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**Datasheet for the decision  
of 22 October 2015**

**Case Number:** T 0215/12 - 3.3.07

**Application Number:** 05700976.3

**Publication Number:** 1715893

**IPC:** A61K47/00

**Language of the proceedings:** EN

**Title of invention:**

DIRECT COMPRESSION FORMULATION AND PROCESS

**Patent Proprietor:**

Novartis AG  
Novartis Pharma GmbH

**Opponents:**

Teva Pharmaceutical Industries Ltd.  
KRKA, d.d., Novo mesto

**Relevant legal provisions:**

EPC Art. 114(2), 113(1), 56  
RPBA Art. 12(4), 13(1)  
EPC R. 106

**Keyword:**

Late-filed documents - admitted (no)

Obligation to raise objections - objection dismissed

Inventive step - all requests (no)



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Case Number: T 0215/12 - 3.3.07

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.07**  
**of 22 October 2015**

**Appellants:**

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**Decision under appeal:**      **Decision of the Opposition Division of the  
European Patent Office posted on 19 December  
2011 revoking European patent No. 1715893  
pursuant to Article 101(3) (b) EPC.**

**Composition of the Board:**

**Chairman**                    D. Semino  
**Members:**                    R. Hauss  
                                      P. Schmitz

## Summary of Facts and Submissions

- I. European patent No. 1 715 893 was granted on the basis of twenty-six claims.
- II. Three oppositions were filed, in which the patent was opposed under Articles 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.
- III. Opponent 1 later withdrew its opposition.
- IV. The documents cited during the opposition and appeal proceedings included the following:
  - D5: EP 1 537 880 A1 (European patent application issued from D5b, publication under Article 158(3) EPC)
  - D5b: WO 2004/024184 A1
  - D5c: Computer translation of D5b
  - D6: WO 00/34241 A1
  - D7: Lieberman et al.: Pharmaceutical Dosage Forms - Tablets, Vol. 1, 2nd ed. New York 1989, 195-220
  - D16: J. Med. Chem. 46, 2274-2789 (2003)
  - D19: Lieberman et al.: Pharmaceutical Dosage Forms - Tablets, Vol. 1, New York 1980, 3-4
  - D22: Lieberman et al.: Pharmaceutical Dosage Forms - Tablets, Vol. 1, 2nd ed. New York 1989, 1-24
  - D27: Canadian J. Pharm. Sci., 11(1), 1-10 (1976)
  - D28: Brittain: Physical Characterization of Pharmaceutical Solids, New York 1995, chapters 1 and 6
  - D29: Lachman et al.: The Theory and Practice of Industrial Pharmacy, Philadelphia 1970, 305-319

- D30: Hunnius Pharmazeutisches Wörterbuch, 8th ed.  
Berlin 1998, 424-425
- D31: Pakistan J. Pharm. Sci., 16(2), 13-16 (2003)
- D32: Technical data regarding the development of  
Vildagliptin (LAF237) oral dosage forms as covered  
by European Patent 1715893 B1
- D33: Parikh: Handbook of Pharmaceutical Granulation  
Technology, New York 1997, 194-195

- V. The appeal by the patent proprietors (appellants) lies from the decision of the opposition division, pronounced on 23 November 2011 and posted on 19 December 2011, revoking the patent.
- VI. The decision under appeal is based on a main request and two auxiliary requests.

The opposition division held, with regard to the main request and second auxiliary request, that the subject-matter of claim 1 of each request did not involve an inventive step (Articles 52(1) and 56 EPC). Claim 1 of the first auxiliary request contained subject-matter going beyond the content of the application as filed (Article 123(2) EPC).

Claim 1 of the second auxiliary request reads as follows:

*"1. A direct compressed pharmaceutical tablet, wherein the dispersion contains particles comprising a DPP-IV inhibitor which is (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyanopyrrolidine in free form or in acid addition salt form, and wherein at least 60% of the particle size distribution in the tablet is between 10 to 250  $\mu\text{m}$ ."*

The DPP-IV inhibitor compound according to claim 1 is also known as "vildagliptin" or "LAF237".

According to the decision under appeal, starting from the teaching of document D6 or D16, the objective technical problem with regard to claim 1 of the second auxiliary request was the provision of a stable tablet formulation. Document D7, representing general knowledge, would direct the skilled person seeking to avoid chemical instability of the drug towards direct dry compression, and the skilled person would use common particle sizes. For those reasons, the use of the active agent with the claimed particle size distribution in a tablet obtained by direct compression was regarded as obvious (Articles 100(a), 52(1) and 56 EPC).

Late-filed documents D27 and D28 were not admitted into the proceedings, since they were not more relevant than the documents already on file.

VII. With the statement setting out the grounds of appeal the appellants filed experimental data (document D32), a new main request and five auxiliary requests.

The wording of claim 1 of the **main request** is identical to that of claim 1 of the former second auxiliary request considered in the decision under appeal (see point VI above).

Claim 1 of the **first auxiliary request** reads as follows:

*"1. A direct compressed pharmaceutical tablet, wherein the dispersion contains particles comprising a DPP-IV inhibitor which is (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyanopyrrolidine in free form or in acid addition salt form, and wherein*

*i) at least 60% of the particle size distribution in the tablet is between 10 to 250  $\mu\text{m}$ , and*

*ii) the water content of the tablet is less than 5% after 1 week at 25°C and 60% RH."*

Claim 1 of the **second auxiliary request** reads as follows:

"1. A direct compressed pharmaceutical tablet, wherein the dispersion contains particles comprising a DPP-IV inhibitor which is (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyanopyrrolidine in free form or in acid addition salt form, and wherein

- i) at least 60% of the particle size distribution in the tablet is between 10 to 250  $\mu\text{m}$ , and
- ii) the water content of the tablet is less than 10% after 1 week at 25°C and 60% RH, and
- iii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg."

Claim 1 of the **third auxiliary request** reads as follows:

"1. A direct compressed pharmaceutical tablet, wherein the tablet comprises

- (a) 5-60% by weight on a dry weight basis of a DPP-IV inhibitor which is (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyanopyrrolidine in free form or in acid addition salt form;
- (b) 40-95% by weight on a dry weight basis of a pharmaceutical acceptable diluent;
- (c) 0-20% by weight on a dry weight basis of a pharmaceutical acceptable disintegrant; and optionally
- (d) 0.1-10% by weight on a dry weight basis of a pharmaceutical acceptable lubricant,

and wherein at least 60% of the particle size distribution in the tablet is between 10 to 250  $\mu\text{m}$ ."

Claim 1 of the **fourth auxiliary request** reads as follows:

"1. A direct compressed pharmaceutical tablet, obtainable by a process comprising the steps of

- (a) blending as a % by weight on a dry weight basis:



(i) 6-60% by weight on a dry weight basis of DPP-IV inhibitor which is (S)-1-[(3-hydroxy-1-adamantyl)-amino]acetyl-2-cyano-pyrrolidine in free form or in acid addition salt form; and

(ii) and at least one excipient selected from a diluent, a disintegrant and a lubricant,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form,

and wherein at least 60% of the particle size distribution in the tablet is between 10 to 250  $\mu\text{m}$ ."

Claim 1 of the **fifth auxiliary request** reads as follows:

"1. Process for preparing a direct compressed tablet, in unit dosage form, which comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 6-60% by weight on a dry weight basis of DPP-IV inhibitor which is (S)-1-[(3-hydroxy-1-adamantyl)-amino]acetyl-2-cyano-pyrrolidine in free form or in acid addition salt form; and

(ii) and at least one excipient selected from a diluent, a disintegrant and a lubricant,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form,

and wherein at least 60% of the particle size distribution in the tablet is between 10 to 250  $\mu\text{m}$ ."

- VIII. With letters in reply to the appellants' statement setting out the grounds of appeal, the respondents (opponent 2 and opponent 3) contested the appellants' arguments. Respondent-opponent 3 submitted additional documents (D29, D30 and D31).
- IX. In a communication issued in preparation for oral proceedings and advising the parties of the board's preliminary opinion, the board observed *inter alia* that document D6 appeared to be the most appropriate starting point for the assessment of inventive step. While tablets obtainable by ethanolic wet granulation were exemplified in D6, the skilled person considering document D6 would also envisage conventional dry preparation methods for tablets, such as direct compression (see point 3.2.7 of the board's communication). The board also observed that document D5, proposed by respondent-opponent 3 as a possible starting point for the assessment of inventive step, had been published after the filing date of the patent in suit and therefore did not form part of the state of the art according to Article 56 EPC (see point 3.2.6 of the board's communication).
- X. With a further submission dated 16 September 2015 respondent-opponent 3 filed document D5c as a translation of document D5b and requested that documents D5c, D27 and D28 be admitted into the proceedings.
- XI. With letter dated 23 September 2015 the appellants filed document D33.
- XII. Oral proceedings took place on 22 October 2015.

XIII. The appellants' arguments can be summarised as follows:

*Admission of evidence*

The additional document D5c filed by respondent-opponent 3 should not be admitted into the proceedings, since documents D5 and D5b to which it pertained had never been used by the respondents to support an argument against inventive step until shortly before the oral proceedings in appeal, and this therefore represented a new case.

Document D33, providing general textbook knowledge on melt granulation, had been submitted in reply to the board's written communication, and merely served to corroborate the appellants' known argument that it was not obvious for the skilled person to prepare the claimed tablets by direct compression. Shortening a reference to include only the relevant text passage was normal practice; nothing else had been intended by filing an incomplete second page of D33.

*Inventive step*

The technical effects provided by the tablet of claim 1 of the main request in comparison with the tablets disclosed in document D6 were sufficient drug stability and tablet shelf life, achieved by preparing the tablet by a direct compression process with a specifically adapted drug particle size distribution. From the point of view of stability, the specific surface area of the drug particles should not be too large (accordingly, the particle size should not be too small), in order to avoid exposure of the hygroscopic drug to humidity, which would impair its stability. The particles should however be small enough to provide sufficient tablet hardness.

The objective technical problem was the provision of a sufficiently stable solid oral dosage form of vildagliptin which overcame the stability problems occurring with the method of document D6.

Neither document D6 nor document D16 suggested a direct compression method or dry method. D6 described alcoholic wet granulation. Hence, water was not excluded from the tablets of D6, since alcohol usually contained water. D16 taught that vildagliptin was the DPP-IV inhibitor with the highest stability, so the skilled person attempting to solve the technical problem would have no initial concerns about stability. Even in the knowledge that vildagliptin was to some extent water-sensitive, the skilled person would not resort to a direct compression method (known to have its drawbacks) but would first attempt to stabilise the drug or to use a melt granulation method. Even if the skilled person envisaged direct compression as a dry technique in order to avoid stability problems caused by water, it was not derivable from the cited prior art that persisting stability problems could only be overcome by adapting the particle size in order to control humidity. The invention was thus based on the selection of a non-obvious direct compression process and, in view of the formulation difficulties which had been encountered, on the surprising successful optimisation of the parameters involved, which was achieved by a strict control of both humidity and particle size distribution.

The same reasoning applied to claim 1 of the first auxiliary request; additionally, it was not derivable from the prior art that vildagliptin had to be stabilised by protecting it from moisture during long-term storage.

While admittedly in the usual range, the "tablet thickness to tablet weight" ratio defined in claim 1 of

the second auxiliary request was still relevant to the properties of the claimed tablet and served to avoid undesired moisture absorption and thus to ensure moisture control.

Claim 1 of the third auxiliary request defined preferred excipients, concomitantly limiting the presence of humidity in terms of residual water. The corresponding technical advantage was shown in table 9 of document D32.

The subject-matter of the fourth auxiliary request involved an inventive step for the same reasons as explained for the main request.

Starting from the technical teaching of document D6, it would not have been obvious to the skilled person to use a direct compression process according to claim 1 of the fifth auxiliary request. D6 disclosed wet granulation and provided no incentive for the reader to change the process of preparation to a process not involving water. The state of the art was silent about the advantages of direct compression of vildagliptin tablets, in particular in the case of high-dose formulations.

XIV. The respondents' arguments can be summarised as follows:

*Admission of evidence*

In direct response to the board's written communication (see point IX above), respondent-opponent 3 had clarified that it was not document D5, but document D5b (an international application published in Japanese) which formed part of the state of the art relevant for the assessment of inventive step. Document D5c was a machine translation of document D5b, filed merely in order to confirm the content of D5b and its translation D5. Thus D5c had been submitted in reply

to the board's communication and its inclusion did not alter the respondents' case.

Document D33, filed less than a month before the oral proceedings, should not be admitted, since it was being used by the appellants to introduce a new line of reasoning. Furthermore, D33 showed two pages from a textbook, but part of the second page (containing relevant information which was potentially unfavourable to the appellants' case) had been deleted.

*Inventive step*

The tablet defined in claim 1 of the main request differed from the tablets disclosed in document D6 in that it was direct compressed and had a particle size distribution with 60% of the particles between 10 and 250  $\mu\text{m}$ . The appellants had failed to show any technical effect linked to those distinguishing features; in particular they had not presented an appropriate comparison of the claimed tablet with the prior art D6. The data submitted with D32 was largely irrelevant in that respect. Also, the technical effects alleged by the appellants could not be obtained over the entire scope claimed, and thus could not serve to establish an inventive step.

Hence the objective technical problem with regard to claim 1 of the main request was the provision of alternative tablets of vildagliptin.

Direct compression was a standard method of tablet preparation; furthermore it was known (D7: page 199) that fewer chemical stability problems were encountered in tablets prepared by direct compression than in those made by a wet granulation process. It was within the routine practice of a person skilled in the art to prepare tablets of a water-sensitive drug like

vildagliptin using a conventional dry method, i.e. dry granulation or direct compression. Contrary to the appellants' assertions, the skilled person would not readily turn to melt granulation, since such a process involved heat exposure, which was generally regarded as unfavourable (D7: page 198). The skilled person's routine practice would also include the consideration of particle size as an essential step for meeting the requirements of the tableting process with respect to flowability, compressibility and hardness, as well as the requirements of disintegration, dissolution and of bioavailability. Grinding to a defined particle size in the range required in claim 1 was usually recommended (D19, D22); beyond that, the size distribution defined in claim 1 was arbitrary and also quite unspecific, since nearly half of the particles could have sizes outside the range of 10 to 250  $\mu\text{m}$ . Thus the features of the claimed tablet were obvious to the person skilled in the art.

The limitation of the water content of the tablet as specified in claim 1 of the first auxiliary request reflected the known routine measure of preventing moisture uptake of tablets during storage (D31) and could not give rise to a surprising technical effect on which an inventive step could be based.

The ratio of tablet thickness to tablet weight as defined in claim 1 of the second auxiliary request was typical for tablets generally and had not been shown to result in a surprising technical effect.

The excipient concentration ranges defined in claim 1 of the third auxiliary request were arbitrary, broad and within conventional limits, and they were mostly not even distinguishing features over D6. Since the claim did not specify any preferred individual excipients or

classes with common properties, but defined the excipients merely by their most general functions, no specific effect would be obtained over the entire scope of the claim.

As far as the fourth auxiliary request was concerned, the same arguments as presented with regard to the main request applied.

Claim 1 of the fifth auxiliary request was a process claim but corresponded in its relevant technical features to claim 1 of the main request; the arguments with regard to inventive step remained therefore the same. Contrary to what was alleged by the appellants, the claimed process did not actually exclude water, which could, for instance, be present in the excipients or in a coating liquid.

XV. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or one of the first to fifth auxiliary requests filed with the statement setting out the grounds of appeal.

The appellants raised an objection under Rule 106 EPC with regard to the non-admittance of document D33, which they considered to violate their right to be heard.

XVI. The respondents requested that the appeal be dismissed.

## **Reasons for the Decision**

1. Admission of evidence into the proceedings

1.1 Documents D29, D30, D31 and D32 were filed with the statement setting out the grounds of appeal (D32, see point VII above) or with a reply thereto (D29 to D31,



see point VIII above). The board is not aware of any reason for not admitting those documents into the present proceedings, nor was any request to that effect made by the parties. Pursuant to Article 12(1) RPBA, documents D29 to D32 are thus admitted into the proceedings.

- 1.2 Documents D27 and D28, representing the general knowledge of the person skilled in the art regarding solid pharmaceutical dosage forms, were filed by opponent 2 after the expiry of the nine-month opposition period under Article 99(1) EPC and shortly before the oral proceedings before the opposition division. The documents were not admitted by the opposition division, since they were not considered to be more relevant than the documents already on file (see the decision under appeal, points VI and 3.3). The board has no reason to believe that the opposition division applied its discretion incorrectly. Moreover, the board sees no particular relevance in D27 and D28, and the parties did not rely upon those documents in their written submissions during the appeal proceedings. For these reasons, documents D27 and D28 are not admitted into the proceedings (Rule 12(4) RPBA, Article 114(2) EPC).

- 1.3 In its written communication issued in preparation for oral proceedings, the board observed that document D5, proposed by respondent-opponent 3 as a starting point for the assessment of inventive step, did not actually form part of the state of the art under Article 56 EPC, since that document had only been published after the filing date of the patent in suit (see point 3.2.6 of the board's communication).

In reply, respondent-opponent 3 clarified that document D5b, not D5, was the prior-art document

considered relevant to inventive step, and submitted document D5c, which is a machine translation of D5b.

Both D5 and D5b (formerly designated D14a and D14b) were previously submitted with the notice of opposition of opponent 3. Document D5b is an international application published in Japanese in the interval between the first and the second priority date claimed for the patent in suit. Document D5 is the corresponding European patent application published in accordance with Article 158(3) EPC. It was not contested by the parties that D5 is an adequate translation of D5b. An additional machine translation (which would in any case not be expected to be more useful than D5) is therefore not required. Hence the board finds it appropriate to exercise its discretion under Article 114(2) EPC and Article 13(1) RPBA by not admitting document D5c into the proceedings.

- 1.4 In its written communication issued in preparation for oral proceedings the board mentioned the argument that the skilled person, aware of the water-sensitivity of the active agent, would envisage conventional dry methods for preparing tablets, such as direct compression (see point IX above and point 3.2.7 of the board's communication). That argument had previously been discussed during the opposition and appeal proceedings, and in fact it was used in the reasoning given in the decision under appeal (see point VI above and the decision under appeal, Reasons point 7.4.3). Thus the relevant passage in the board's communication did not introduce any new aspect into the discussion which necessitated the filing of further evidence. In fact, the appellants stated that D33 was merely additional evidence submitted in support of their known arguments.

The respondents did not contest the fact that melt granulation was a known processing method which might be considered for processing water-sensitive materials. Document D33 does not contain any information which is more specific than that; it represents general textbook knowledge and does not refer to vildagliptin.

Thus, D33 was not filed in reaction to new arguments, nor does it possess any particular relevance going beyond the appellants' general argument that the skilled person, in view of common general knowledge, would have considered a melt granulation process. The board therefore finds it appropriate in the interest of procedural economy to exercise its discretion under Article 114(2) EPC and Article 13(1) RPBA by not admitting document D33 into the proceedings.

2. Objection under Rule 106 EPC, Article 113(1) EPC
  - 2.1 In the oral proceedings it was discussed whether, *inter alia*, D33 was to be admitted into the proceedings. After the chairman had announced that D33 was not admitted, the appellants raised an objection under Rule 106 EPC and expressed their opinion that their right to be heard was violated.
  - 2.2 The right to be heard encompasses the right to comment on the grounds on which the decision is based (Article 113(1) EPC). In the present case, the question which had to be decided was whether or not D33 was to be admitted into the proceedings. The appellants could present all their arguments as to this regard.
  - 2.3 Thus the appellants' right to be heard has been respected and the objection under Rule 106 EPC is unfounded.

3. Inventive step - main request

*Patent in suit*

3.1 The patent in suit seeks to provide an acceptable solid pharmaceutical dosage form of the DPP-IV inhibitor compound (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyanopyrrolidine, also known as "vildagliptin" or "LAF237" (see paragraphs [0036] to [0038], [0074] and [0120] of the patent specification).

3.2 Claim 1 of the present main request is directed to a direct compressed tablet with a defined particle size distribution.

3.2.1 The term "direct compressed" implies that the claimed tablet is obtainable by direct compression, i.e. it has the technical features which would inevitably result from direct compression. It was not contested by the parties that such tablets differ from tablets prepared by a granulation method.

3.2.2 As can be inferred from the wording of claim 1 and from paragraphs [0077] and [0094] to [0096] of the patent specification, the parameter "particle size distribution" relates to the particles containing the DPP-IV inhibitor, i.e. vildagliptin.

*Starting point in the prior art*

3.3 Documents D6 or D16 have previously been considered as suitable starting points for the assessment of inventive step.

3.3.1 Document D6 discloses N-substituted 2-cyanopyrrolidine compounds, described as new dipeptidyl peptidase-IV inhibitors, in particular vildagliptin (D6: claim 4, example 1 on page 9; page 5, lines 22 to 23), and pharmaceutical compositions containing such compounds

(D6: claim 5; page 5, lines 6 to 9). Enteral dosage forms, e.g. tablets, and parenteral dosage forms are envisaged for administration (D6: page 9, lines 1 to 4); those dosage forms may be prepared "by conventional means". Tablets containing vildagliptin and prepared by ethanolic wet granulation are disclosed (D6: formulation example on pages 17 to 18).

- 3.3.2 Document D16 discloses vildagliptin as a DPP-IV inhibitor with favourable oral bioavailability (D16: abstract). 2-cyanopyrrolidines are stable as dry solids but convert to cyclic amidines in a buffered aqueous medium (D16: page 2775, column 2, lines 10 to 13). It is mentioned that vildagliptin ("compound 12j" of D16) is comparatively stable (D16: page 2780, column 2, bottom paragraph). D16 does not describe solid formulations of vildagliptin.
- 3.3.3 Neither D6 nor D16 mentions the particle size of vildagliptin particles, nor do they specifically disclose tablets prepared by direct compression.
- 3.4 While either of D6 and D16 might serve as a starting point for the assessment of inventive step, it is, in the board's opinion, more appropriate to start from the disclosure of D6, due to its greater similarity to claim 1 in terms of technical features, since D6 discloses solid dosage forms. While tablets prepared by ethanolic wet granulation are specifically disclosed in D6 (see formulation example on pages 17 to 18), the person skilled in the art is aware that conventional methods of tablet preparation (as proposed on page 9 of D6) include direct compression.
- 3.5 The parties agreed that D6 was a suitable starting point for the assessment of inventive step.

*Technical problem and solution*

- 3.6 The tablet defined in claim 1 of the main request differs from the tablets of D6 in that it is obtainable by direct compression, and in that at least 60% of vildagliptin particles have a particle size between 10 and 250  $\mu\text{m}$ .
- 3.7 Direct compression means that a dry powder blend of the drug and excipients is subjected to compression (without any preceding granulation steps). In this manner, any stability issues which might occur due to processing vildagliptin with water are avoided.
- 3.8 However, no experimental data has been provided comparing tablets prepared by direct compression with tablets prepared by ethanolic wet granulation according to the formulation example of document D6. The granulation experiments described in document D32 involve aqueous wet granulation at 20% water content and thus do not use the preparation method of D6. It is therefore not known whether an advantage in stability is obtained with the claimed tablet compared to a tablet obtained with ethanolic wet granulation according to D6.
- 3.9 The patent in suit mentions that the specified particle size of 10 to 250  $\mu\text{m}$  is advantageous for tablet compaction (see the patent specification: paragraphs [0077] and [0094]). It is preferred but not mandatory that the excipients have similar particle sizes (paragraphs [0095] to [0096]).
- 3.10 In the board's opinion, it has not however been rendered credible that any specific technical effect is achieved by tablets in which at least 60% of the drug particles have a particle size between 10 and 250  $\mu\text{m}$ .

3.10.1 The patent itself does not provide evidence in the form of experimental data comparing technical effects obtained with different particle size distributions.

3.10.2 The experimental data provided in document D32 with regard to compression and compaction properties (see D32: Figures 6 to 8) do not compare samples falling within and outside the definition of claim 1.

According to the established jurisprudence of the boards of appeal, a surprising technical effect demonstrated in a comparative test can be taken as an indication of inventive step. If comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect, the nature of the comparison must be such that the alleged advantage or effect is convincingly shown to have its origin in the distinguishing feature of the claimed subject-matter compared with the closest prior art (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, I.D.10.9).

D32 suggests that compaction properties are less favourable with larger particle sizes. As conceded by the appellants, the two batches of drug particles which were examined (described in table 8 of D32) are however both likely to have a particle size distribution in line with the definition of claim 1. The appellants argued in this context that the data in D32 showed at least that the desired properties were obtained within the scope of the claim. However, the experimental data presented in D32 do not show that acceptable compaction properties are only obtained with particle size distributions which are within the scope of claim 1, or in other words that those properties have their origin in a distinguishing feature of the claimed tablet over the closest prior art. As a consequence, the alleged technical effect

cannot be used, within the framework of the problem-and-solution approach, in the formulation of the technical problem, nor to support a case in favour of inventive step.

- 3.10.3 The appellants further argued that particle size affected both the compaction properties and moisture resistance of the powder blend pre-mix and the tablets. Thus it had not been trivial, during development of the dosage form, to identify the proper balance which had to be struck, with regard to particle size, between compaction properties and humidity control.

This assertion has not, however, been backed up by experimental data. Even if it may be assumed from common general knowledge that particle size may have an influence (see D22, stating on page 5, penultimate paragraph, that size can be a factor in stability and that fine materials are more open to attack from e.g. humidity), it has not been shown that the specific size requirement defined in claim 1 (60% of particles having a size within the range of 10 to 250  $\mu\text{m}$ ) has actual relevance for the chemical stability of vildagliptin.

- 3.11 In the absence of proof of a technical effect, the technical problem starting from the technical teaching of document D6 must be defined as the provision of further tablets containing vildagliptin.
- 3.12 The board is satisfied that the technical problem is solved by the tablets defined in claim 1.

*Obviousness of the solution*

- 3.13 Document D6 describes tablets of vildagliptin prepared by ethanolic wet granulation, but also discloses dosage forms, including tablets, "prepared by conventional means" (D6: page 9, lines 3 to 4).



- 3.14 It is common general knowledge that direct compression is a conventional method of preparing tablets. This is acknowledged in paragraph [0019] of the patent in suit, where it is mentioned that "there are three commercially important processes for making compressed tablets: wet granulation, direct compression and dry granulation (slugging or roller compaction)".
- 3.15 Thus the skilled reader would infer that tablets obtainable by conventional direct compression methods are within the ambit of document D6.
- 3.16 The board is not aware of any specific reason for technical prejudice against direct compression in the case of vildagliptin. While it may take some work to find the most suitable combination of tableting excipients and process conditions, such optimisation, including that of particle size, is typical routine work for the formulator (see D7: page 196 to page 197, first paragraph; D22: pages 5 to 6) and would not deter him from using that preparation method.
- 3.17 It was also known that 2-cyanopyrrolidine DPP-IV inhibitors may present stability problems and, in particular, may deteriorate in an aqueous medium (see the patent in suit, paragraph [0010] and D16: page 2775, column 2, lines 10 to 13; as confirmed by the appellants' experiments shown in D32, pages 3 ff.). According to the formulation example of document D6, ethanolic and not aqueous granulation was used. While ethanol may contain water, there would still be much less water present in the granulation liquid than with aqueous granulation.
- 3.17.1 Based on these indications in the prior art, the respondents argued that the known water-sensitivity of vildagliptin provided a reason for the formulator to

favour a processing method which does not involve contacting the vildagliptin with water, such as direct compression.

3.17.2 The appellants argued that, even in the knowledge that 2-cyanopyrrolidine compounds could be sensitive to moisture and gave rise to stability problems, the person skilled in the art would still not change the method taught in D6, i.e. wet granulation. Since it was known from document D16 that vildagliptin had excellent bioavailability and was the most stable DPP-IV inhibitor (see D16: page 2780, column 2, bottom paragraph), the person skilled in the art would assume that its stability was sufficient or could at least be satisfactorily improved by adding stabilisers. This realistic approach had in fact been tried by the appellants, as described at length in document D32. Surprisingly, it had however been found that sufficient stability could not be achieved. Alternatively, the appellants argued that the person skilled in the art would consider melt granulation as a suitable "dry method", in order to preserve the advantages of a granulation method over direct compression.

3.18 The appellants' arguments cannot however succeed, since they do not provide a plausible reason why the person skilled in the art, seeking to provide further acceptable tablets of vildagliptin, would refrain from considering direct compressed tablets. While the board accepts that variations of granulation methods would have been considered, it is not credible that the skilled person would have focused exclusively on wet granulation or melt granulation, but would not at all have considered a conventional direct compression method, i.e. an equivalent conventional option against which no specific technical prejudice was known. The

mere selection of one of several equally possible options cannot be regarded as inventive.

3.19 No technical advantage has been shown in connection with the particle size distribution specified in claim 1. The choice of the particle size distribution is thus arbitrary. Furthermore, it does not involve unusual particle sizes: drug materials are usually ground or micronised to ensure homogeneity in the tablet, with 10 to 40  $\mu\text{m}$  typically being regarded as a favourable range (see D19: page 4, paragraphs 2 to 3; D22: pages 5 to 6).

3.20 For these reasons, the board finds that the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

4. Inventive step - first auxiliary request

4.1 Claim 1 of the first auxiliary request corresponds to claim 1 of the main request, with the additional requirement that *"ii) the water content of the tablet is less than 5% after 1 week at 25°C and 60% RH"*.

4.2 While the claim does not indicate the actual technical features required for meeting this parametric criterion, the board considers that such tablets may in principle be obtained by known measures, e.g. the choice of non-hygroscopic excipients, tablet coating, or the selection of suitable tablets after one week's storage under the specified conditions.

4.3 In support of inventive step, the appellants referred to data in D32 (III.1 on pages 16 to 17) illustrating improved drug stability when tablet samples were stored with a desiccant.

4.4 Actually, claim 1 merely specifies an upper limit for the moisture content which has to be met at the end of a one-week storage period, and does not contain any technical features requiring prolonged storage with a desiccant. On the other hand, figure 9 of document D32 shows improved stability of the sample designated "with desiccant" only between 3 and 12 months of storage. Document D32 neither reports the water content of the tested samples after one week, nor does it report whether storage with a desiccant of the sample "with desiccant" was continued after one week. Thus the data reported in D32 do not in fact reflect the impact of feature ii) added to the claim.

4.5 Based on common general knowledge, the person skilled in the art would in any case expect drug stability to improve with reduced exposure to moisture, in particular in the case of a drug like vildagliptin which is known to be water-sensitive.

Irrespective of that, the board is however of the opinion that feature ii) (less than 5% water content after 1 week at 25°C and 60% RH) does not in any case express a concept involving long-term humidity control or protection from moisture during storage. As a matter of fact, feature ii) only defines a specific water concentration measured after one week. It has not been shown that all tablets which meet this condition would have extended storage stability.

There is also no reason to assume that the added feature interacts with the other technical features of the claim to give rise to an unexpected technical effect.

Since the added feature must therefore be regarded as arbitrary, it cannot contribute to inventive step.

- 4.6 As a consequence, the subject-matter of claim 1 of the first auxiliary request does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as explained with regard to claim 1 of the main request (see section 3 above).
5. Inventive step - second auxiliary request
- 5.1 Claim 1 of the second auxiliary request corresponds to claim 1 of the main request, with the additional requirements that
- *"ii) the water content of the tablet is less than 10% after 1 week at 25°C and 60% RH" and*
  - *"iii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg" [sic].*
- 5.2 With regard to feature ii), the same reasoning applies as for feature ii) of claim 1 of the first auxiliary request. The fact that the upper limit of the water content is defined as 10% instead of 5% makes no difference.
- 5.3 It has not been shown that feature iii) is linked to any technical effect. In particular, it has not been shown that the ratio of tablet thickness to tablet weight contributes to moisture control, as asserted by the appellants. Moreover, the appellants did not contest the respondents' argument that the specified ratio is met by all usual tablets. Thus the board finds that feature iii) cannot contribute to inventive step.
- 5.4 As a consequence, the subject-matter of claim 1 of the second auxiliary request does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as explained with regard to claims 1 of the main

request and first auxiliary request (see sections 3 and 4 above).

6. Inventive step - third auxiliary request

6.1 The tablet defined in claim 1 of the third auxiliary request corresponds to the tablet of claim 1 of the main request, with the following further limitations:

(a) vildagliptin is present at 5 to 60% by weight on a dry weight basis,

(b) a diluent is present at 40 to 95%,

(c) a disintegrant is optional, with an upper concentration limit of 20%,

(d) a lubricant may be present at 0.1 to 10%.

6.2 The specified concentration range of vildagliptin is quite broad and has not been linked to any specific technical effect.

6.3 Features (b) to (d) relate to the presence of conventional generic classes of tableting excipients, present in typical concentrations; no evidence is on file showing any technical effect produced by those features, apart from the known, expected effects of diluents, disintegrants and lubricants.

6.4 The data presented in table 9 of document D32, cited by the appellants in support of an inventive step, report water concentrations between 2.5% and 3.5% in three different powder blends. However, the board is at a loss to see how those results could establish a causal link between the drug and excipient concentrations of the tablet defined in claim 1 of the third auxiliary request and any benefit with regard to humidity control, as asserted by the appellants. Apart from the obvious fact that the use of typically dry components would not carry

water into the formulation, nothing can be deduced from D32 in that respect, especially since the concentrations and components defined in claim 1 do not deviate from those typically used in a conventional formulation.

6.5 Hence the amendments proposed in claim 1 of the third auxiliary request do not introduce additional technical features upon which an inventive step could be based.

6.6 As a consequence, the subject-matter of claim 1 of the third auxiliary request does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as explained with regard to claim 1 of the main request (see section 3 above).

7. Inventive step - fourth auxiliary request

7.1 Claim 1 of the fourth auxiliary request is drafted in the form of a product-by-process claim. Assuming that the parameter concerning the particle size distribution is still intended to refer to the vildagliptin-containing particles (nothing else having been indicated by the appellants), the tablets defined in this way present all the technical features of the tablets according to claim 1 of the main request.

Additionally, the concentration of vildagliptin must be in the range of 6 to 60% by weight and at least one excipient selected from a diluent, a disintegrant and a lubricant must be present.

7.2 The presence of an excipient is arguably not an additional limitation compared to claim 1 of the main request, as it would be inferred to be technically necessary.

In any case, these additional limitations have not been linked to any specific technical effect and cannot therefore contribute to inventive step.

- 7.3 As a consequence, the subject-matter of claim 1 of the fourth auxiliary request does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as explained with regard to claim 1 of the main request (see section 3 above).
8. Inventive step - fifth auxiliary request
- 8.1 Claim 1 of the fifth auxiliary is directed to a process of preparing a direct compressed tablet by direct compression. The tablet has the same technical features as the tablet according to claim 1 of the fourth auxiliary request. Hence the assessment of inventive step involves the same technical features as discussed with respect to claim 1 of the fourth auxiliary request (see section 7 above).
- 8.2 The formulation of the claim as a process claim does not give rise to further issues which could be relevant to inventive step.
- 8.3 As a consequence, the subject-matter of claim 1 of the fifth auxiliary request does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as explained with regard to claim 1 of the fourth auxiliary request (see section 7 above).



## Order

### For these reasons it is decided that:

1. The appellants' objection in respect of a procedural defect under Rule 106 EPC is dismissed.
2. The appeal is dismissed.

The Registrar:

The Chairman:



S. Fabiani

D. Semino

Decision electronically authenticated