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Datasheet for the decision of 14 July 2022

Case Number: T 2269/19 - 3.3.07

Application Number: 10704517.1

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Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITIONS COMPRISING PRASUGREL BASE OR ITS PHARMACEUTICALLY ACCEPTABLE ACID ADDITION SALTS AND PROCESSES FOR THEIR PREPARATION

Patent Proprietor:
KRKA, D.D., Novo Mesto

Opponents:
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EGIS Gyógyszergyár Zártkörüen Müködö Részvénytársaság
Cooke, Richard
Patentree, Lda

Headword:
Pharmaceutical compositions comprising Prasugrel / KRKA

Relevant legal provisions:
EPC Art. 56, 100(a)
RPBA Art. 12(4)

Keyword:
Inventive step - (no)
Late-filed auxiliary requests - admitted (no)

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Beschwerdekammern

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Case Number: T 2269/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 July 2022

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Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 June 2019 concerning maintenance of the European Patent No. 2398468 in amended form.

Composition of the Board:

Chairman A. Usuelli
Members: E. Duval
L. Basterreix

Summary of Facts and Submissions

I. European patent 2 398 468 (the patent) was granted on the basis of 17 claims.

Claim 1 of the patent read as follows:

"A process of forming a compressed mixture comprising
a.) an effective amount of prasugrel base or its pharmaceutically acceptable salt,
b.) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms,
characterized in that lactose is not used,
by solvent free technological methods comprising the steps of
i.) optionally grinding the active agent and pharmaceutical additives, mixing them, or mixing them first and grinding them together,
ii.) subjecting a homogenous mixture of the active agent and additives to compression,
the average particle size of prasugrel or its pharmaceutically acceptable salt being in the range of 0.2 µm to 150 µm."

Claim 7 read as follows:

"Pharmaceutical composition comprising or consisting of a compressed mixture, said compressed mixture being obtainable according to the process of claim 1."

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

III. The appeals were filed by the patent proprietor (appellant P), by opponent 3 (appellant O3) and by opponent 4 (appellant O4) against the interlocutory decision of the opposition division finding that, on the basis of auxiliary request 1 filed during the oral proceedings and corresponding to auxiliary request 3 filed on 20 April 2018, the patent met the requirements of the EPC.

IV. The appealed decision cited the following documents among others:

D1: WO 2006/135605 A2
D6: Pharmaceutical Dosage Forms: Tablets, Vol. 1, 2nd ed., p. 1-24
D11: F. Asai, "CS-747, a new Platelet ADP Receptor Antagonist", Annu. Rep. Sankyo Res. Lab. 51,1-44 (1999)
D37: Efient® Summary of Product Characteristics
D39: Experimental data filed by P with letter of 12 February 2019
D40: D.M. Parikh, "Handbook of Pharmaceutical Granulation Technology", Vol. 81, 1997, pages 8-9 and 194-198
D41: M. A. Repka et al., "Pharmaceutical Applications of Hot-Melt Extrusion: Part II", Drug Development and Industrial Pharmacy, 2007, 33:10, pages 1043-1057

V. The opposition division decided in particular the following:

(a) The main request, i.e. the patent as granted, did not meet the requirements of inventive step.

The subject-matter of claim 1 of the main request differed from the closest prior art D1 by the

average particle size of prasugrel in the range of 0.2-150 µm. The technical problem was to find an alternative process for preparing a prasugrel composition. The claimed solution did not involve an inventive step in light of D6.

(b) Auxiliary request 1 met the requirements of inventive step.

The claimed subject-matter differed from D1 by:
- the average size of the prasugrel particles of 0.2-20 µm, and
- the use of prasugrel base instead of the prasugrel salt used in D1.

The presence of prasugrel base plausibly had an effect on the stability of the composition, although no improvement in stability over D1 had been shown. The technical problem was to provide an alternative stable composition comprising prasugrel. The claimed solution involved an inventive step.

VI. With the statement of grounds of appeal dated 4 November 2019, appellant P defended its case on the basis of the patent as granted as the main request, and submitted auxiliary requests 1-7.

By letter dated 8 January 2021, appellant P introduced a further auxiliary request 3A and renumbered the auxiliary requests as follows:

In claim 1 of the first auxiliary request (corresponding to auxiliary request 1 upheld by the opposition division), prasugrel was limited to prasugrel base, and its average particle size was limited to the range 0.2-20 µm.

In the second auxiliary request (filed as auxiliary request 3A on 8 January 2021), claim 1 incorporated the limitations of the first auxiliary request, and additionally mandated that "the active ingredient and solid additives are subjected to solvent free granulation using at least one additive having melting or glass transition point below 180°C by melt extrusion or melt granulation".

Claim 1 of the third auxiliary request (filed as auxiliary request 1 on 4 November 2019) differed from claim 1 as granted in that prasugrel was limited to prasugrel base, and in that the grinding/mixing step (i) was no longer optional.

Claim 1 of the fourth auxiliary request (filed as auxiliary request 3 on 4 November 2019) differed from claim 1 as granted in that "the active ingredient and solid additives are subjected to solvent free granulation using at least one additive having melting or glass transition point below 180°C by melt extrusion or melt granulation". In claim 1 of the fifth auxiliary request (filed as auxiliary request 4 on 4 November 2019), prasugrel was additionally limited to prasugrel base.

Claim 1 of the sixth auxiliary request (filed as auxiliary request 5 on 4 November 2019) differed from claim 1 as granted by the feature "prasugrel base or its pharmaceutically acceptable salt is ground to a particle size of between 1 and 10 micrometers".

Claim 1 of the seventh auxiliary request (filed as auxiliary request 6 on 4 November 2019) differed from claim 1 as granted by the feature "said compressed

mixture being in the form of a core or a tablet core in a solid oral dosage form or forming part of said core or tablet core".

Claim 1 of the eighth auxiliary request (filed as auxiliary request 7 on 4 November 2019) differed from claim 1 as granted by the feature "unbound water of the composition is controlled to be below 4 weight% of the composition".

VII. In the statement of grounds of appeal dated 24 September 2019, appellant O3 referred to the following documents D42-D44:

D42: Remington: The Science and Practise of Pharmacy, 20th Edition, 2000, 704-707
D43: US 6,693,115
D44: Pharmaceutics: The Science of Dosage Form Design, pages 116-117

VIII. Documents D46 and D47 were submitted together with appellant O4's grounds of appeal dated 4 November 2019.

D46: “Importance of Prasugrel's conversion from a salt to the base form”, FDA Center for Drug Evaluation and Research, 25 September 2008
D47: Summary review of prasugrel hydrochloride tablets, FDA Center for Drug Evaluation and Research, 9 January 2009

IX. The Board issued a communication under Article 15(1) RPBA setting out its preliminary opinion.

X. Oral proceedings before the Board were held on 14 July 2022.

XI. Appellant P requests that the decision under appeal be set aside and that the patent be maintained as granted (main request), or, alternatively, that the patent be maintained on the basis of:
- as first auxiliary request, auxiliary request 1 upheld by the opposition division, or
- as second auxiliary request, auxiliary request 3A filed on 8 January 2021, or
- as third to eighth auxiliary request, auxiliary requests 1 and 3-7 filed with the grounds of appeal dated 4 November 2019.
Appellant P further requests that:
- documents D41-D44, D46 and D47,
- the arguments of appellant O4 regarding the lack of evidence of a technical effect for the melt extrusion alternative of claim 1, and
- the arguments of opponent 1 (respondent O1) regarding the important impact on the stability of changes to the excipients shown by a comparison of example 66 with example 70,
not be admitted into the proceedings.

XII. Appellant O3 requests that the decision under appeal be set aside and that the patent be revoked. It further requests that:
- the second auxiliary request (filed as auxiliary request 3A on 8 January 2021),
- the third auxiliary request (filed with the grounds of appeal dated 4 November 2019 as auxiliary request 1), and
- the argument of appellant P based on the comparison of examples 66 and 70 with example 74b (all from item J of the opposed patent)
not be admitted into the appeal proceedings.

XIII. Appellant O4 requests that the decision under appeal be set aside and that the patent be revoked.

XIV. Respondent O1 requests that the appeal filed by the patent proprietor be rejected. It further requests that the third auxiliary request (filed with the grounds of appeal dated 4 November 2019 as auxiliary request 1) not be admitted into the appeal proceedings.

XV. Respondent O2 did not make any submission in the appeal proceedings.

XVI. Appellant P's arguments may be summarized as follows:

(a) Admittance of documents D41-D44, D46 and D47

D41-D44 had been filed late and were not highly relevant. D46 and D47 had allegedly been already filed in the proceedings before the opposition division. Hence none of these documents were to be admitted into the proceedings.

(b) Admittance of the third auxiliary request (filed as auxiliary request 1 on 4 November 2019)

The third auxiliary Request had been drafted in direct response to the opposition division's decision, and was to be regarded as an admissible normal procedural development. All features of claim 1 of the third auxiliary request were already present in granted claim 1. Hence the third auxiliary request was to be admitted into the proceedings.

(c) Main request (patent as granted)

D1 aimed at improving stability and shelf life of prasugrel formulations by providing an improved package, and was thus concerned with a problem different from the problem of the present invention. Hence the commercially available composition Efient®, and not D1, was to be regarded as the most promising and most realistic springboard to the invention.

Even if D1 was selected as starting point, the claimed subject-matter involved an inventive step. D1 described a formulation comprising prasugrel HCl packaged in an air and moisture impervious gas-inerted blister pack. D1 neither disclosed an average particle size of prasugrel of 0.2-150 µm, nor the presence of "a homogenous mixture of the active agent and additives", nor the optional grinding step i.). As shown in item J of the patent, this resulted in an improvement as regards the amount of total impurities.

The technical problem was to provide an improved pharmaceutical composition comprising prasugrel or a pharmaceutically acceptable salt thereof as active pharmaceutical ingredient, or at least an alternative process for preparing a prasugrel composition with good stability and low total impurity content.

D1 merely provided hints in view of packaging materials and packaging procedures, but not towards the claimed solution. As to D6, the grinding procedures mentioned therein were explicitly directed to new drugs, i.e. not to prasugrel, and would thus have been disregarded by the skilled person. Furthermore, D6 taught to avoid particle size reduction. The skilled person, knowing of

the rapid bioavailability of prasugrel from D11, would not have worked on improving its bioavailability. Thus the main request met the requirements of inventive step.

(d) First auxiliary request

D1 did not disclose a formulation comprising prasugrel base having an average particle size of 0.2-20 µm. The objective technical problem was to provide an improved pharmaceutical composition comprising prasugrel as active pharmaceutical ingredient.

It was plausible that the presence of prasugrel base had an effect on the stability of the pharmaceutical compositions. Furthermore, the claimed solution involved an inventive step considering the indication in D1 that prasugrel base was disadvantageous under efficacy and stability aspects. The narrow average particle size range indicated in claim 1 also involved an inventive step, as particle size was known to have an effect on stability.

(e) Second, fourth and fifth auxiliary requests

D1 taught to subject prasugrel HCl with excipients to roller compaction, followed by blending with excipients and compressing the resulting blend to tablets. Neither D1 nor any other item of the prior art suggested to subject prasugrel base or a salt thereof to melt extrusion or melt granulation, as mandated by claim 1 of the second, fourth and fifth auxiliary requests, nor did they provide any hint to the resulting improvement in stability shown in D39 and item J of the patent.

(f) Sixth to eighth auxiliary requests

Regarding the sixth auxiliary request, the particle size of 1-10 µm was not to be regarded as an arbitrary range. The experimental data supported advantageous effects for the particle size claimed.

The additional features in claim 1 of the seventh auxiliary request distinguished the invention from the cited documents.

Lastly, with respect to the eighth auxiliary request, the prior art provided no hints to a process where unbound water of the composition was controlled to be below 4 wt% of the composition.

Accordingly each of these requests met the requirements of inventive step.

XVII. The arguments of appellants O3 and O4, and of respondent O1, may be summarized as follows:

(a) Admittance of documents D41-D44, D46 and D47

The patentee had not objected to the admissibility of D41 at first instance. Thus D41 formed part of the proceedings, and there was no legal basis for D41 to be excluded on appeal. D42 and D44 did not represent a fresh case on appeal. The submission of D43 in appeal was a justified reaction to the opposition division's decision. D46-47 had already been included in a document filed in the first instance proceedings. Accordingly, these documents were to be admitted into the proceedings.

(b) Admittance of the third auxiliary request (filed as auxiliary request 1 on 4 November 2019)

This request essentially corresponded to an auxiliary request which appellant P had withdrawn at the oral proceedings before the opposition division, thus preventing the opposition division from reaching a decision thereon. Accordingly, the third auxiliary request was not to be admitted under Article 12(4) RPBA.

(c) Main request (patent as granted)

D1 related to the same general problem of improving stability and was the closest prior art. D1 disclosed a lactose-free prasugrel (CS-747) formulation prepared by blending the active ingredient and excipients and then compressing to form a tablet. The only distinguishing feature was the particle size defined in claim 1. Neither the feature "homogenous mixture" nor the optional grinding step represented a difference over D1.

No improved stability has been shown to arise from the particle size of 0.2-150 µm. The data in item J of the patent, comparing the claimed composition with the commercial product Efient®, were flawed, because the particle size in Efient® was unknown, and because the data additionally differed in other, unclaimed ways. The objective technical problem was the provision of an alternative process for preparing a prasugrel composition. The claimed solution was obvious in view of the common general knowledge as reflected in D6.

(d) First auxiliary request (upheld by the opposition division)

The subject-matter of claim 1 differed from D1 by the particle size of 0.2-20 µm and by the use of prasugrel base rather than its HCl salt. Starting from D1, the problem to be solved was the provision of an alternative stable composition of prasugrel.

The range of 0.2-20 µm overlapped with the range of 10-40 µm suggested in D6. Furthermore, nothing in D1 or in D43 would have reduced the skilled person's expectation that prasugrel base compositions would have acceptable stability. Consequently, the first auxiliary request did not meet the requirements of inventive step.

(e) Second, fourth and fifth auxiliary requests

In addition to the particle size and the use of prasugrel base, the subject-matter of claim 1 of the the second auxiliary request differed from the closest prior art D1 by the use of at least one additive having a melting or glass transition point below 180°C, and in that the composition was prepared by melt granulation or melt extrusion.

No technical effect could be attributed to the use of melt extrusion and melt granulation process. The comparison reported in D39 did not demonstrate any technical effect, because the tablets of experiments A and B differed additionally in several unclaimed ways. As to the data of item J of the patent, it showed that the stability of example 74b, obtained by hot melt granulation, was extremely close to that of example 66, obtained by direct compaction.

The objective technical problem remained the provision of a further process for preparing a prasugrel composition. The solution was obvious in light of the common general knowledge reflected in D40 and D41. Thus the second auxiliary request, and, for the same reasons, the fourth and fifth auxiliary requests, contravened Article 56 EPC.

(f) Sixth to eighth auxiliary requests

Regarding the sixth auxiliary request, the further feature that "prasugrel base or its pharmaceutically acceptable salt is ground to a particle size of between 1 and 10 micrometers" was not associated with any technical effect. This range was common in the field of pharmacy and overlapped with the range 10-40 µm suggested in D6.

The feature of claim 1 of the seventh auxiliary request, according to which the compressed mixture was in the form of a core or a tablet core in a solid oral dosage form or forming part of said core or tablet core, did not distinguish its subject-matter from D1, because in D1 the mixture 1 was blended and compressed to form tablets (see page 19).

Regarding the eighth auxiliary request, the limitation to an amount of unbound water controlled below 4wt% of composition was arbitrary. Moreover, D1 taught that prasugrel was sensitive to moisture (see page 9, third paragraph). Thus it would have been obvious to control the water content.

Consequently, none of the sixth to eighth auxiliary requests met the requirements of inventive step.

Reasons for the Decision

1. Admittance of D41-D44, D46 and D47

1.1 Both appellant O3 and respondent O1 relied on document D41 in their respective replies to appellant P's grounds of appeal filed on 4 November 2019. Appellant P contested the admittance of D41 into the appeal proceedings.

Following the transitional provisions set out in Article 25(2) RPBA 2020, Article 12(4) RPBA 2007 is applicable. Article 12(4) RPBA 2007 gives the Board discretion not to admit, on appeal, facts and evidence which could have been presented or were not admitted in the opposition proceedings.

D41 had already been filed during the first instance proceedings. The opposition division did not take any decision not to admit this document. Hence, D41 is neither a document which could have been presented in the first instance proceedings (i.e. but was not), nor a document which was not admitted in the first instance proceedings. Thus the discretionary power not to admit evidence under Article 12(4) RPBA 2007 does not apply to D41.

Accordingly, D41 was taken into account in the appeal proceedings.

1.2 D42-D44 were filed together with appellant O3's ground of appeal dated 24 September 2019, and D46 and D47 together with appellant O4's grounds of appeal dated 4 November 2019.

The admittance of D42-D44, D46 and D47 is also subject to the provisions of Article 12(4) RPBA 2007.

According to established case law, documents filed with the statement of grounds of appeal should not be held inadmissible if they are an appropriate and immediate reaction to developments in the previous proceedings, for example where they give the losing party in the opposition proceedings an opportunity to fill in the gaps in its arguments by presenting further evidence on appeal (see cases reported in Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, V.A.4.13.1).

In the case at hand, appellant O3 filed D43 to contest the opposition division's finding that D1, citing US 6 693 115 (i.e. D43), taught that the free base was unstable. D42 and D44 reflect the common general knowledge in relation to salts, and were filed to support the argumentation of lack of inventive step based on D1. Likewise, D46 and D47 were filed with the aim to support the objection based on D1 regarding the respective stabilities of prasugrel and its salts. None of D42-D44, D46 or D47 amount to presenting a fresh case in appeal.

Accordingly, the Board admitted D42-D44, D46 and D47.

2. Main request (patent as granted), inventive step

2.1 Starting point for the assessment of inventive step

2.1.1 The claimed invention relates to a process of forming a compressed mixture comprising the active pharmaceutical ingredient prasugrel in the absence of lactose, and to

pharmaceutical compositions comprising a compressed mixture obtainable by this process.

According to the patent, lactose may impair the stability of prasugrel (see page 1). The aims stated in the patent pertain primarily to the development of a stable pharmaceutical composition comprising prasugrel, obtainable by a simple, straightforward manufacturing process (see paragraphs [0012], [0014]). The patent also mentions further aspects such as a low impurity content (see paragraphs [0174]-[0176], item J) or dissolution properties of prasugrel (see paragraphs [0102]-[0103]).

2.1.2 D1 represents the closest prior art.

D1 relates to compositions comprising prasugrel hydrochloride (i.e. CS-747 HCl) and addresses the similar problems of stability, shelf life and efficacy of individual doses of prasugrel (see page 1, lines 17-24; page 10, lines 26-30). D1 discloses the preparation of a lactose-free compressed mixture comprising prasugrel HCl and excipients wherein the ingredients are blended and then roller compacted (which is a solvent free technique) to produce a granulation (see page 19, e.g. Formulation 1). The mixture is then incorporated in the core of coated tablet formulations, and the tablets are packaged in a blister pack filled with an inert gas.

2.1.3 According to appellant P, the commercially available composition Efient® should be regarded as the most promising and most realistic springboard, rather than D1. Appellant P regards the commercial product Efient® as a superior starting point on account that it

necessarily fulfills marketing requirements, including that of stability.

The Board does not share this opinion. D1 addresses a problem similar to that of the patent, namely the stability of the prasugrel composition, and shares the most relevant features with claim 1, in particular the absence of lactose. D1 thus represents a more suitable starting point for the assessment of inventive step. This conclusion is not changed by the fact that, in D1, the tablets are packaged in an inert blister pack to improve stability, because such a packaging is not excluded by claim 1.

In contrast, Efient® is further away from the subject matter of claim 1 than D1. Efient® contains lactose (see D37, page 17), its average particle size is unknown, and it does not come closer in terms of the problem addressed. The simple fact that Efient® is marketed does not disqualify D1 as a suitable starting point for an inventive-step reasoning.

2.2 Differentiating features

The subject-matter of claim 1 of the main request differs from the teaching of D1 solely by the specified average particle size of prasugrel or its pharmaceutically acceptable salt in the range of 0.2-150 µm.

The Board concurs with the opposition division that the step of blending shown in D1 necessarily leads to an homogeneous mixture of the ingredients. Hence the feature "homogenous mixture" of claim 1 does not represent a differentiating feature over D1. The

mixing/grinding step (i) of claim 1 is optional and thus does not constitute a difference over D1 either.

2.3 Technical effect

Appellant P contended that item J of the patent (paragraphs [0174]-[0176]) showed that the claimed process led to an improved stability. However, in the Board's opinion, the patent does not contain any meaningful comparison establishing an effect associated with the sole differentiating feature over the closest state of the art D1, namely the prasugrel average particle size of 0.2-150 µm, for the following reasons.

Item J of the patent compares the compositions of examples 66, 70 and 74b, prepared according to the process of claim 1 with prasugrel base having a mean average particle size of 4 µm, with the commercially available composition Efient®. However the particle size of prasugrel in Efient® is not known, which makes any comparison regarding this feature or its effect impossible. In addition, Efient® differs from the compositions of examples 66, 70 and 74b by features other than the particle size, such as the excipients, in particular the presence of lactose, and the use of prasugrel hydrochloride (HCl) instead of free base (see D37, pages 2 and 17). Thus, the data in the patent do not convincingly show any effect having its origin in the distinguishing feature of the invention compared with D1.

2.4 Objective technical problem

According to established case law, the technical problem has to be determined on the basis of objectively established facts, since for the

determination of the objective technical problem, only the effect actually achieved vis-à-vis the closest prior art should be taken into account (see the Case Law of the Board of Appeal, 9th edition 2019, I.D.4.1).

Here, the claimed subject-matter is not shown to achieve any technical effect vis-à-vis the closest prior art D1. The evidence on file and the alleged improvements in comparison with Efient® do not allow any meaningful conclusion as to an effect in comparison with D1: it is simply not known whether, as a result of the prasugrel average particle size of 0.2-150 µm, the claimed compositions are any better or worse, in terms of stability or impurity, than those of D1.

Therefore, the problem to be solved is to find an alternative process for preparing a prasugrel composition.

2.5 Obviousness

2.5.1 The skilled person, faced with the problem of providing an alternative to D1, would consider modifying any well-known parameter of the pharmaceutical composition, such as the particle size of the active ingredient. Contrary to the appellant's opinion, the fact that D1 addresses the problem of improving stability and shelf life of prasugrel compositions by providing an improved package does not mean that the skilled person starting from D1 would only work on the packaging materials and procedures.

2.5.2 The choice of the average particle size specified in claim 1 of the main request is, in the absence of any associated effect, arbitrary and does not involve an inventive step. The broad range 0.2-150 µm does not

depart from the values which the skilled person would routinely select. On the contrary, D6, which reflects the common general knowledge in the field, generally indicates that particles above approximately 100 µm should be ground, that grinding is not necessary when the particles are around 30 µm or less of diameter, and that the grinding should reduce coarse material to preferably 10-40 µm (see pages 5-6).

2.5.3 The fact that this passage of D6 refers to "new drugs" does not mean that the skilled person would disregard its application to the known drug prasugrel, because the expression "new drug" is of no technical relevance to the suitability of a given particle size for the formulation of a drug.

2.5.4 According to appellant P, the skilled person would refrain from reducing the particle size of prasugrel to the recited range of 0.2-150 µm, for two reasons: firstly, D6 taught that lower particle sizes or grinding may lead to drawbacks in terms of e.g. stability, aggregation, flowability or dissolution rate (see page 6, penultimate paragraph, and table 2); and secondly, prasugrel HCl was known to be soluble and have rapid bioavailability, such that the skilled person would have no motivation to improve its bioavailability.

The Board cannot follow this reasoning. The achievement of any given stability or bioavailability properties is not part of the problem which the skilled person seeks to solve. Furthermore, the fact that D6 generally recommends the range of 10-40 µm while mentioning the possible influence of particle size / grinding on e.g. stability, solubility and bioavailability, means that this range is recommended in view of these factors.

Hence there is no indication in D6 that the recommended range is unsuitable for formulation of a drug. Appellant P further referred to the data in table 2 of D6, in which an active agent particle size of 387 µm provides the highest stability. However, these data only pertain to a different active ingredient, namely sulfacetamide, and, in as far as they departs from the general recommendation in D6, would be regarded as an exception rather than the rule.

Consequently, the skilled person would know, from common general knowledge as reflected in D6, that particle sizes in the range of 10-40 µm are in general suitable for the preparation of solid pharmaceutical compositions, and would therefore consider that using this particle size in the case of prasugrel would solve the technical problem of providing an alternative to D1.

2.6 Accordingly, the main request does not meet the requirements of inventive step.

3. First auxiliary request (upheld by the opposition division), inventive step

3.1 Claim 1 of the first auxiliary request (corresponding to the request upheld by the opposition division) differs from claim 1 of the main request in that:
- the active ingredient is limited to prasugrel base, i.e. it no longer covers its pharmaceutically acceptable salt, and
- its average particle size range is limited to 0.2-20 µm.

3.2 These two features are also the differentiating features over the closest prior art D1.

As for the main request, no technical effect has been shown to arise from the above differentiating features. In particular, the Board sees no support for the allegation that any improved stability of examples 66, 70 and 74b should be linked to the presence of prasugrel base. No valid comparison between prasugrel base and prasugrel HCl was presented. The compositions of examples 66, 70 and 74b differ from Efient® not only by the use of prasugrel base vs HCl, but also by the excipients, such that no meaningful conclusion can be drawn as to the effect of using the free base (see 2.3 above regarding item J of the patent). None of the advantages to which appellant P referred, namely a simple and straightforward manufacturing process, a low impurity content, an advantageous stability or dissolution of the active agent from the composition, is objectively shown to arise in the claimed compositions in comparison with the closest prior art D1.

3.3 The technical problem is thus to provide an alternative process for preparing a prasugrel composition.

3.4 The solution defined in claim 1 of the first auxiliary request does not involve an inventive step for the following reasons.

3.4.1 The average particle size specified in claim 1 overlaps with the range of 10-40 µm mentioned in D6. In the absence of associated effect, the selection of the range 0.2-20 µm remains arbitrary.

3.4.2 The limitation in claim 1 to prasugrel free base cannot establish an inventive step either for the following reasons.

Appellant P contended that the skilled person would not consider replacing the prasugrel HCl used in D1 with its free base in view of the following passage of D1 (page 1):
"US patent 6,693,115 B2 discloses and claims the hydrochloric acid and maleic acid salts of 2-Acetoxy-5-(a-cycloprpylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine. The HCl and maleate salt forms provide unexpected and unobvious improvements in their efficacy and stability profiles compared to other salts and also compared to the free base molecule."
The cited document US 6,693,115 B2 corresponds to D43.

The parties debated whether the improvements in efficacy and stability mentioned in D1 were actually supported by the content of D43. It is however not necessary to decide on this point. D1 does not state that prasugrel base is not to be used in a compressed mixture or solid pharmaceutical formulation, but only that it does not exhibit the advantages of e.g. the HCl salt. Considering additionally that prasugrel base and its properties are known from common general knowledge as reflected in D11, there is no reason for the skilled person, even taking into account the above statement in D1, to conclude that prasugrel base is unsuitable for use in solid forms. And even if it were accepted that prasugrel base is shown in D1/D43 to lead to some drawbacks when formulated, there is no demonstration that such drawbacks do not arise in the compositions prepared according to present claim 1. As explained above, the technical problem consists merely in providing an alternative to D1 and does not specify further any level of stability or efficacy.

Thus the skilled person, seeking an alternative to D1, would consider replacing the prasugrel HCl salt of D1 with its known free base in the expectation that this would still lead to a compressed mixture usable in a pharmaceutical composition.

Hence, the first auxiliary request does not meet the requirements of inventive step.

4. Second, fourth and fifth auxiliary requests (i.e. auxiliary request 3A filed on 8 January 2021, and auxiliary requests 3-4 filed with the grounds of appeal dated 4 November 2019)

4.1 The Board admitted the second auxiliary request into the appeal proceedings. A reasoning as to admittance is not necessary, because the Board rejected the second auxiliary request for lack of inventive step for the following reasons.

4.2 Claim 1 of the second auxiliary request differs from claim 1 of the first auxiliary request by the following additional feature:

"said process being characterized in that the active ingredient and solid additives are subjected to solvent free granulation using at least one additive having melting or glass transition point below 180°C by melt extrusion or melt granulation."

4.3 In the closest prior art D1, prasugrel HCl and the additives are blended and then subjected to roller compaction to produce a granulation (see 2.1.2 above).

Thus, starting from D1, the differentiating features of claim 1 are the use of prasugrel base with an average

particle size of 0.2-20 µm and the above feature regarding melt extrusion/granulation with an additive having melting or glass transition point below 180°C.

4.4 Appellant P relies on D39 and on the data in the patent (item J, table, paragraph [0174]) as evidence of a technical effect associated with the melt extrusion or melt granulation.

4.4.1 D39 compares the stability, under stress conditions, of formulations prepared according to Experiment A, involving compaction, and Experiment B, using melt granulation. However, Experiments A and B additionally differ in respect of the excipients used, in particular:
- mannitol and hydroxypropyl methylcellulose are present in the tablets of Experiment A but not Experiment B;
- Poloxamer® 188, xylitol, and talc are present in the tablets of Experiment B but not Experiment A;
- other excipients are present in both Experiments but in different proportions;
Thus, the excipients in experiments A and B differ to a much larger extent than the mere presence of an "additive having melting or glass transition point below 180°C". Contrary to appellant P's position, the above differences cannot be regarded as minor adaptions required by the use of different preparation procedures. As a result, no meaningful conclusion can be drawn from D39 as to any effect of using melt granulation technique.

4.4.2 As to the data in the patent (part J, table, paragraph [0174]), the following was submitted during the oral proceedings:

- appellant P relied on a comparison of examples 66 and 70, both involving direct compression and roller compaction, with example 74b, from hot melt granulation;
- appellant O3 requested that appellant P's arguments, based on the comparison of examples 66 and 70 with example 74b, not be admitted into the proceedings;
- appellants O3 and O4 additionally provided counter-arguments based on a comparison of example 66 with example 70, and on a lack of evidence of a technical effect for the melt extrusion alternative of claim 1;
- appellant P requested that none of these counter-arguments of appellants O3 and O4 be admitted into the proceedings.

The Board does not regard appellant P's comparison to be convincing, even without taking into account the counter-arguments of appellants O3 and O4. Thus it is not necessary to consider the question of the admittance of these counter-arguments here.

The stress stability for examples 66 and 70 barely differs from that of example 74b: depending on the packaging under normal or nitrogen atmosphere, the melt granulation example 74b leads to either slightly less or slightly more impurities than the direct compression / roller compaction example 66 (see paragraph [0174] of the patent: 0.56% vs 0.51%, or 0.46% vs 0.51%). At the same time, examples 66 and 74b do not use the same excipients in the same proportions (see tables 13-15 of the patent).

If the patent proprietor alleges the fact that the claimed invention improves a technical effect, then the burden of proof for that fact rests upon him. Furthermore, if comparative tests are chosen to

demonstrate an inventive step on the basis of an improved effect over a claimed area, the nature of the comparison with the closest state of the art must be such that the alleged advantage or effect is convincingly shown to have its origin in the distinguishing feature of the invention compared with the closest state (see the Case Law of the Boards of Appeal, 9th edition, 2019, I.D.4.1 and I.D.4.2).

Here, appellant P did not prove that the small difference (if any) in stability observed between examples 66/70 and example 74b is due to the use of melt granulation, rather than the differences in excipients. Accordingly, no effect has been shown to arise from the distinguishing features.

4.5 Consequently, the objective technical problem remains the provision of an alternative process for preparing a prasugrel composition.

4.6 D1 provides a general teaching that wet granulation is not recommended, because of known issues with the stability of prasugrel (D1, page 9, third paragraph). Furthermore, at the priority date, melt granulation and melt extrusion were well-known solvent-free granulation processes. The handbook D40 (see pages 8-9 and 194-198) and the review D41 (see pages 1043 and 1055) show that these techniques were part of the common general knowledge, and that their applicability, advantages and disadvantages over solvent-based techniques were known to the skilled person. There is no indication that the application of e.g. melt granulation to the present compositions leads to results which depart in any way from what the skilled person could expect considering D40 and D41. Consequently, starting from D1, the skilled person, seeking to provide an alternative

process for preparing a prasugrel composition, would have selected melt granulation or melt extrusion without exercising inventive skills. Furthermore, it was not contested that the presence of an additive having a melting or glass transition point below 180°C is dictated by the use of the melt extrusion/ granulation techniques. Appellant P did not identify this excipient as being of any other relevance. Thus, the presence of this usual additive, in the absence of associated effect, does not involve an inventive step either.

Accordingly, the subject-matter of claim 1 of the second auxiliary request, and, for the same reasons, of the broader fourth and fifth auxiliary requests, does not meet the requirements of inventive step.

5. Third auxiliary request, admittance

Appellant P filed the third auxiliary request (as auxiliary request 1) together with the grounds of appeal on 4 November 2019. Its admittance is subject to the provisions of Article 12(4) RPBA 2007.

Claim 1 of the third auxiliary request, as compared with claim 1 of the main request, is limited to prasugrel base and in that the grinding/mixing step (i) is not longer optional. This request had not been filed during the proceedings before the opposition division. The sole request filed during the first instance proceedings in which the grinding/mixing step (i) is not optional is auxiliary request 1 filed on 20 April 2018. This request was however withdrawn during the oral proceedings before the opposition division (see point 15 of the minutes), with the result that the opposition division was prevented from assessing the

relevance of this amendment. The Board accordingly finds that the submission in appeal of a request which essentially results from the reintroduction of this limitation runs against the provisions of Article 12(4) RPBA 2007. In addition, the third auxiliary request does not contain the limitation, present in the first auxiliary request, regarding the particle size range of 0.2-20 µm, and is therefore not convergent.

Accordingly, the Board did not admit the third auxiliary request.

6. Sixth to Eighth auxiliary requests (filed on 4 November 2019 as auxiliary request 5-7)

6.1 Claim 1 of the sixth auxiliary specifies that prasugrel base or its pharmaceutically acceptable salt is ground to a particle size of between 1 and 10 micrometers.

As for the higher-ranking requests, no effect is shown to arise from the particle size (see 2.3 above), irrespective of whether the selected range is 0.2-150 µm, 0.2-20 µm or 1-10 µm. The skilled person, starting from D1 and seeking an alternative process for preparing a prasugrel composition, would consider that particle sizes in the claimed range would solve the problem. In the Board's opinion, the expression "between 1 and 10 micrometers" does not clearly exclude the value 10 µm, such that the claimed range still overlaps with the range 10-40 µm suggested in D6. And in any case, this would not change the fact that the selected particle sizes lead to no demonstrated technical effect in comparison with D1, and cannot be considered to depart in any significant way from values which are common in the field of pharmacy, considering D6.

Thus the limitation introduced in the sixth auxiliary request does not change the finding of lack of inventive step.

6.2 The feature introduced in claim 1 of the seventh auxiliary request, according to which the compressed mixture is in the form of a core or a tablet core in a solid oral dosage form or forming part of said core or tablet core, does not distinguish its subject-matter from D1, because D1 discloses the incorporation of the granulate in the core of coated tablet formulations (see page 19, e.g. Formulation 1).

Accordingly, the seventh auxiliary request lacks an inventive step for the same reason as the main request.

6.3 Claim 1 of the eighth auxiliary request recites an amount of unbound water controlled below 4wt% of composition. The skilled person would learn from D1 that prasugrel is susceptible to hydrolysis (see page 9, third paragraph), and would consequently take measures to control the water content. As acknowledged by appellant P, finding such measures to control unbound water below 4wt% does not present difficulties. Consequently, the skilled person would arrive at the claimed subject-matter without exercising inventive skills.

Consequently, none of the sixth to eighth auxiliary requests meet the requirements of inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated