy (1999), 25(10), 1129-1135
D60: WO 2010/092125 A1

The opposition division arrived at the following conclusions:

(a) Document D60 was not admitted for being late filed and lacking *prima facie* relevance.

(b) Claims 9, 14, 33 and 34 as granted related to subject-matter extending beyond the content of the application as filed

(c) Auxiliary request 1 complied with Article 84 EPC. Claim 1 was based on claim 2 as granted. Claim 1 was not limited to tablets obtained by co-granulation and thus covered the tablets of comparative example 10 of the patent. Claim 19 evidently referred with "a binder", "a filler", "a disintegrant" and "a lubricant" to the specific excipients defined in claim 1.

(d) Auxiliary request 1 complied with Article 123(2) EPC. Claim 1 found an adequate basis in claims 1 and 4 as originally filed and claim 19 found an adequate basis in claims 35-36 as originally filed taking account of the disclosure in Figure 3.

(e) Auxiliary request 1 complied with Article 83 EPC. The patent presented with the exemplified immediate release formulations, including example 10, sufficient guidance for the skilled person to select appropriate amounts of the tablet components to prepare the immediate release tablets of claim 1 and to carry out the method of claim 19 taking account of the common general knowledge presented in document D38.

(f) Auxiliary request 1 complied with the requirement of novelty. Document D14 described a pharmaceutical composition comprising a biguanide and a SGLT2 inhibitor wherein, contrary to the claims of the patent, at least one active agent is in slow release form. Moreover, within document D14 multiple selections of components were required to arrive at the tablets as defined in the claims of auxiliary request 1.

(g) Document D2, in particular the tablets of example 7, represented the closest prior art. The difference between the subject-matter of auxiliary request 1 and this prior art concerned the additional presence of metformin hydrochloride, hydroxypropyl cellulose (HPC) as binder and sodium starch glycoloate (SSG) or hydroxypropyl cellulose, low substituted (LS-HPC) as disintegrant.

The objective technical problem was the provision of a dosage form with increased efficacy in treating hyperglycemia, while maintaining immediate release and ease of administration.

In view of the physicochemical properties of the drugs involved and the unpredictable outcome of tableting two drugs together it was not obvious to co-formulate the two active agents with the defined excipients to provide a tablet for immediate release of the active agents.

IV. With the statement of grounds of appeal the patent proprietors upheld their main request concerning the patent as granted and filed auxiliary requests 1a, 1b, 1c. With the reply to the appeals by the opponents the patent proprietors further filed auxiliary requests 2-10, 11a, 11b, 11c and 12-19. In the course of the appeal proceedings, the patent proprietors withdrew the request for the patent to be maintained as granted as well as auxiliary requests 1a, 10 and 11a.

Auxiliary request 1b, which became the patent proprietors' new main request, corresponds to auxiliary request 1 on which the decision under appeal was based.

Auxiliary request 1c corresponds to auxiliary request 1b, except for the amendments in the method of claim 19, which defines:

"A method of preparing an immediate release pharmaceutical formulation according to claim 1; the method comprising:
(a) dissolving the binder in water;
(b) adding the SGLT2 inhibitor to the binder and the water to obtain an SGLT2 inhibitor-binder-water solution or a suspension of SGLT2 inhibitor-binder-water;
(c) spraying the SGLT2 inhibitor-binder-water solution or suspension on the metformin hydrochloride in a fluidised bed, thereby performing a fluid bed granulation to obtain granules;
(d) milling the granules;
(e) mixing the granules with the filler and the disintegrant;
(f) further mixing with the lubricant to obtain a final mixture;
(g) compressing the final mixture into tablets; and
(h) optionally coating the tablets." [underlining by the Board to identify the amendments with respect to claim 19 of auxiliary request 1b]

Claim 1 of auxiliary request 2 corresponds to claim 1 of auxiliary request 1b, except that the formulation is further defined by the feature that "the formulation is 0.1-2% dapagliflozin or dapagliflozin (S) propylene glycol hydrate; 55-85% metformin hydrochloride; 1-15% hydoxypropyl cellulose; 2-25% microcrystalline cellulose; 1-12% sodium starch glycolate or 3-10% hydroxypropyl cellulose, low substituted; and 0.25-5% magnesium stearate."

Claim 1 of auxiliary request 3 corresponds to claim 1 of auxiliary request 1b, except that the formulation is further defined by the feature that "the formulation is 0.25-0.8% dapagliflozin or dapagliflozin (S) propylene glycol hydrate; 62-77% metformin hydrochloride; 3-10% hydoxypropyl cellulose; 5-21% microcrystalline cellulose; 5-9% sodium starch glycolate or 5-8% hydroxypropyl cellulose, low substituted; and 0.6-1.4% magnesium stearate."

Claim 1 of auxiliary request 4 corresponds to claim 1 of auxiliary request 3, except that the formulation is further defined by the feature that "the percentage relative standard deviation of the content uniformity of the tablet is less than or equal to 6% of the target amount of dapagliflozin and dapagliflozin (S) propylene glycol hydrate per tablet as measured by either (a) dissolving 6-10 tablets in separate flasks and analyzing each using high performance liquid chromatography or (b) dissolution of 3 to 6 tablets in 1000 mL of phosphate buffer pH at 6.8 at 37°C and 75 rpm paddle speed before increasing the paddle speed to 250 rpm in each vessel for 15 minutes and then withdrawing a sample for each vessel and analyzing by high performance liquid chromatography."

Claim 1 of auxiliary request 5 corresponds to claim 1 of auxiliary request 3, except that the formulation is further defined by the feature that the formulation comprises a co-granulation of the defined active agents.

Claim 1 of auxiliary request 6 corresponds to auxiliary request 3, except that the formulation is further defined by the feature that the formulation comprises a fluid bed co-granulation of the defined active agents.

Claim 1 of auxiliary request 7 corresponds to claim 1 of auxiliary request 3, except that the formulation is further defined by the feature that "the immediate release pharmaceutical formulation is obtainable by a method comprising a step of spraying a solution or suspension comprising dapagliflozin (S) propylene glycol hydrate and a binder onto metformin particles in a fluid bed equipment." The wording of the method claim 10 of auxiliary request 7 corresponds to the wording of claim 19 of auxiliary request 1c.

Claim 1 of auxiliary request 8 corresponds to claim 1 of auxiliary request 3, except that the formulation is further defined by the feature that the formulation is obtainable by a method comprising similar steps (a) to (h) as defined in claim 19 of auxiliary request 1c. Claim 1 of auxiliary request 9 corresponds to claim 1 of auxiliary request 1b, except that the formulation is further defined by the feature that the formulation comprises a fluid bed co-granulation of the defined components and comprises specific amounts defined in mg of the defined components. The wording of claim 10 in auxiliary requests 8 and 9 corresponds to the wording of claim 19 in auxiliary request 19.

Claim 1 in auxiliary requests 11b, 11c and 12-19 corresponds, respectively, to claim 1 in the main request (filed as auxiliary requests 1b), and auxiliary requests 1c and 2-9. The wording of the independent method claim in auxiliary requests 11b, 11c and 12-19 corresponds to the wording of claim 19 of auxiliary request 1c, except for the amendment in steps (a) and (b) that the SGLT2 inhibitor is added to the binder-solution or simultaneous added with the binder to water.

Claim 1 of auxiliary request 17 thus defines:

"An immediate release pharmaceutical formulation in the form of an optionally coated tablet comprising: (1) an SGLT2 inhibitor selected from dapagliflozin and dapagliflozin (S) propylene glycol hydrate; (2) metformin hydrochloride; hydroxypropyl cellulose as a binder; microcrystalline cellulose as a filler; sodium starch glycolate or hydroxypropyl cellulose, low substituted as a disintegrant; and magnesium stearate as a lubricant; wherein the is 0.25-0.8% dapagliflozin or dapagliflozin (S) propylene glycol hydrate; 62-77% metformin hydrochloride; 3-10% hydoxypropyl cellulose; 5-21% microcrystalline cellulose; 5-9% sodium starch glycolate or 5-8% hydroxypropyl cellulose, low substituted; and 0.6-1.4% magnesium stearate; and the immediate release formulation is obtainable by a method comprising a step of spraying a solution or suspension comprising dapagliflozin (S) propylene glycol hydrate and a binder onto metformin particles in a fluid bed equipment."

Claim 10 of auxiliary request 17 thus defines:

"A method of preparing an immediate release pharmaceutical formulation according to claim 1; the method comprising:
(a) dissolving the binder in water to obtain a binder-solution;
(b) adding the SGLT2 inhibitor to the binder-solution to obtain an SGLT2 inhibitor-binder-water solution or a suspension of SGLT2 inhibitor-binder-water; or
(a) simultaneously adding the binder and the SGLT2 inhibitor to water;

(b) dissolving the binder and part or all of the SGLT2 inhibitor to obtain an SGLT2 inhibitor-binder-water solution or a suspension of SGLT2 inhibitor-binder-water;
(c) spraying the SGLT2 inhibitor-binder-water solution or suspension on the metformin hydrochloride in a fluidised bed, thereby performing a fluid bed granulation to obtain granules;
(d) milling the granules;
(e) mixing the granules with the filler and the disintegrant;
(f) further mixing with the lubricant to obtain a final mixture;
(g) compressing the final mixture into tablets; and
(h) optionally coating the tablets."

V. In the letter of 28 June 2022 opponent 1 presented objections against auxiliary requests 2-9, 11b, 11c and 12-19.

VI. The following additional documents have been cited during the appeal procedure:

A65: WO2007/041053 A2
A66: Fachinformation, metformin Aristo N 500 mg /- 850 mg /- 1000 mg Filmtabletten, July 2017

A67: https://www.medicines.org.uk/emc/medicine/-27188#gref, SmPC "Forxiga 5 mg film coated tablets"
A68: https://www.medicines.org.uk/emc/medicine/23244#gref, SmPc Metformin 500mg (PL 16363/0111) tablets

A69: BMS press release from March 2009

Documents A65 and A66 were filed by opponent 2 with the statement of grounds of appeal.

Documents A67 and A68 were filed by the proprietors with their letter of 17 October 2022. Document A69 was filed by the proprietors with their letter of 21 December 2023.

VII. In its communication pursuant to Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that

- documents A65-A68 and D60 as well as an objection of lack of novelty from opponent 1 by mere reference to submissions during the first instance proceedings were not to be admitted

- claim 24 of the patent as granted comprised subject-matter extending beyond the application as originally filed

- subject-matter of the claims 1 and 24 as granted was sufficiently disclosed in the patent, but did not involve an inventive step in view of document D2 or any of documents D9 and D37 as starting point in the prior art

- the amendments in the auxiliary requests did not overcome the objection of lack of inventive step.

VIII. Oral proceedings were held on 29 February 2024.

IX. The arguments of the opponents relevant to the present decision are summarized as follows:

(a) Admittance documents A65-A69 and D60

Documents A65 and A66 were to be admitted as legitimate response to the finding on inventive step in the decision under appeal. Document D65 represented evidence of the common general knowledge that the binder HPC and the disintegrant SSG allowed the preparation of fixed dose combinations of relatively large amounts of Metformin HCl with relatively low amounts of a further antidiabetic agent. Document A66 demonstrated that it was well known how to prepare high dose (500-1000 mg) metformin tablets for immediate release; starting from such tablets the skilled person would not expect any problem from adding minor amounts of a further antidiabetic agent.

Document D60 represented a relevant alternative starting point in the prior art, which should be considered for the assessment of inventive step during the appeal proceedings.

Documents A67-A69 lacked relevance and their admittance into the appeal proceedings was not justified.

(b) Main request - Inventive step

The tablet defined in claim 1 of the main request was characterized by the defined components and not by any method for their preparation. Document D2 represented a suitable starting point in the prior art describing examples of immediate release tablets comprising dapagliflozin as well as the possible combination with metformin. The difference of the claimed tablet with the tablets in document D2 concerned the selection of the excipients. No

unexpected effects had been demonstrated for the claimed tablets in comparison with the prior art. The claimed subject-matter was obvious as an alternative with respect to the tablets of document D2, because document D2 already described the excipients defined in claim 1 of the main request in lists of suitable excipients for formulating dapagliflozin tablets and indicated the possible formulation of dapagliflozin in a fixed dose combination with metformin. Any effect of the use of HPC as binder on the tensile strength of the tablets was obvious in view of document D58, which described the binder HPC as providing optimal mechanical properties for tablets.

(c) Auxiliary requests

Auxiliary requests 1c, 2-9, 11b, 11c and 12-17 should not be admitted, because they were late filed, gave rise to new objections and anyway did not overcome the objections raised.

In particular, auxiliary request 7 did not meet the requirement of Article 123(2) EPC, because process claim 10 of auxiliary request 7 included methods in which the SGLT2 inhibitor is added to an aqueous suspension of the binder, whereas the original disclosure only mentions the addition of the SGLT2 inhibitor to a solution of the binder or the simultaneous addition of the binder and the SGLT2 inhibitor to water.

Auxiliary request 17 did not comply with Article 84 EPC. Claim 1 defined a tablet comprising metformin hydrochloride, but defined for its preparation the use of metformin particles. Claim 1 further failed

to define the necessary product-by-process features for preparing a tablet, including the use of HPC as the binder in the liquid to be sprayed on the metformin particles.

Auxiliary request 17 did furthermore not comply with Article 123(2) EPC. Claim 1 covered tablets which were not necessarily prepared by the defined process, whereas the patent only disclosed those tablets which were actually prepared by the defined process. The product-by-process feature in claim 1 further failed to include the steps of the original process claim 35. This feature could not be based on a passage of page 2 of the application as filed, which referred to spraying the granulating liquid "onto **the** metformin particles" as opposed to "onto metformin particles" as defined in the claim. Claim 1 also involved the undisclosed combination of multiple selections of features. Furthermore, process claim 10 defined the spraying of a granulating liquid on the metformin hydrochloride and required the binder HPC in the liquid, whereas originally filed claim 35 referred to the spraying of the liquid on metformin and did not require HPC as binder in the liquid.

The subject-matter of claim 1 of auxiliary request 17 lacked an inventive step starting from document D2 for the same reasons as the main request. Moreover, documents D9 and D37 described tablets with fixed dose combinations of metformin with additional antidiabetic agents obtained by co-granulation under fluidized bed conditions. The skilled person would combine the teaching of documents D9 or D37 with the teaching in document D2 to arrive at the claimed tablets, especially

because it was common knowledge that fluidized bed granulation was suitable for achieving high content uniformity as evidenced by document D25.

Documents D9 and D37 also represented suitable alternative starting points for the assessment of inventive step of the subject-matter of claim 1 of auxiliary request 17. The claimed tablets differed from the tablets of documents D9 and D37 in the nature of the additional antidiabetic agent. Whilst the examples in document D9 involved copovidone as binder, this document mentioned HPC as an alternative binder. The objective technical problem in view of documents D9 or D37 concerned the provision of an alternative fixed dose formulation with metformin. The choice of dapagliflozin as alternative antidiabetic agent for combination with metformin was obvious to the skilled person in view of documents D2 or D34, which already described the combination of metformin with dapagliflozin.

X. The arguments of the patent proprietors relevant to the present decision are summarised as follows:

(a) Admittance documents A65-A69, D60

Documents A65, A66 and D60 lacked relevance and their admittance into the appeal proceedings was not justified.

Documents A67-A69 confirmed the common general knowledge that the maximum dose for dapagliflozin is far below the minimum recommended dose for metformin. In this context document A69 was to be admitted in response to the Board's preliminary

opinion that documents A67 and A68 were not to be admitted.

(b) Main request - Inventive step

In line with the teaching of the patent as a whole the tablet defined in claim 1 of the main request was to be interpreted as a co-granulated tablet. Document D2 represented the closest prior art describing in examples 3 and 7 immediate release formulations comprising dapagliflozin. The differences of the claimed tablet with this prior art were the presence of metformin hydrochloride and the selection of excipients, including HPC as binder. As demonstrated by the experimental results in the patent the combination of dapagliflozin with metformin hydrochloride provided for increased efficacy in treatment of hyperglycemia. The data in the patent further indicated that the use of HPC as binder together with the further defined excipients allowed for the preparation of co-granulated tablets having particularly good content uniformity and tensile strength. The experimental data presented in Table B of the letter from opponent 1 of 12 August 2020 demonstrated in this respect unexpected advantages with regard to the content uniformity and tensile strength of the tablets resulting from the use of HPC as binder over povidone, which is described in document D2 as an alternative binder for use with dapagliflozin. The objective technical problem was therefore the provision of a dosage form with increased efficacy for treating hyperglycemia and optimized content uniformity and tensile strength while maintaining immediate release and ease of administration. No prior art suggested the choice of the defined

excipients, including HPC as a binder, together with the combination with metformin hydrochloride as solution. Document D58 described the use of HPC as binder in a mono-formulation for a different drug and would therefore not have been considered by the skilled person faced with the identified objective technical problem other than by impermissible hindsight. Moreover, document D1 suggested that a fixed dose combination of dapagliflozin with metformin required an extended release form of metformin ("methformin XR").

(c) Auxiliary requests

Auxiliary requests 1c and 2-9, 11b, 11c and 12-17 addressed issues raised by the opponents and closely resembled auxiliary requests as filed during the first instance proceedings. The filing of auxiliary requests 1c and 2-17 by the patent proprietors with the statement of grounds of appeal and the reply to appeals by the opponents was justified following the findings in the decision under appeal. By contrast, the opponents had failed to address the auxiliary requests filed during the first instance proceedings and their subsequently raised objections to the patent proprietors' auxiliary requests 2-9, 11b, 11c and 12-17 should not be admitted as unjustified late amendments to their appeal case.

Process claim 10 of auxiliary request 7 complied with Article 123(2) EPC. This claim included a method in which the SGLT2 inhibitor is added to a mixture of the binder with water in which the binder was not yet completely dissolved. The application as filed described on page 16 the

addition of the SGLT2 inhibitor to a solution of the binder and alternatively the simultaneous addition of the binder and the SGLT2 inhibitor to water. The skilled person understood from the schemes in Figure 3 of the application as filed that the SGLT2 inhibitor could be added at any stage of dissolution of the binder.

Auxiliary request 17 complied with Article 84 EPC. Claim 1 defined a tablet comprising metformin hydrochloride, which meant that the defined metformin particles in the product-by-process feature consisted of metformin hydrochloride. The product-by-process feature in claim 1 furthermore clearly defined the tablet as obtainable by a method including the step of spraying the defined granulating liquid onto metformin particles.

Auxiliary request 17 also complied with Article 123(2) EPC. The definition of the formulation as a tablet, dapagliflozin or its defined hydrate form as the SGLT2 inhibitor and the defined excipients and their concentration ranges were based on a preferred embodiment as defined by original claims 1-4 and 7. The product-by-process feature of claim 1 was explicitly described on page 2 of the originally application as a key feature of the disclosed invention. The spraying of the granulating liquid "on metformin particles" instead of "on the methformin particles" implied in the context of the patent no technical difference. The application as filed described the tablets as obtainable by a method comprising the defined process step, which corresponded to the definition in claim 1. Claim 10 related to the preparation of the preferred tablet of claim 1 in accordance with

the methods disclosed on page 16 of the application as filed.

Document D2 represented the closest prior art with respect to claim 1 of auxiliary request 17. The defined tablets allowed for the improved treatment of hyperglycemia due to the combination with metformin. As demonstrated by the experimental results in the patent and in in Table B of the letter from opponent 1 of 12 August 2020 the defined excipients, in particular the binder HPC, and their amounts allowed in combination with the product-by-process feature to achieve unexpected content uniformity as well as tensile strength of the tablets. The objective technical problem was the provision of a dosage form with increased efficacy for treating hyperglycemia and optimized content uniformity and tensile strength while maintaining immediate release and ease of administration. No prior art suggested the solution as defined in claim 1 of auxiliary request 17

Documents D9 and D37 described fixed dose combinations of metformin with additional antidiabetic agents. These documents did not mention dapagliflozin as the additional antidiabetic agent and therefore represented more remote prior art than document D2. The skilled person had without any mention of dapagliflozin in documents D9 or D37 also no reason to consult documents D9 or D37 when starting from document D2. In as far as documents D9 or D37 would nevertheless be consulted, the skilled person would with the teaching of these documents still not arrive at the claimed subject-matter, because neither document D9 nor document D37 suggested optimized tablet

properties from using HPC together with the dapagliflozin in the granulating liquid.

XI. Opponents 1-3 (appellants) requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

They further requested that auxiliary requests 1c and 2-9, 11b, 11c and 12-19 not be admitted and that documents A67-A69 not be admitted.

Opponent 4 (party as of right) did not submit any requests or observations during the appeal proceedings.

XII. The patent proprietors (appellants) requested that the decision under appeal be set aside and that the patent be maintained on the basis of auxiliary request 1b or 1c as filed with the statement of grounds of appeal or auxiliary requests 2-9, 11b, 11c or 12-19 as filed with the reply to the appeals by the opponents.

The patent proprietors further requested that documents A65 and A66 not be admitted and that amendments to the appeal case by opponent 1 in the letter of 28 June 2022 not be admitted.

Reasons for the Decision

1. Admittance documents A65-A69 and D60

1.1 Document A65 is a patent application and can as such not be considered as relevant evidence of the common knowledge as suggested by opponent 2.

With its reliance on document A66 as alternative starting point in the prior art for the assessment of

inventive step opponent 2 presented without justification during the appeal proceedings for the first time a fundamentally new line of argument.

In view of the dates of the latest revisions of the text in documents A67 and A68 (11 May 2022 and 3 July 2020) these documents cannot be considered as relevant evidence of the common general knowledge at the priority date of the patent (13 November 2009) as suggested by the patent proprietors. During the oral proceedings the patent proprietors withdrew their request for admittance of documents A67 and A68.

The Board has therefore not admitted documents A65-A68 into the appeal proceedings under Article 12(4) RPBA.

1.2 Document A69, which concerns a press release by Bristol Myers Squibbfrom 2009, was filled by the patent proprietors in response to the Board's communiciation under Article 15(1) RPBA indicating that documents A67-A68 were not to be admitted. The Board does not recognize any exceptional circumstances justified with cogent reasons for admitting document A69.

The Board has therefore not admitted document A69 into the appeal proceedings under Article 13(2) RPBA.

1.3 Document D60, which had been filed by opponent 1 as alternative starting point in the prior art with the letter of 2 March 2021, *i.e.* at a late stage in the procedure, was not admitted by the opposition division (see decision, pages 10-11, section 2.6) for lack of *prima facie* relevance. According to the opposition division this document did not address galenical aspects of combining the two active agents defined in

the patent and only presented "prophetic" examples of tablets with active antidiabetic agents.

The Board does not recognize any error in the use of discretion in the opposition division's decision not to admit document D60 nor any circumstance of the appeal case that justifies the admittance of document D60.

The Board has therefore not admitted document D60 into the appeal proceedings under Article 12(6) RPBA.

Main request

2. Main request (filed as auxiliary request 1b with the statement of grounds of appeal) - Inventive step

2.1 Starting point in the prior art

The parties agree that document D2 represents a suitable starting point in the prior art.

Document D2 describes immediate release pharmaceutical compositions comprising dapagliflozin (see D2, paragraph [0008]). The document mentions microcrystalline cellulose (MC) in a list of suitable fillers, hydroxypropyl cellulose (HPC) in a list of suitable binders, sodium starch glycolate (SSG) and hydroxypropyl cellulose, low substituted (LS HPC) in a list of suitable disintegrants, and magnesium stearate in a list of suitable lubricants (see D2, paragraphs [0038] to [0041]). Document D2 describes the possible combination of dapagliflozin with one or more other therapeutic agents, for instance an antidiabetic agent such as metformin. Such combination may according to document D2 involve separate dosage forms or a fixed dose combination which may be prepared by mixing

separate dry granulations of the active agents for compression into tablets (see D2, paragraphs [0079] to [0081] and [0107]). The document describes broad ranges for the weight percentages of the active agent and excipients in tablets or capsules (see D2, Table 1, paragraph [0050]) and presents an example of a stock granulation comprising dapagliflozin as only active agent together with *inter alia* MC, SSG and magnesium stearate as excipients (see D2, paragraph [00125], example 3) as well as an example of a tablet comprising dapagliflozin as only active agent together with *inter alia* MC and magnesium stearate as excipients (see D2, paragraph [00149], example 7).

In accordance with the considerations in T 1287/14 (section 5.2.1) the specific starting point for assessing inventive step is normally a set of features disclosed in combination in a document, such as an embodiment or example, and the assessment of inventive step involves the identification of the distinguishing features with respect to such embodiment or example. The differences of the subject-matter of claim 1 of the main request with the exemplified compositions in document D2 (examples 3 and 7) concern the co-formulation with metformin hydrochloride and the specific combination of excipients, including the use of HPC as binder.

The Board considers that for the assessment of the differences with the closest prior art the possible combination of dapagliflozin with metformin as generically described in document D2 cannot be imposed on an example in document D2 to create a new starting point in the form of an altered example representing all features of the original example together with the feature of the combination with metformin, because such

a modified example had not been specifically disclosed in document D2. As a matter of course, the information in document D2 regarding the possible combination with metformin is to be taken into account in the subsequent assessment of obviousness.

Regarding the differences with the closest prior art the Board further observes that the definition of the immediate release tablet in claim 1 of the main request by way of listing the comprised components does not in any way indicate that the tablets necessarily result from co-granulation, let alone from co-granulation in the form of spraying a granulation liquid comprising the dapagliflozin together with HPC as binder on metformin particles. Such co-granulation is described in paragraph [0011] of the patent as a key feature for preparing tablets with favourable characteristics, in particular in terms of content uniformity. However, in view of the purpose of the claims stipulated in Article 84 EPC, namely the definition of the subject-matter for which protection is sought, the Board considers that no limiting feature of the claimed subject-matter with regard to the co-granulation can be derived from the description, in particular considering that the claims themselves provide no indication for such limitation.

2.2 Objective technical problem

The patent reports results from a clinical trial involving the administration of dapagliflozin as add-on to treatment of type II diabetic patients with metformin. These results indicate that the combination allows for more effective treatment with respect to the treatment with metformin alone (see the patent, paragraphs [0138]-[0142]).

The patent further describes in examples 1-14 the preparation of tablets for fixed dose combinations of dapagliflozin with metformin hydrochloride comprising the excipients as defined in claim 1 of the main request (see the patent, paragraphs [0144]-[0186]). The preparation of the tablets in examples 1-9 and 11-14 involves the co-granulation of the active agents by spraying a granulation liquid comprising the dapagliflozin together with HPC as binder on metformin hydrochloride. Example 10 concerns tablets prepared from separate granulates of the active agents (see the patent, paragraphs [0165]-[0171]).

The following results for the content uniformity for dapagliflozin and the tensile strength of the exemplified tablets are presented in Table 1 of the patent (see page 29):

Table 1. Content uniformity, tensile strength and disintegration for Examples 1-14.

Example	Content uniformity of Dapa (% RSD, n=tablets tested)	Tensile strength (MPa, CP[a])	Disintegration time (minutes, n=tablets tested)
1	NA	2.03, 255	approx. 15[c], n=3
2	1.0, n=10	1.92, 246	15-16, n=3
3	0.6, n=3[b]	1.96, 204	16, n=3
4	0.5, n=3[b]	2.31, 204	17-18, n=6
5	0.8, n=3[b]	2.13, 204	15-17, n=6
6	1.6, n=3[b]	2.27, 199	13-15, n=6
7	0.5, n=3[b]	2.02, 201	10-11, n=6
8	0.6, n=3[b]	1.96, 209	12-13, n=6
9	0.5, n=3[b]	1.87, 193	approx. 12, n=3
10	7.6, n=6[b]	1.44, 202	11-12, n=3
11	0.7, n=3[b]	1.80, 205	7-8, n=6
12	0.7, n=10	1.97, 231	approx. 17[c], n=3
13	0.6, n=10	1.87, 231	approx. 16[c], n=3
14	0.5, n=5[b]	2.18, 200	approx. 17, n=6

[a] CP = Compaction Pressure (MPa); [b] Infinity testing; [c] Coated tablets

The letter from opponent 1 of 12 August 2020 (see page 8) presented in Table B the following comparative data

concerning the content uniformity and tensile strength of tablets prepared in accordance with examples 1 and 4 of the patent and corresponding tablets in which the binder HPC was replaced by povidone:

Table B:

	example	binder	CU[1] no of tbls (% RSD)	TS[2] (MPa, Compaction Pressure)
B.1	Patent opposed - Example 1 (data as shown in the patent)	HPC SSL	none	2.03 unc; 255
B.2	Repetition of Example 1	HPC SSL	0.8; 6[1.1]	1.73 unc; 204
B.3	Experimental repetition of modified Example 1 (applying a different binder but still according to the invention)	povidone (96.6 mg/tablet)	1.7; 6[1.1]	0.57 unc; 115
B.4	Patent opposed - Example 4 (data as shown in the patent)	HPC SSL	0.5; 3	2.31 unc; 204
B.5	Repetition of Example 4	HPC SSL	0.7; 6[1.1]	2.78 unc; 190
B.6	Experimental repetition of modified Example 4 (applying a different binder but still according to the invention)	povidone (62.9 mg/tablet)	4.4; 6[1.1]	0.52 unc; 194
B.7	Experimental repetition of modified Example 4 (applying a different binder but still according to the invention)	povidone (62.9 mg/tablet, povidone solution at 32%)	3.2; 6[1.1]	0.59 unc; 194

1=CU=content uniformity:
1.1. Each of a number of tablets (6-10 units) were dissolved in a separate flask and analyzed using HPLC (High Performance Liquid Chromatography). The relative standard deviation in percent (%RSD) was calculated on the obtained results.
unc=uncoated
2=TS=tensile strength:
The crushing strength of the tablets was determined by the diametral compression method using a Holland C50 equipment. The crushing strength was then divided by the tablet break area to obtain the TS value.

The results in Table 1 of the patent and Table B of the letter of 12 August 2020 indicate that the fixed dose tablets comprising dapagliflozin and metformin in which HPC is used as binder, including the tablets of example 10, show improved tensile strength in comparison to tablets in which the HPC is replaced by copovidone as binder.

At the same time, the resuls in Table 1 of the patent indicate that the preparation of the tablets of example 10 from separate granulates of the active agents does not achieve the high content uniformity of the tablets of examples 1-9 and 11-14 prepared from a co-

granulation of the active agents by spraying a granulation liquid comprising the dapagliflozin together with HPC as binder on metformin hydrochloride. The importance of the particular co-granulation method involving the spraying of a granulation liquid comprising the dapagliflozin together with a binder onto the metformin particles is indeed explicitly mentioned in paragraph [0011] of the patent. The results in Table B only indicate an improved content uniformity from the use of HPC as binder instead of povidone as binder for tablets prepared by a method involving the mentioned particular co-granulation. This effect of the use of HPC on the content unity can therefore not be taken into account in relation to the subject-matter of claim 1 of the main request, which is not restricted to tablets prepared from a corresponding co-granulate.

In view of the available evidence the Board identifies the objective technical problem starting from document D2 as the provision of a dosage form with increased efficacy for treating hyperglycemia having optimized tensile strength while maintaining immediate release and ease of administration.

2.3 Assessment of the solution

Starting from document D2 the skilled person had a reasonable expectation of success that co-administration of dapagliflozin and metformin hydrochloride will lead to improved efficacy. Document D2 itself already suggested the combination of dapagliflozin with metformin (see D2, paragraphs [0079]-[0081]). Moreover, document D22, a review article on fixed-dose single tablet antidiabetic combinations, indicates that therapy with metformin is

commonly combined with further antidiabetic agents to enhance treatment efficacy (see D22, page 527, right column and page 528, right column). In fact, document D34 (see abstract under "Results") reports essentially similar beneficial results from treatment with dapagliflozin as add-on to treatment with metformin as relied upon in the patent.

Document D2 further suggested that in case of combination treatment the agents may be administered in the form of a fixed dose tablet (see D2, paragraph [0107]). It is evident that such a fixed dose combination will maintain the ease of administration by avoiding extra tablets (compare the review in D22, page 532, under "Conclusion").

Document D1 describes a bioavailability study of fixed dose formulations of dapagliflozin and Metformin Extended Release (XR) (see D1, page 3, under "Study Identification"). However, neither the reference in document D2 to the combination of dapagliflozin with metformin nor the study in document D34 provide any indication that the use of an extended release form of metformin was required for providing a fixed dose combination of dapagliflozin and metformin.

Faced with the identified objective technical problem the skilled person would therefore be motivated to combine dapagliflozin and metformin, for instance in the form of its commonly used hydrochlorde, in a fixed dose combination tablet for immediate release and to select suitable excipients for such a tablet.

The mechanical strength of tablets is evidently a property which the skilled person seeks to optimize. For the actual selection of the excipients, in

particular the binder, the skilled person would therefore therefore take account of available information concerning the effect of binders on the mechanical strength of tablets and thus consider the teaching of document D58, which describes a study investigating the effects of different binders on physical characteristics of tablets (see D58, Abstract). Whilst document D58 refers to experimental results from tablets comprising acetaminophen, the document recommends HPC in general as a binder in tablets which provides optimal physical characteristics of the tablets, including tensile strength (see D58, pages 1131-1132, under "Mechanical Experiments" and Figures 2 and 5; see also page 1134, under "Conclusions"). The skilled person would therefore in view of the information in document D58 be motivated to select HPC as binder to achieve optimal physical characteristics, including tensile strength, in a fixed dose combination tablets for dapagliflozin and metformin.

As observed in section 2.1 above document D2 already describes the binder HPC together with the further excipients defined in claim 1 of the main request as conventional excipients which are suitable for use in tablets for dapagliflozin (see D2, paragraphs [0038] to [0041]). The skilled person had no reason to doubt that these conventional excipients were indeed compatible with metformin in a fixed dose combination tablet.

Faced with the objective technical problem the skilled person would therefore on the basis of the prior art arrive at the fixed dose combination of dapagliflozine and metformin hydrochloride in a tablet for immediate release defined in claim 1 as an obvious solution to the identified objective technical problem.

2.4 Accordingly, the Board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step.

Auxiliary requests

3. Admittance of auxiliary requests 1c and 2-9, 11b, 11c and 12-17 and admittance of the opponents' objections against the auxiliary requests

3.1 Except for the amendments in the method claims by the use of the definite article before the tablet components in steps (a), (c), (e) and (f) and the specification in step (c) of "metfromin HCL" auxiliary requests 1c, 2-9, 11b, 11c and 12-17 reflect the amendments in auxiliary requests which had previously been submitted by the patent proprietors before the opposition division. Auxiliary requests 1c, 2-9, 11b, 11c and 12-17 address objections raised by the opponents before the opposition division. The Board considers that following the finding in the decision by the opposition division that auxiliary request 1 (corresponding to the final main request in the appeal proceedings) complied with the requirements of the EPC and in reaction to the appeals from the opponents against this decision the filing of auxiliary requests 1c, 2-9, 11b, 11c and 12-17 by the patent proprietors is justified under Article 12(4) RPBA.

3.2 The Board considers the opponents' objections regarding the allowability of auxiliary requests 2-9, 11b, 11c and 12-17 as first raised in the letter of 28 June 2022 from opponent 1 justified under Article 13(1) RPBA as response to the filing of these requests in the reply to the appeal by the patent proprietors.

4. Auxiliary requests 1c and 2-6

4.1 Claim 1 of auxiliary request 1c corresponds to claim 1 of the main request. Auxiliary request 1c does therefore not comply with the requirement of inventive for the same reason as the main request.

4.2 Claim 1 of auxiliary request 2 further defines the amounts of the defined components of the tablet as 0.1-2% dapagliflozin or dapagliflozin (S) propylene glycol hydrate, 55-85% metformin hydrochloride, 1-15% hydoxypropyl cellulose, 2-25% microcrystalline cellulose, 1-12% sodium starch glycolate or 3-10% low substituted hydroxypropyl cellulose and 0.25-5% magnesium stearate.

Claim 1 of auxiliary request 3 further defines the amounts of the defined components of the tablet as 0.25-0.8% dapagliflozin or dapagliflozin (S) propylene glycol hydrate, 62-77% metformin hydrochloride, 3-10% hydoxypropyl cellulose, 5-21% microcrystalline cellulose, 5-9% sodium starch glycolate or 5-8% low substituted hydroxypropyl cellulose and 0.6-1.4% magnesium stearate.

The amounts of dapagliflozin and the excipients as defined according to auxiliary requests 2 and 3 are in line within the ranges for suitable amounts of these components as indicated in document D2 (see D2, paragraphs [0029]-[0036] and paragraph [0050] Table I; see also paragraph [0147] the tablet composition of example 7). The defined amount of metformin hydrochloride corresponds to conventional amounts of metformin in fixed dose combinations (see document D22,

page 530, Table 1). As no evidence of any unexpected effect associated with the defined amounts of the tablet components can be recognized, the Board considers that auxiliary requests 2 and 3 do also not comply with the requirement of an inventive step.

4.3 Claim 1 of auxiliary request 4 further defines with respect to claim 1 of auxiliary request 3 the percentage relative standard deviation of the content uniformity of the tablet to be less than or equal to 6% of the dapaglilfozin target amount.

Claim 1 of auxiliary request 5 further defines with respect to claim 1 of auxiliary request 3 that the tablet comprises a "co-granulation" of the defined active agents.

Claim 1 of auxiliary request 6 further defines with respect to claim 1 of auxiliary request 3 that the tablet comprises a "fluid bed co-granulation" of the defined active agents.

The definitions for the tablet in auxiliary requests 4-6 thus still lack the feature of the preparation by the particular co-granulation method by spraying of a granulation liquid comprising the dapagliflozin together with a binder onto the metformin particles, which according to paragraph [0011] of the patent allows for achieving the very high content uniformity described for examples 1-9 and 11-14 in Table 1 of the patent as discussed in section 2.2 above.

Fluidized bed granulation was a well known technique to achieve acceptable content uniformity (see document D25, page 86, under "Summary"). Moreover, fluidized bed granulation had according to document D37 already been

successfully applied in the preparation of fixed dose tablets of metformin with repaglinide using HPC as binder (see document D37, page 5, lines 28-32 and pages 17-19, example 14).

The additional features in auxiliary requests 5 and 6 are therefore considered to relate to obvious techniques for achieving acceptable content uniformity. The additional feature in auxiliary request 4 is considered to relate merely to such acceptable content uniformity which is achievable using such techniques.

Auxiliary requests 4 to 6 do therefore also not comply with the requirement of an inventive step.

5. Auxiliary request 7

5.1 The wording of claim 10 of auxiliary request 7, which relates to a method for preparing an immediate release pharmaceutical formulation corresponds to the wording of claim 19 of auxiliary request 1c.

As confirmed by the patent proprietors during the oral proceedings the method of claim 10 of auxiliary request 7 includes in steps (a) and (b) the possibility of adding the SGLT2 inhibitor to a combination of the binder and the water in which the binder is not yet fully dissolved to form a binder-solution.

5.2 The application as filed states on page 16, lines 17-18:

"Preferred methods of preparing the formulations of the present invention are described in Figure 3."

Figure 3 presents the following scheme:

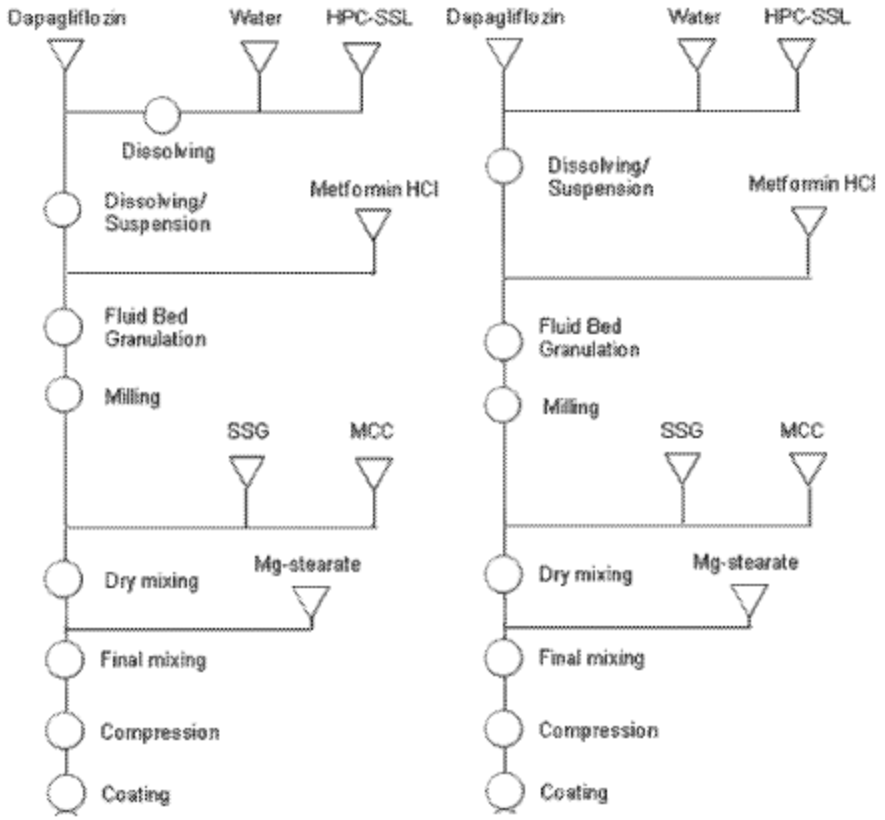

Figure 3

The statement in the application as filed concerning the preferred methods of Figure 3 is immediately followed by the following explanations (see page 16, lines 18-31):

"One method comprises: (a) dissolving a binder in water to obtain a binder-solution; (b) adding a SGLT2 inhibitor to the binder-solution to obtain an SGLT2 inhibitor-binder-water solution or a suspension of SGLT2 inhibitor-binder-water (...) and (h) optionally coating the tablets. An alternative method comprises:

(a) simultaneously adding a binder and an SGLT2 inhibitor to water; (b) dissolving the binder and part or all of the SGLT2 inhibitor to obtain a SGLT2 inhibitor-binder-water solution or a suspension of SGLT2 inhibitor-binder-water (...)and (h) optionally coating the tablets."

Claims 35 and 40 of the application as filed define these two alternative methods by steps (a) to (h) in the same wording.

5.3 According to the alternative methods described on page 16 and defined in claims 35 and 40 of the application as filed the SGLT2 inhibitor is either added to a solution of the binder in water or added together with the binder to the water. These methods do therefore not include the possibility of adding the SGLT2 inhibitor to a combination of the binder and the water in which the binder is not yet fully dissolved to form a binder-solution.

The patent proprietors argued that the skilled person nevertheless understood from the schemes of Figure 3 that the SGLT2 inhibitor could be added at any stage of dissolution of the binder between the extremes of the alternatives described on page 16. However, in the scheme on the left side of Figure 3 the uninterrupted line from the supply of the binder (HPC-SSL) and the water to the circle labeled "Dissolving" indicates that the binder is first dissolved in the water before the SGLT2 inhibitor (dapagliflozin) is added, which corresponds to the first alterative described on page 16. Moreover, in the scheme on the right side of Figure 3 the uninterrupted line from the supply of the SGLT2 inhibitor (dapagliflozin), the binder (HPC-SSL) and the water to the circle labeled "Dissolving/Suspension"

indicates that the SGLT2 inhibitor, the binder and the water are simultaneously combined to provide the granulation liquid in the form of a solution or suspension, which corresponds to the second alternative described on page 16. The method in which the SGLT2 inhibitor may possibly be added to a combination of the binder and the water in which the binder is not yet fully dissolved to form a binder-solution can therefore not be directly and unambiguously derived from the schemes of Figure 3.

5.4 Accordingly, the Board concludes that the subject-matter of claim 10 of auxiliary request 7 does not comply with Article 123(2) EPC.

6. Auxiliary requests 8-9

The wording of claim 10 in auxiliary requests 8 and 9 corresponds to the wording of claim 10 of auxiliary request 7. Auxiliary requests 8 and 9 do therefore not comply with Article 123(2) EPC for the same reason as set out in section 4 above for auxiliary request 7.

7. Auxiliary requests 11b, 11c, 12-16

The wording of claim 1 in auxiliary requests 11b, 11c and 12-16 corresponds, respectively, to the wording of claim 1 in the main request, auxiliary request 1c and auxiliary requests 2-6.

Auxiliary requests 11b, 11c and 12-16 do therefore not meet the requirement of inventive step for the same reasons as set out for the main request, auxiliary request 1c and auxiliary requests 2-6 in sections 2 and 4 above.

8. Auxiliary request 17

8.1 Article 84 EPC

Claim 1 defines a tablet comprising an SGLT2 inhibitor and metformin hydrochloride which is obtainable by a method comprising a step in which a granulation liquid comprising the SGLT2 inhibitor (dapagliflozin (S) glycol hydrate) and a binder is sprayed onto metformin particles. According to the Board it is in the context of the present patent clear that the metformin particles consist of metformin hydrochloride.

The Board further considers that the skilled person recognizes that the defined spraying of the granulation liquid onto the metformin particles in a fluid bed equipment results in a granulate which can be processed into tablets by conventional procedures.

The Board therefore concludes that auxiliary request 17 is not affected by the objections raised by the opponents under Article 84 EPC.

8.2 Article 123(2) EPC

8.2.1 The application as originally filed defines in claim 1 an immediate release pharmaceutical formulation comprising an SGLT2 inhibitor and metformin (or pharmaceutically acceptable salts or solvates of these agents). The tablet form was originally described as the preferred form (see for instance the application as filed, page 4, lines 20-21). The application as originally filed discloses dapagliflozin and dapagliflozin (S) propylene glycol hydrate as the SGLT2

inhibitor, the metformin hydrochloride together with the excipients as well as the defined concentration ranges for the tablet components defined in claim 1 of auxiliary request 17 in the context of a preferred embodiment (see claim 7 as originally filed with reference by dependency to claims 2-4 as originally filed).

The application as originally filed further comprises the following statement (see page 2, line 27 to page 3, line 1) regarding the importance of the co-granulation involving a granulation liquid comprising the SGLT2 inhibitor and the binder:

"After several unsuccessful attempts, including dry granulation by roller compaction and traditional wet granulation, it has now been found that both of the above requirements can be met by spraying a solution or a suspension comprising dapagliflozin or dapagliflozin (S) propylene glycol hydrate and a binder onto the metformin particles in a fluid bed equipment, thereby producing granules that have uniform dapagliflozin or dapagliflozin (S) propylene glycol hydrate content and good compaction properties."

The application as filed thus discloses in this passage a process feature required for achieving optimized content uniformity. The skilled person therefore directly and unambiguously derives from this passage that the tablets of the above mentioned preferred embodiment are to be prepared by a method comprising this key process feature in order to achieve optimized content uniformity. In this context the Board considers that the omission of the definitive article in the feature of spraying the liquid "onto metformin particles" in claim 1 of auxiliary request 17 does not

introduce any technical information extending beyond the original disclosure and merely reflects that the term "metformin particles" has no antecedent in the claim.

Accordingly, the definition of claim 1 of auxiliary request 17 does not include technical information extending beyond the content of the application as filed.

8.2.2 Claim 10 of auxiliary request 17 defines a method of preparing the tablet of claim 1 in accordance with steps (a) to (h) of the originally disclosed two alternative preferred methods cited in section 5.2 above. The use of the binder HPC in the granulating liquid and the spraying on metformin hydrochloride as defined in claim 10 of auxiliary request 17 results form the definition of the components of the tablet claim 1.

8.2.3 Accordingly, the Board concludes that auxiliary request 17 complies with Article 123(2) EPC.

8.3 Novelty

In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that the objection of lack of novelty was not to be admitted.

No substantive arguments regarding a lack of novelty of the subject-matter as defined in the claims of auxiliary request 17 were subsequently presented by the opponents.

Accordingly, the Board concludes that auxiliary request 17 complies with the requirement of novelty.

8.4 Inventive step

8.4.1 The subject-matter of claim 1 of auxiliary request 17 differs from the exemplified compositions in document D2 not only by the co-formulation with metformin hydrochloride and the specific combination of excipients, including the use of HPC as binder (as discussed in section 2.1 in relation to claim 1 of the main request), but also by the product-by-process feature of the tablets being obtainable by the method involving the spraying of the solution or suspension comprising the SGLT2 inhibitor and the binder onto metformin particles in a fluid bed equipment.

In accordance with the teaching in the patent (see page 2, line 27 to page 3, line 1) this feature contributes to the content uniformity and tensile strength of the tablets prepared from the resulting co-granulate. As specifically pointed out in the patent (see paragraph [0193]) these effects are demonstrated by the experimental results in Table 1 of the patent (see section 2.2 above), which indicate the higher content uniformity and strength for the tablets of examples 1-9 and 11-14 prepared from such a co-granulate in comparison to the tablets of example 10 prepared from separate granulates of the active agents. Moreover, the experimental results in Table B of the letter of 12 August 2020 (see section 2.2 above) indicate improved content uniformity from the use of HPC as binder instead of povidone as binder for tablets prepared by a method involving the use of a liquid comprising the SGLT2 inhibitor and the binder as defined in claim 1 of auxiliary request 17.

The objective technical problem starting from document D2 may therefore be formulated as the provision of a dosage form with increased efficacy for treating hyperglycemia having optimized content uniformity and tensile strength while maintaining immediate release and ease of administration.

Document D25, which represents textbook information on the formulation of low-dose oral drug products and thus common general knowledge in the relevant field, describes the suitability of fluid bed granulation for achieving good content uniformity, including such granulation in which a low-dose active agent is incorporated in the granulation liquid (see D25, page 78, "The third option (...)" and page 86, under "Summary"). Document D9 describes the preparation of a mono-layer fixed dose tablet comprising metformin HCl and a DPP-4 inhibitor (exemplified by "BI-1356") by a method involving the spraying a granulation liquid containing the DPP-4 inhibitor and a binder (exemplified by copovidone) on metformin under fluid bed conditions (see D9, page 23, line 19 to page 24 line 14 and pages 31-34). However, documents D25 and D9 do thereby not provide the skilled person with any information suggesting that the use of HPC as binder allows for the optimization of the content uniformity and tensile strength in a fixed dose tablet comprising dapagliflozin and metformin HCL as defined in claim 1 of auxiliary request 17.

Document D37 describes the preparation of a fixed dose tablet comprising metformin hydrochloride and the antidiabetic agent repaglinide having good content uniformity by co-granulation of the active agents under fluid bed condition (see page 5, lines 28-34). In accordance with document D37 a mixture of the

repaglinide and the metformin with a binder solution is dried in a fluidized bed granulation process (see D37, page 9, lines 1-3), which is exemplified in examples 1-13 and 20 by spraying a solution of povidone on a mixture of metformin HCl and repaglinide titurate and in examples 14-19 by spraying are a solution of HPC on such mixture in a fluid bed granulator. However, document D37 does not describe the particular co-granulation method in which the granulation liquid comprises one of the active agents as defined in claim 1 of auxiliary request 17. Moreover, document D37 does not indicate any particular advantage with regard to the content uniformity from the use of HPC as a binder instead of povidone. Accordingly, document D37 also fails to provide the skilled person with any suggestion that the use of HPC as binder allows for the optimization of the content uniformity and tensile strength in a fixed dose tablet comprising dapagliflozin and metformin hydrochloride as defined in claim 1 of auxiliary request 17.

The subject-matter of claim 1 of auxiliary request 17 was therefore not obvious to the skilled person starting from document D2.

8.4.2 The subject-matter of claim 1 of auxiliary request 17 differs from the fixed dose combination tablets of documents D9 and D37 mentioned in section 8.4.1 above in the first place in the nature of the additional antidiabetic agent to be combined with metformin HCl. Moreover, the exemplified mono-layer tablets described in document D9 comprise different excipients, including copovidone instead of HPC as binder, whereas the exemplified tablets of document D37 are not prepared by a method in which the metformin is sprayed with a

liquid comprising the binder with the additional active agent.

The experimental results from Table 1 in the patent and Table B of the letter of 12 August 2020 as discussed in section 8.4.1 above indicate that the combined effect of these differences, namely the selection of HPC as a binder together with the particular method in which a liquid comprising HPC and the SGLT2 inhibitor is sprayed on metformin particles, allows for optimized content uniformity and tensile strength of the tablets. The objective technical problem may therefore not be simply formulated as the provision of an alternative fixed dose formulation with metformin, but should take account of the demonstrated combined effect resulting from the differences over the prior art. Accordingly, the objective technical problem starting form documents D9 or D37 additionally involves the optimization of content uniformity and tensile strength in such an alternative fixed dose formulation with metformin.

The skilled person may in view of documents D2 or D34 have considered to formulate dapagliflozin with metformin hydrochloride in a fixed dose tablet. However, as explained in section 8.4.1, no prior art suggested the skilled person that the selection of HPC as binder in combination with the defined particular method of preparing the tablets allowed for the optimization of content uniformity and tensile strength in such an alternative fixed dose formulation with metformin.

The subject-matter of claim 1 of auxiliary request 17 was therefore also not obvious to the skilled person starting from documents D9 or D37.

8.4.3 Accordingly, the Board concludes that auxiliary request 17 also complies with the requirement of inventive step.

8.5 Sufficiency

In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that the patent as granted sufficiently disclosed the claimed invention.

No substantive arguments regarding any lack of sufficient disclosure of the invention as claimed in accordance with auxiliary request 17 were subsequently presented by the opponents.

Accordingly, the Board concludes that auxiliary request 17 also complies with Article 83 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside

2. The case is remitted to the opposition division with the order to maintain the patent in amended form based on the claims of the auxiliary request 17 as filed with the reply of the appellants (patent proprietors) on March 2022 and a description to be adapted thereto.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated