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Datasheet for the decision of 22 August 2019

Case Number: T 2101/15 - 3.3.01

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Language of the proceedings: EN

Title of invention:
FORMULATION COMPRISING METFORMIN AND VILDAGLIPTIN

Patent Proprietors:
Novartis AG
Novartis Pharma GmbH

Opponents:
Teva Pharmaceutical Industries Ltd.
Gallafent, Alison
Actavis Group Ptc Ehf
Sanovel Ilaç Sanayi Ve Ticaret Anonim Sirketi

Relevant legal provisions:
EPC Art. 123(2), 56

Keyword:

Amendments - added subject-matter (yes) - main request, auxiliary request 1
Inventive step - (yes) - auxiliary request 2

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Beschwerdekammern

Boards of Appeal

Chambres de recours

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

Case Number: T 2101/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 22 August 2019

Appellants: (Patent Proprietors)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
	Novartis Pharma GmbH Brunner Strasse 59 1230 Wien (AT)
Representative:	Warner, James Alexander Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Appellant: (Opponent 3)	Actavis Group Ptc Ehf Reykjavikurvegi 76-78 220 Hafnarfjörour (IS)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Appellant: (Opponent 4)	Sanovel Ilaç Sanayi Ve Ticaret Anonim Sirketi Istinye Mah. Balabandere Cad. No:14 34460 Sariyer/Istanbul (TR)
Representative:	Beckmann, Claus Kraus & Weisert Patentanwälte PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)

Respondent: (Opponent 1)	Teva Pharmaceutical Industries Ltd. 5 Basel Street P.O. Box 3190 49131 Petah Tiqva (IL)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent 2)	Gallafent, Alison Alison Gallafent Ltd 21 Bridge St Llandeilo SA19 6BN (GB)
Representative:	Gallafent, Alison HGF Limited Saviour House 9 St Saviourgate GB-York YO1 8NQ (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 29 September 2015 concerning maintenance of the European Patent No. 1948149 in amended form.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	M. Blasi

Summary of Facts and Submissions

I. European patent No. 1 948 149 was granted on the basis of 37 claims.

II. Four notices of opposition were filed, opposing the patent under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was insufficiently disclosed and extended beyond the content of the application as filed.

III. In the course of the opposition proceedings, the patent proprietors submitted an amended main request and 11 auxiliary requests (all filed by letter dated 16 February 2015).

Independent claims 1 and 2 of auxiliary request 6 relate to specified processes for preparing a pharmaceutical composition or tablet comprising both vildagliptin and metformin (or their salts). These processes involve an initial step of granulating metformin and a binder by melt granulation. Further independent claims relate to defined compositions or tablets obtainable by these processes.

IV. The documents cited in the opposition and appeal proceedings include the following:

C1: Diabetes Care 28(8), 1936-1940 (August 2005)

C11: WO 02/28181 A1

C27: Lachman et al: The Theory and Practice of Industrial Pharmacy, 3rd ed., 233-234, Varghese, Bombay (1987)

C33: WO 01/52825 A2

C35: Parikh: Handbook of Pharmaceutical Granulation Technology, 8-9, 194-199; Marcel Dekker, New York (1997)

C49: Diabetes Care 27(12), 2874-2880 (2004)

V. The decision under appeal is the opposition division's interlocutory decision, announced on 17 April 2015 and posted on 29 September 2015, rejecting the patent proprietors' main request and auxiliary requests 1 to 5 and finding that the patent as amended in the form of auxiliary request 6 met the requirements of the EPC.

VI. According to the decision under appeal, the claims of the main request and of auxiliary requests 1 and 2 contained added subject-matter (Article 123(2) EPC). Claim 1 of each of auxiliary requests 3, 4 and 5 lacked clarity (Article 84 EPC).

These objections did not apply to auxiliary request 6. The person skilled in the art also received sufficient guidance in the patent in suit for preparing tablets as claimed (Article 83 EPC). The novelty of the claimed subject-matter was acknowledged (Article 54 EPC).

Starting from the technical teaching of document C33, the objective technical problem to be solved was to provide a process for preparing a fixed-combination administration unit with more favourable properties, comprising vildagliptin and metformin. None of the cited prior-art documents disclosed or suggested a specific fixed-ratio co-formulation of vildagliptin and metformin, and a number of choices were necessary to arrive at the subject-matter defined in auxiliary request 6. The patent proprietors had shown that an improved product was obtained when a melt granulation technique was employed. Thus the processes

and products claimed in auxiliary request 6 involved an inventive step.

VII. Three appeals were filed against that decision:

(a) The patent proprietors appealed against the rejection of their higher-ranking requests (i.e. the main request and auxiliary requests 1 to 5) and stated that the appeal proceedings should be based on their main request and auxiliary requests 1 to 11 submitted in the proceedings before the opposition division (see point III above).

(b) Opponents 3 and 4 each filed an appeal requesting that the patent be revoked.

VIII. With a letter dated 16 August 2019, the patent proprietors submitted six sets of claims as their new main request and auxiliary requests 1 to 5, intended, if admitted, to replace all pending claim requests.

IX. Oral proceedings before the board were held on 22 August 2019.

The patent proprietors stated that auxiliary request 1 of 16 August 2019 was to become their new main request and the previous main request of 16 August 2019 was to become their new auxiliary request 1.

The opponents did not object to the admission of the claim requests of 16 August 2019. The new requests were admitted into the proceedings.

In the course of the oral proceedings, the patent proprietors submitted a new set of claims as auxiliary request 2, which was also admitted. As a consequence, the former auxiliary requests 2 to 5 of 16 August 2019 were re-numbered auxiliary requests 3 to 6.

X. Claim 1 of the **main request** reads as follows:

__1.__ A pharmaceutical tablet comprising as active ingredients,

i) between 1.5 to 20% of vildagliptin, or a pharmaceutically acceptable salt thereof,

ii) between 80 to 98.5% of metformin or a pharmaceutically acceptable salt thereof,

and wherein metformin is in the form of granules wherein said granules comprise;

i) between 1 to 20% or between 3 and 13%, by weight on a dry weight basis of a pharmaceutically acceptable binder,

ii) between 4.9 and 12% or between 7.5 and 10.5% by weight on a dry weight basis of a pharmaceutically acceptable binder, or

iii) between 7.5 and 17.5% or between 12.5 and 17.5% by weight on a dry weight basis of a pharmaceutically acceptable binder;

wherein;

- the tablet hardness is comprised between 60 and 340 N,

- the tablet friability is lower than 0.8%,

- the tablet thickness is comprised between 4.5 and 8.3 mm,

- at least 70% of vildagliptin is dissolved within 30 minutes by using the Paddle method, and

- at least 80% of metformin HCl is dissolved within 45 minutes by using the Paddle method

and wherein the tablet comprises between 80 to 96% by weight on a dry weight basis of active ingredients, wherein the active ingredients consist of vildagliptin and metformin, or in each case a pharmaceutically acceptable salt thereof.

XI. Claim 1 of **auxiliary request 1** reads as follows:

1. *A pharmaceutical tablet comprising as active ingredients,*

i) between 1.5 to 20% of vildagliptin, or a pharmaceutically acceptable salt thereof,

ii) between 80 to 98.5% of metformin or a pharmaceutically acceptable salt thereof,

and wherein metformin is in the form of granules wherein said granules comprise;

i) between 1 to 20% or between 3 and 13%, by weight on a dry weight basis of a pharmaceutically acceptable binder,

ii) between 4.9 and 12% or between 7.5 and 10.5% by weight on a dry weight basis of a pharmaceutically acceptable binder, or

iii) between 7.5 and 17.5% or between 12.5 and 17.5% by weight on a dry weight basis of a pharmaceutically acceptable binder;

and wherein the tablet comprises between 80 to 96% by weight on a dry weight basis of active ingredients, wherein the active ingredients consist of vildagliptin and metformin, or in each case a pharmaceutically acceptable salt thereof.

XII. The sole independent claim of **auxiliary request 2**, which is identical to claim 23 of auxiliary request 1, reads as follows:

1. *A process for preparing a pharmaceutical tablet comprising between 80 to 96% by weight on a dry weight basis of active ingredients, wherein the active ingredients consist of a DPP-IV inhibitor which is vildagliptin or a pharmaceutical salt thereof and metformin or in any case a pharmaceutical salts thereof* [sic]*, which comprises;*

i) granulating metformin and a binder,

ii) drying granules containing metformin and the binder,

iii) blending the DPP-IV inhibitor, drug substance which is vildagliptin or a pharmaceutical salt thereof with the granules containing metformin and the binder,

iv) optionally a lubricant e.g. magnesium stearate is blended with the mixture obtained on step iii),

v) compressing the resulting blend to form tablets in unit dosage form,

wherein the granulation of step i) is a melt granulation.

XIII. The patent proprietors' arguments may be summarised as follows.

Amendments (Article 123(2) EPC)

Claim 1 of the main request found support in claims 13, 12, 3, 51 and 50 of the application as filed. Claims 13 and 12 of the application as filed could furthermore be combined with the paragraph bridging pages 20 and 21, the paragraph bridging pages 38 and 39, and page 39, lines 9 to 13. These comments applied equally to claim 1 of auxiliary request 1.

Claim 23 of auxiliary request 1 found support in claims 38, 44 and 48 of the application as filed and in the combination of claim 38 with page 32, paragraphs 4 and 5, page 33, last paragraph, page 39, paragraph 3, and the paragraph bridging pages 20 and 21.

Inventive step (Articles 52(1) and 56 EPC)

Documents C1 and/or C49 relating to the combined administration of metformin and vildagliptin were suitable starting points for the assessment of inventive step. The key differences of the claimed process from the disclosure of C1 and C49 were the mandatory melt granulation step and the requirement

that the tablet must contain a high drug load in the range of 80% to 96% by weight on a dry weight basis.

The objective technical problem was the preparation of a dosage form containing metformin and vildagliptin which had good stability, was physically acceptable and pharmacologically effective and which provided good convenience for the patients to be treated.

That problem was solved by the process of claim 1. For instance, example 1B of the patent in suit described the preparation of tablets with acceptable properties by a process in conformity with the definition of claim 1.

The challenge had been to combine two drugs with conflicting properties in a formulation with a limited proportion of excipients.

On the basis of common general knowledge and the cited prior art, it would not have been obvious for the person skilled in the art to combine metformin and vildagliptin in a tablet with a high drug load, or to employ a melt granulation technique for processing metformin in order to do so.

Document D11, which disclosed melt granulation of metformin, was an isolated patent reference which did not represent the skilled person's common general knowledge and could only have been chosen by the opponents with hindsight knowledge of the invention. D11 did not relate to fixed combinations and was primarily concerned with preparing sustained-release forms, thus teaching away from the invention.

Moreover, it was surprising that melt granulation was the only formulation technique which provided pharmaceutically acceptable tablets (as shown in two declarations by the inventors).

There was no prior evidence showing that a preparation process involving melt granulation as defined in claim 1 could solve the technical problem and furthermore provide tablets with superior properties.

XIV. The opponents' arguments may be summarised as follows.

Amendments (Article 123(2) EPC)

The combinations of features defined in claims 1 and 23 of both the main request and auxiliary request 1 were not specifically disclosed in the application as filed. In particular, the combinations of dependent claims relied on by the patent proprietors in support of the claimed subject-matter were not straightforward, instead involving multiple selection steps. In much the same way, the passages from the description additionally invoked by the patent proprietors in support of the claims were combined in an arbitrary manner that did not amount to individualised disclosure of the required combinations of technical features.

Inventive step (Articles 52(1) and 56 EPC)

The opponents' sole objection with respect to auxiliary request 2 concerned lack of inventive step.

Starting from the technical teaching of document C1 or C49, both relating to the co-administration of metformin and vildagliptin in separate formulations, the technical problem to be solved was to find a process well-suited to provide an alternative treatment with both metformin and vildagliptin. Since it would have been an obvious idea to prepare a fixed-dose composition of these drugs, as a conventional measure for improving patient convenience and compliance, the actual objective technical problem to be solved was to

provide a particular process for preparing a fixed-dose composition of metformin and vildagliptin.

Metformin was known to be typically processed by granulation. While the patent proprietors argued that formulation techniques other than melt granulation failed to provide pharmaceutically acceptable tablets, the opponents had presented data showing that both wet granulation and dry granulation were suitable alternative techniques. The patent proprietors had not shown that any actual improvement was attained by melt granulation.

While wet granulation was more frequently used in pharmaceutical manufacturing, melt granulation was a well-known technique (C35) and was also known to have been used for processing metformin hydrochloride to prepare high-load metformin tablets (C11). A process did not become inventive merely because it used a less common preparation technique. Moreover, the known moisture sensitivity of vildagliptin would have been a pointer for the skilled person to avoid wet granulation.

XV. The appellants-patent proprietors requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of:

- the main request, filed as auxiliary request 1 by letter dated 16 August 2019; or
- auxiliary request 1, filed as the main request by letter dated 16 August 2019;

or, in the alternative,

- auxiliary request 2, filed on 22 August 2019;

or, in the further alternative,

- one of auxiliary requests 3 to 6 (auxiliary request 3 amounting to a request for the dismissal of the opponents' appeals), filed as auxiliary requests 2 to 5 by letter dated 16 August 2019.

XVI. Appellant-opponent 3 and appellant-opponent 4 requested that the decision under appeal be set aside and the patent be revoked.

XVII. Respondent-opponent 1 and respondent-opponent 2 requested that the patent proprietors' appeal be dismissed.

Reasons for the Decision

1. Admissibility of the appeals

The appeals comply with Articles 106 to 108 EPC and Rule 99 EPC and are therefore admissible.

2. Admission of claim requests (Article 13(1)-(3) RPBA)

2.1 The main request and auxiliary request 1 are largely identical to former auxiliary requests 5 and 3 of 16 February 2015 (see points III and VII above).

2.2 The sole independent claim of auxiliary request 2, filed on the day of the oral proceedings before the board, is identical to independent claim 2 of former auxiliary request 6 of 16 February 2015 (see points III, VII and XII above).

2.3 Since these requests did not raise any new issues and the opponents did not object to their admission, the board exercised its discretion pursuant to Article 13 RPBA to admit them into the proceedings.

3. Amendments (Article 123(2) EPC)

3.1 Claim 1 - main request and auxiliary request 1

3.1.1 In support of the subject-matter of claim 1 within the meaning of Article 123(2) EPC, the patent proprietors relied on claims 12 and 13 of the application as filed, to be combined with further claims or with certain passages of the description as filed (see point XIII above).

3.1.2 Combination of claims 12 and 13 with further claims

Claim 13 as filed refers back to any of claims 7, 8, 11 or 12. The selected combination of claims 12 and 13 as filed supports a composition or tablet containing metformin (in the form of granules) and vildagliptin, or their pharmaceutically acceptable salts, the concentration ranges of vildagliptin, metformin and binder being the same as defined in claim 1 of the main request. A selection has to be made since claim 1 of the main request is restricted to tablets.

Claim 12 in turn refers back to any of claims 1 to 11 as filed. The selected combination with claim 3 adds the restriction that the active ingredients consist of vildagliptin and metformin, or their respective pharmaceutically acceptable salts, and provides four options for the concentration range of the active ingredients.

It is readily apparent that the claim dependencies in the application as filed do not necessarily (i.e. inevitably) result in a combination of claim 13 with claims 12 and 3 since claims 13 and 12 both refer back to more than just one claim.

These considerations apply to claim 1 of the main request and of auxiliary request 1. Since several choices have to be made regarding claim combinations

and particular options within the selected claims in order to arrive at the subject-matter of claim 1, the combination of claims indicated by the patent proprietors does not provide direct and unambiguous disclosure of the subject-matter of claim 1 of the main request and of auxiliary request 1.

3.1.3 Combination of claims 12 and 13 with passages in the description

The passage on page 39 (third paragraph) defines a high-drug-load composition or tablet, with the active ingredients consisting of metformin and vildagliptin or their salts, and gives several options for the content of active ingredients. This is similar in content and relevance to claim 3 as filed and to the paragraph bridging pages 20 and 21.

In order to arrive at the subject-matter of claim 1 in this case, claim 13 would still have to be combined specifically with claim 12, and the above-mentioned passage of the description would have to be selected from among other possible options to be combined with these claims and restricted to a tablet.

3.1.4 Further combinations (and thus, selections) would be required to cover the tablet parameters specified in claim 1 of the main request - the patent proprietors named claim 51 or the paragraph bridging pages 38 and 39.

3.1.5 In conclusion, the combination of features defined in claim 1 of the main request and of auxiliary request 1 is not individualised and is not directly and unambiguously disclosed in the application as filed.

3.2 The board also found that independent claims 22 and 23 of the main request and independent claim 22 of auxiliary request 1 extended beyond the content of the

application as filed. A detailed reasoning is not required in view of the findings concerning claim 1 of each of these requests.

3.3 Claim 1 - auxiliary request 2

3.3.1 This claim is identical to claim 23 of auxiliary request 1 (see point XII above).

3.3.2 The passage on page 31, line 24 to page 32, line 3 of the description as filed defines a process for preparing a pharmaceutical tablet comprising metformin and a DPP-IV inhibitor, preferably LAF 237 (another name for vildagliptin), or pharmaceutical salts of these compounds. The process comprises steps (i) to (v) as defined in claim 1 of auxiliary request 2.

This passage reads on to page 32, lines 14 to 20 of the description as filed, which specifies that the granulation in step i) is preferably a wet granulation or a melt granulation.

3.3.3 The passage on page 39 (lines 9 to 13) of the application as filed provides general disclosure of "any of the herein described compositions or tablet (...) wherein the active ingredients consist of vildagliptin or metformin, or in each case a pharmaceutically acceptable salt thereof", and gives eight options for the concentration range of active ingredients on a dry weight basis, including the range of 80% to 96%.

"Any of the herein described (...) tablet" includes the tablets produced by a process of the invention.

The application mentions that metformin requires high dosage strengths of 500 to 1000 mg. To keep the size of the tablets within acceptable limits, there was a need to prepare high-drug-load tablets (see page 1, paragraph 2 and page 16, lines 21 to 28 of the

application as filed). Tablets with a high drug load are thus strongly preferred. The passage on page 39 provides general disclosure of eight embodiments of the preferred high-drug-load tablet, each defining a concentration range for the drug load. Any of these embodiments is thus a generally disclosed preferred embodiment that may be combined with the process described in the paragraph bridging pages 31 and 32.

3.3.4 In these appeal proceedings, it was not disputed that vildagliptin was generally disclosed in the application as filed as the most preferred DPP-IV inhibitor (see also page 33, last sentence).

3.3.5 The only selection required to arrive at the subject-matter of claim 1 of auxiliary request 2 is thus the selection of melt granulation as the granulation method (see point 3.3.2 above). As a consequence, the subject-matter of claim 1 of auxiliary request 2 meets the requirements of Article 123(2) EPC.

4. Inventive step (Articles 52(1) and 56 EPC)

Patent in suit

4.1 The patent in suit seeks to provide a dosage form for co-administering metformin and a DPP-IV inhibitor, preferably vildagliptin, and a process for its preparation (see paragraph [0001] of the patent and page 1, paragraph 1 of the application as filed).

4.2 Metformin had been widely prescribed as diabetes medication. As a short-acting drug, it required twice-daily or three-times-daily dosing. It was marketed in 500-mg to 1000-mg strengths (see the patent in suit, paragraph [0002] and the application as filed, page 1, paragraph 2). It was also known to be difficult to process, the usual method used being wet granulation

(see the patent in suit, paragraph [0071] and the application as filed, page 17, lines 10 to 18).

4.3 Like metformin, DPP-IV inhibitor compounds were useful in treating non-insulin-dependent diabetes mellitus. (see the patent in suit, paragraph [0046]). The envisaged compounds including vildagliptin were known to be sensitive to moisture (paragraph [0070]).

4.4 Claim 1 of auxiliary request 2 relates to a process for preparing a tablet containing both metformin and vildagliptin as a fixed-dose combination that involves a process step of granulating metformin and a binder by melt granulation.

Starting point in the prior art

4.5 It was common ground that documents C1 and/or C49 were suitable starting points for the assessment of inventive step. Three further documents of similar content cited by the opponents (numbered C2, C3 and C4 in these proceedings) did not contain relevant information beyond the disclosure of C1 and C49.

Both documents relate to the same trial, which compared the effects of 12-week and 52-week treatment with vildagliptin (50 mg daily) and placebo in patients with type 2 diabetes continuing on a stable dosage of an existing metformin treatment (1500 to 3000 mg/day) (see C1: page 1937, column 1, first paragraph; C49: page 2874, column 3, bottom paragraph). Hence, this involved the administration of separate (i.e. unfixed) doses of metformin and vildagliptin.

According to the authors of C1 and C49, the co-administration of metformin and vildagliptin was safe and effective (see C1: page 1938, column 3, "Conclusions" and the paragraph bridging pages 1939

and 1940; C49: abstract, "Conclusions" and page 2879, paragraph bridging columns 1 and 2).

While C1 and C49 disclose the co-administration and appropriate dosages of vildagliptin and metformin, they are silent about galenic aspects.

4.6 Document C33, previously favoured as the starting point by the patent proprietors and the opposition division, is considered less relevant than C1 and C49.

This document provides the general idea (as a theoretical possibility) that DPP-IV inhibitors, including vildagliptin, may be combined with all kinds of other anti-diabetic drugs, including metformin (see C33: claims 1, 6 and 10). The combinations are not restricted to fixed combinations and encompass the simultaneous, separate or sequential use of the drugs (see C33: claim 1 and page 30, bottom paragraph).

Beyond the examples (see pages 37 to 40), which do not include a combination of metformin and vildagliptin and are in fact restricted to mono-formulations of nateglinide without a combination partner, C33 does not teach specific galenic formulations or preparation processes. It does not contain any specific disclosure of vildagliptin and metformin as a fixed-dose combination, or any experimental data relating to the co-administration of metformin and vildagliptin.

Technical problem and solution

4.7 The subject-matter of claim 1 differs from the disclosure of C1 and C49 on account of

- the provision of a tablet containing both drugs as a fixed combination at a drug load of 80% to 96% by weight on a dry weight basis;
- the mandatory process steps i) to iii) and v), the granulation in step i) being a melt granulation.

4.8 If two drugs are to be co-administered, fixed combinations provide ease of administration resulting in improved patient compliance.

4.9 It was not in dispute that the process according to claim 1 was suitable for providing tablets combining metformin and vildagliptin with a drug load of 80% to 96% by weight (see also example 1B in paragraphs [0204] to [0209] of the patent in suit and on pages 42 to 43 of the application as filed - while this example does not mention a drying step, further drying may not have been necessary after the melt granulation step; see C35: page 195, advantage 2).

4.10 The assessment of inventive step has been based on the assumption, in the opponents' favour, that it has not been shown that formulation techniques other than melt granulation of metformin (in particular, wet granulation) are unsuitable for preparing tablets containing the two drugs in combination at a high drug load, or that melt granulation results in tablets with superior properties.

4.11 Starting from the teaching of documents C1 and/or C49 and on the basis of the considerations in points 4.7 to 4.10 above, the objective technical problem to be solved is the preparation of a dosage form for improved co-administration of metformin and vildagliptin.

4.12 The board is satisfied that this problem is solved by the process according to claim 1 as it provides a fixed-dose combination tablet with the advantage of improved ease of administration in comparison with the co-administration of the two drugs in separate formulations.

Obviousness of the solution

4.13 It was not in dispute that it is, and was at the relevant date, common practice to provide a single ("fixed") composition containing two drugs which are to be used together in one patient (see also C27: page 234, column 1, first full paragraph). On the basis of common general knowledge, the person skilled in the art was aware that fixed-dose combinations were one obvious way of formulating active ingredients which are to be administered together because doing so improved patient convenience and compliance.

4.14 The patent proprietors argued

(a) that the person skilled in the art in this case would not have considered combining metformin and vildagliptin in the same tablet, in view of the compounds' known properties and the high drug load required;

(b) that melt granulation was not a widely employed technique and would not have been self-evident to the skilled person as an obvious technique to be used to overcome the difficulties in formulating the desired tablets.

4.15 With regard to these issues, the board comes to the conclusion that, while fixed-dose combinations would have been considered, melt granulation would not have been obvious as a formulation technique.

4.16 It was known from C1 and C49 that the co-administration of metformin and vildagliptin was expected to bring a therapeutic benefit with acceptable safety. The required dosages of both drugs were known. On the basis of that knowledge, it would have been regarded as

desirable to provide a fixed-dose combination tablet, tablets being a practical and usual form for marketing.

4.17 Regarding point (a), there was also no prejudice in the art which would have deterred the skilled person from attempting to formulate a fixed-dose combination tablet.

4.17.1 It was known that comparatively high single doses of metformin were required and that this entailed the need to formulate tablets with a high proportion of drug and, conversely, a low content of excipients, in order to keep the tablet size within acceptable limits (see paragraph [0067] of the patent in suit). It was also known that metformin was difficult to process. Due to poor compaction properties, it could not be processed into tablets by direct compression (see point 4.2 above and paragraphs [0002] and [0071] of the patent in suit). Nevertheless, as acknowledged in the patent in suit (and the application as filed), these difficulties had already been overcome, and metformin tablets with a high drug load were known to be typically manufactured by a process involving wet granulation of metformin (see the patent in suit, paragraph [0071]).

4.17.2 Single doses of vildagliptin were ten times lower (50 mg according to C1 and C49, in comparison with 500 mg to 1000 mg of metformin; the patent in suit envisages 25 mg to 100 mg vildagliptin - see paragraph [0072]), so this dosage would not pose much of a problem with regard to bulk.

4.17.3 The patent proprietors stressed that vildagliptin was known to be sensitive to moisture (see the patent in suit, paragraph [0070]) and that this would have dissuaded the person skilled in the art from combining it with hygroscopic metformin in the same tablet. According to the patent proprietors, there was also

an inherent chemical incompatibility between the vildagliptin carbonyl and metformin amine groups (see the patent proprietors' reply to the opponents' statements of grounds, point 2.56).

4.17.4 However, on the mere basis of these rather speculative considerations it cannot be confirmed that the person skilled in the art would have been deterred from even attempting to formulate the desired tablets.

Tablets are not an environment high in moisture. There is no evidence on file that a reaction between the functional groups of metformin and vildagliptin would have been expected, nor that metformin is so hygroscopic and vildagliptin so moisture-sensitive that they would have been thought to be incompatible during manufacture or in the finished tablet.

The skilled person would merely have taken care to formulate vildagliptin under non-aqueous conditions.

Moreover, it was not a necessary condition (nor is it a mandatory requirement of claim 1) that vildagliptin should be in close physical contact with metformin during processing or in the finished tablet. For example, vildagliptin could have been used in coated form if required.

4.18 As far as point (b) is concerned, the person skilled in the art would not have been deterred from using the standard wet granulation process for processing metformin, either.

4.18.1 The opponents argued that the known moisture sensitivity of vildagliptin would have served as a pointer prompting the person skilled in the art to replace wet granulation with a different technique.

4.18.2 In the envisaged circumstances of tablet preparation, this argument is not convincing.

In particular, the opponents' argument that melt granulation would have been an obvious choice because it was advantageous for processing water-sensitive materials (see C35: page 195, advantages/point 3) must fail.

Firstly, it was not established as fact that the water-sensitivity of vildagliptin would pose problems for the preparation of the desired fixed-dose combination tablets (see point 4.17.4 above).

Secondly, it was in any case metformin and not vildagliptin which must be granulated (see point 4.17.1 above).

In common practice, metformin granules obtained by wet granulation would be dried before further processing, and if required, both the choice of excipients (including the granulating liquid) and the form in which vildagliptin was to be introduced into the formulation could be optimised.

As also mentioned in the patent in suit (see paragraph [0053]), the choice of excipients will normally depend on the properties of the drugs and of the mixture to be processed and also on the properties desired in the final tablets, and will be optimised in pre-formulation studies.

4.19 It was not in dispute that melt granulation was a known standard granulation technique (see also the patent in suit, paragraph [0112]), although it was not as common as other methods for granulation. However, without any incentive to deviate from the conventional wet granulation technique (which was known to be suitable for producing tablets containing a high proportion of metformin), the person skilled in the art would have had no reason to change the granulation method,

especially since the restrictions imposed by the required high drug load posed an additional challenge.

4.20 The opponents also argued that the teaching of document C11 would have prompted the person skilled in the art to employ a melt granulation technique.

4.21 The board comes to a different conclusion, for the following reasons.

4.21.1 Document C11 is an international patent application. It is, therefore, an isolated patent reference which does not represent common general knowledge and which would not necessarily have been consulted by the person skilled in the art without a particular reason for doing so.

4.21.2 Document C11 discloses a process for preparing a sustained-release composition of metformin HCl, which is a highly water-soluble drug (see C11: page 1, lines 7 to 18). The process involves granulating metformin HCl and a hydrophobic material by hot-melt granulation or by extrusion. The dried granules may be compressed into tablets (see C11: claims 8 and 10).

As pointed out by the patent proprietors, vildagliptin requires an immediate-release dosage form while C11 is concerned with sustained-release forms and does not discuss combination products of metformin. In any case, the prior art would not have prompted the person skilled in the art to consult documents concerned with sustained-release forms.

4.21.3 Furthermore, even if C11 had been consulted, it would not have been very hepful for developing the desired preparation process.

C11 teaches primarily that sustained-release properties are achieved by granulating metformin HCl with hydrophobic materials. These hydrophobic materials,

such as stearic acid or glycerol monostearate used in the examples, are mandatory according to the teaching of C11.

While the opponents argued that the skilled person would simply omit the hydrophobic materials in order to achieve an immediate-release tablet, C11 lacks any guidance on whether that would be feasible, especially in the case of high-drug-load tablets that allow for only a limited proportion of excipients including binders.

C11 discloses optional binders as auxiliary substances (see page 5, lines 3 to 8), but these are not necessarily used in the melt composition as C11 also describes the option of subjecting metformin granules prepared by melt granulation to a further wet granulation process employing binders (see claim 9 and page 5, lines 15 to page 6, line 2).

4.22 In summary, the person skilled in the art faced with the objective technical problem would have sought to formulate a fixed-dose combination for better convenience, but the known properties of vildagliptin and metformin would not have provided a particular incentive for abandoning the wet granulation technique already known to be suitable for processing metformin and achieving high drug loads. While the person skilled in the art could have decided to investigate melt granulation, they would not have had any particular reason to do so and would not have regarded it as the method of choice since it was far from certain that a melt granulation technique could be implemented with a limited amount of binder (due to the high drug load required). Nor would such an incentive have been provided by document C11, which could only have been

brought in with hindsight knowledge of the process of the invention.

4.23 Thus, while it would have been obvious to prepare a fixed-dose combination tablet, it would not have been obvious to use a melt granulation technique for processing metformin.

4.24 As a consequence, the subject-matter of claim 1, the sole independent claim of auxiliary request 2, and of the dependent claims involves an inventive step within the meaning of Article 56 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 on the basis of claims 1 to 9 of auxiliary request 2 filed at the oral proceedings before the board, and a description to be adapted thereto.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated