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**Datasheet for the decision  
of 8 October 2018**

**Case Number:** T 0376/15 - 3.3.01

**Application Number:** 09175877.1

**Publication Number:** 2329848

**IPC:** A61K31/155, A61K38/26,  
A61K38/28, A61K45/06

**Language of the proceedings:** EN

**Title of invention:**

Lixisenatide as add-on therapy to insulin glargine and metformin for treating type 2 diabetes

**Patent Proprietor:**

Sanofi-Aventis Deutschland GmbH

**Opponent:**

Generics [UK] Limited

**Headword:**

Triple therapy for diabetes type 2/SANOFI

**Relevant legal provisions:**

EPC Art. 54, 56, 83

**Keyword:**

Main request:

Novelty - (yes)

Inventive step - (yes)

Sufficiency of disclosure - (yes)



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Case Number: T 0376/15 - 3.3.01

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.01**  
**of 8 October 2018**

**Appellant:** Generics [UK] Limited  
(Opponent) (trading as Mylan)  
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**Respondent:** Sanofi-Aventis Deutschland GmbH  
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**Representative:** Weickmann & Weickmann PartmbB  
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**Decision under appeal:** **Decision of the Opposition Division of the  
European Patent Office posted on 8 December 2014  
rejecting the opposition filed against European  
patent No. 2329848 pursuant to Article 101(2)  
EPC.**

**Composition of the Board:**

**Chairman** A. Lindner  
**Members:** M. Pregetter  
P. de Heij

## Summary of Facts and Submissions

I. European patent No. 2 329 848 is based on European patent application No. 09175877.1.

II. The patent in suit as granted contains 4 independent claims, claims 1, 10, 11 and 12. Independent claims 1, 10, 11 and 12 of the patent in suit as granted read as follows:

"1. A combination for use in the treatment of diabetes mellitus type 2, the combination comprising  
(a) desPro<sup>36</sup> Exendin-4(1-39)-Lys<sub>6</sub>-NH<sub>2</sub> or/and a pharmaceutically acceptable salt thereof,  
(b) insulin glargine or/and a pharmaceutically acceptable salt thereof, and  
(c) metformin or/and a pharmaceutically acceptable salt thereof."

"10. A pharmaceutical combination comprising (a) desPro<sup>36</sup> Exendin-4(1-39)-Lys<sub>6</sub>-NH<sub>2</sub> or/and a pharmaceutically acceptable salt thereof, (b) insulin glargine or/and a pharmaceutically acceptable salt thereof, and (c) metformin or/and a pharmaceutically acceptable salt thereof."

"11. The combination of claim 10, wherein the combination is for use in the treatment of diabetes mellitus type 2."

"12. Use of a combination of  
(a) desPro<sup>36</sup> Exendin-4(1-39)-Lys<sub>6</sub>-NH<sub>2</sub> or/and a pharmaceutically acceptable salt thereof,  
(b) insulin glargine or/and a pharmaceutically acceptable salt thereof, and  
(c) metformin or/and a pharmaceutically acceptable salt thereof."

thereof,  
for the production of a pharmaceutical composition for  
the treatment of diabetes mellitus type 2."

III. The following documents, cited during the opposition  
and appeal proceedings, are referred to below:

(1) Campas et al., *Drugs Fut*, 2008, 33(10), 838-840

(2) WO2008/028914

(3) Arnolds et al., 2009, *Diabetes*, vol. 58, Suppl. 1,  
page A141, poster abstract P526-P

(7) Barnett, *Vascular Health and Risk Management*, 2006,  
2(1), 59-67

(8) Tews et al., *Horm Metab Res*, 2008, 40, 172-180

(9) "GLP-1 agonist AVE0010 in patients with type 2  
diabetes for glycemc control and safety evaluation, on  
top of basal insulin" NCT00715624, *ClinicalTrials.gov*  
archive, 20 July 2008, 3 pages

(12) Bethel et al., *J Am Board Fam Prac*, 2005, 18(3),  
199-204

(13) "Supplemental experimental data", filed with  
letter of 21 August 2015, 58 pages

IV. The appeal lies from the decision of the opposition  
division rejecting the opposition. The opposition  
division found that the subject-matter of the claims of  
the patent in suit was new, sufficiently disclosed and  
involved an inventive step when starting from  
document (3) as the closest prior art. The opponent

(appellant) filed an appeal.

- V. With its reply to the statement setting out the grounds of appeal, the respondent (patent proprietor) submitted auxiliary requests 1 to 4.
- VI. In a communication pursuant to Article 15(1) RPBA the board indicated its preliminary opinion that the subject-matter of the claims of the patent in suit was novel. Inventive step and sufficiency of disclosure were to be discussed during oral proceedings.
- VII. With letter dated 7 September 2018 the respondent submitted auxiliary request 5.
- VIII. Oral proceedings were held before the board on 8 October 2018, in the absence of the appellant, as indicated in its letter dated 17 July 2018.

During the oral proceedings, the respondent filed a new main request corresponding to the set of claims as granted, with the deletion of independent claim 12.

- IX. The appellant presented the following arguments in writing. Only the arguments relevant for the main request are listed:

*Sufficiency of disclosure*

The claims of the patent in suit covered non-working embodiments since they did not specify routes of administration and did not provide information on administration before or after meals. However, certain routes of administration would not lead to an effective treatment, and untimely administration would lead to considerable risks. The subject-matter as currently

claimed in the second medical use claims was thus not sufficiently disclosed.

### *Novelty*

Documents (1) and (2) were novelty-destroying. Document (1) referred to a clinical trial for which the detail and date was confirmed by document (9). It disclosed the efficacy of combinations of lixisenatide, any form of basal insulin and metformin in the treatment of diabetes mellitus type 2. Not only was the explicit disclosure of said documents of relevance, what would be implicit to the skilled reader had also to be borne in mind. A skilled person would have considered insulin glargine, a well-known form of basal insulin. Document (2) included claims 68, 71 and 75, each being dependent on claims 65 and 64. Only 24 possible combinations arose from the two lists in claims 68 and 71, whereas claim 75 exclusively defined metformin. Thus, there were no lists of "some length" and, consequently, each individual combination was directly and unambiguously disclosed.

### *Inventive step*

Document (1), rather than document (3) represented the closest prior art. Document (1) reported on a phase III clinical study investigating the benefits and risks of a combination of lixisenatide, basal insulin and metformin in the treatment of diabetes type 2. There was no question as to the efficacy of the treatment since the efficacy of all three compounds used in the combination was known. This could also be seen from document (9), which was on the study referenced in document (1). The only difference between the subject-matter of the claims of the patent in suit and the

disclosure of documents (1) or (9) was the identification of a specific form of the basal insulin to be used and the associated duration of the technical effect provided.

Document (3) was less suitable as the closest prior art since it would be necessary to replace either exenatide or sitagliptin with lixisenatide to move from document (3) to the claims of the patent in suit. Such a replacement could be considered as a more significant change than the simple selection of a basal insulin. Although document (3) provided some data, said data still had to be confirmed by studies in a larger population of patients.

Starting from document (1), the problem to be solved was to provide an effective treatment for diabetes mellitus type 2, wherein the specific form of basal insulin to be used was identified. There was a need to optimise glycaemic control based on such a triple therapy whilst still maintaining a safe treatment regimen with respect to the potential risk of hypoglycaemia. There was specific motivation for the skilled person to use insulin glargine in the combination of the closest prior art since documents (7) and (12) described insulin glargine as especially useful for providing glycaemic control and lowering the risk of hypoglycaemia. This was especially important in compositions comprising lixisenatide, an insulin secretagogue. Furthermore, Document (7) explained why insulin glargine was superior to other basal insulins. Insulin glargine being the obvious choice of the skilled person when using a basal insulin and having glycaemic control and the risk of hypoglycaemia in mind, the subject-matter of the patent in suit did not involve an inventive step.



The appellant stated in its statement setting out the grounds of appeal that starting from document (3) it considered it to be obvious to change exenatide to lixisenatide. No further arguments were provided.

- X. The respondent's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

*Sufficiency of disclosure*

Typical routes of administration for lixisenatide, insulin glargine and metformin were known from the prior art and were discussed in the application as filed. It was known to the skilled person that insulin glargine and lixisenatide could be given prior to a meal. The skilled person was thus aware of how to administer the claimed combination.

*Novelty*

Document (1) did not disclose insulin glargine. Due to missing back references the combination of claims 68, 71 and 75 was not disclosed in document (2).

*Inventive step*

Documents (1) and (9) would not be considered by the skilled person as the closest prior art due to shortcomings in their disclosures. They provided some information on a protocol to carry out certain tests without, however, providing any results. Document (1) was a review article focusing on lixisenatide that mentioned some ongoing trials. It was clearly stated on page 840, left-hand column, second paragraph, that the

benefits and risks had to be evaluated. Document (9) provided information on one of the trials mentioned in document (1) regarding the combination of basal insulin, with or without metformin, and lixisenatide. Again, the benefits and risks were to be evaluated ("Brief summary"). Thus, neither the efficacy nor the safety of the tests to be carried out in accordance with document (9) were known. The term "with or without metformin" meant that patients receiving metformin and patients not receiving metformin were included in the study and stratified between the study arms. The difference between the patent in suit and the disclosure of document (9) was the group of patients to be treated. Whereas the patent in suit looked specifically at a group of patients that were (no longer) sufficiently treated by a combination of metformin and insulin glargine, document (9) looked at patients receiving any basal insulin and, optionally, metformin. Since the patients were to be kept on their treatment by their usual basal insulin for the study of document (9), it would have been necessary for the skilled person to decide to replace said usual basal insulin by insulin glargine. The protocol of document (9) contained not teaching to do so. The better starting point for the assessment of inventive step was document (3), which provided disclosure on a double combination of metformin and insulin glargine and taught the addition of a third active. Starting from document (3), the presence of an inventive step was to be acknowledged in line with the opposition division's decision.

XI. The final requests of the parties were as follows:

The appellant requested in writing that the decision under appeal be set aside and the patent be revoked.

The respondent requested that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims of the main request, submitted at the oral proceedings, or of auxiliary requests 1-4, filed with the letter of 21 August 2015, or auxiliary request 5, filed with the letter of 7 September 2018.

### **Reasons for the Decision**

1. The appeal is admissible.
2. Oral proceedings were held in the absence of the duly summoned appellant in accordance with Article 15(3) RPBA and Rule 115(2) EPC. The appellant is treated as relying on its written case.
3. *Main request - admission*

The claims of the main request correspond to the claims of the patent as granted with the sole difference that claim 12 has been deleted. Consequently, the filing of said amended request does not lead to any new subject-matter that could raise complex issues. Furthermore, the appellant is not presented with any new subject-matter on which it has not had the opportunity to comment.

The main request was therefore admitted in accordance with Article 13 RPBA.

4. *Sufficiency of disclosure*

The administration modes of the three actives - lixisenatide, insulin glargine and metformin - are well

established in the art. Also, the patent in suit provides information on how to administer said actives (paragraphs [0013] to [0026]). The appellant has not shown that the combination of said actives would require a change in the administration mode. Consequently, from common general knowledge and the disclosure of the description of the patent in suit, the skilled person gets sufficient instructions on how to administer the combination in order to achieve a safe and effective treatment of diabetes mellitus type 2.

The subject-matter of the claims of the main request is sufficiently disclosed.

5. *Novelty*

The appellant cited documents (1), with reference to document (9), and (2) as being novelty-destroying. The board has come to the conclusion that neither of the three documents discloses the claimed combinations.

Documents (1) and (9) do not explicitly disclose insulin glargine. The board has found no indication that an explicit or implicit, direct and unambiguous disclosure of insulin glargine is made anywhere in document (1). The same is true for document (9).

Starting from the claims of document (2), several selections are needed to arrive at the combination of (a), (b) and (c) as defined in the independent claims of the patent in suit. Three selections (insulin analogs, glucagon-like-peptide-1 receptor agonists and biguanide agent) have to be made in claim 65, which is dependent on claim 64, in order to reach the combination of groups of compounds having the chemical

or functional characteristics required by the three compounds (a), (b) and (c). Claims 68, 71 and 75 refer directly or indirectly to claim 65. Within claims 68 and 71 further selections are necessary in order to arrive at the specific compounds defined in the independent claims of the patent in suit. Thus several selections are required in order to arrive at the combination of the independent claims of the patent in suit. Such multiple selections do not represent a direct and unambiguous disclosure of the subject-matter under consideration.

The subject-matter of the claims of the main request is novel.

6. *Inventive step*

6.1 The object of the patent in suit is the provision of a combination of actives for use in the treatment of diabetes mellitus type 2. Control of diabetes mellitus type 2 by metformin and insulin may be insufficient and additional measures for patients in need of them may be required (paragraphs [0001] and [0004]). A combination of lixisenatide, insulin glargine and metformin (or their pharmaceutically acceptable salts) is offered as a solution [paragraph [0005], claims).

6.2 The appellant has selected document (1) as the closest prior art.

Document (1) relates to a specific glucagon-like peptide 1 (GLP-1) receptor agonist, named AVE-0010 or ZP-10, which are other names for desPro<sup>36</sup> Exendin-4(1-39)-Lys<sub>6</sub>-NH<sub>2</sub> or lixisenatide. It describes lixisenatide being tested in phase III clinical studies for the treatment of diabetes type 2 (abstract), one

study associating it with basal insulin, with or without metformin (p.840, left column, second paragraph). This study is also the subject of document (9).

Document (1) provides no further information on the clinical study. A study protocol is not given, and nor is there any information on primary or secondary objectives. Document (9), which relates to the same study (see reference (16) of document (1)) provides some more details. A skilled person can derive from document (9) that the clinical study has two arms, an experimental arm relying on the administration of lixisenatide and a placebo arm. The primary objective is to assess the effects of lixisenatide on glycaemic control in terms of HbA1c reduction at 24 weeks. The secondary objectives are to assess the effects of lixisenatide on body weight, fasting plasma glucose and insulin doses and to evaluate safety and tolerability.

Document (9) does not give any details on the study protocol or on the evaluation of the data to be obtained, especially in view of the inclusion of patients receiving different treatment regimens. The respondent has argued that patients receiving and patients not receiving metformin would be stratified. This may well be. However, there is no information on this point in document (9).

A further issue are the details on the treatment by basal insulin. The only information to be gained from document (9) is that lixisenatide is to be administered "on top of" basal insulin ("Brief title"). It is an inclusion criterion that any patient to be enrolled in the study suffered from diabetes mellitus type 2 insufficiently controlled with basal insulin, i.e. the

patients were receiving some form of basal insulin before entering the study ("Criteria"). There is, however, no disclosure on the types of basal insulin the patients received before entering the study or on the treatment regimen by basal insulin during participation in the study. There is, furthermore, no information on whether a "switch" to a certain type of basal insulin for all study participants was to take place. If no "switch" was intended, participants could be stratified, groups of participants receiving a certain type of basal insulin could be selected, or evaluation could be performed in various ways taking such inhomogeneous patient groups into account. However, all these considerations are mere speculation since such details do not form part of the disclosure of document (9).

In sum, document (9) provides no detailed treatment protocol. The disclosure regarding the administration of metformin, the details on a treatment regimen by basal insulin, and how variations in treatment are to be handled in view of the study outcome are missing. Such unspecific and general information cannot be used to determine which expectations would be raised by document (9). There is not enough concrete information for a skilled person to build on. The board comes to the conclusion that the skilled person would not regard document (9) (or the even less detailed document (1)) as a promising springboard. Consequently, document (9) (or document (1)) is not considered to be a suitable closest prior art document.

6.3 Having come to the conclusion that the skilled person would not have considered either document (1) or (9) as a promising starting point when looking for an add-on therapy for patients whose diabetes mellitus type 2 is

not adequately controlled by metformin and insulin (glargine), it is necessary to look further for a suitable closest prior-art document.

6.4 The opposition division and the respondent rely on document (3) as the closest prior art. However, in its statement setting out the grounds of appeal, the appellant has not provided a line of argument based on document (3) as the closest prior art. The board had thus to rely on the arguments available from the impugned decision.

6.5 Document (3) discloses a treatment regimen for patients with diabetes type 2 comparing the administration of combinations of insulin glargine and methformin, insulin glargine, metformin and exenatide or insulin glargine, metformin and sitagliptin. The three study arms of document (3) lead to comparable effects in HbA1c control (indicator of glycaemic control), body weight stability and low hypoglycaemia rate. The treatment arm relating to the triple therapy of insuling glargine, metformin and exenatide has the highest number of adverse effects.

The difference between the subject-matter of the independent claims of the main request and the disclosure of document (3) lies in the replacement of either exenatide or sitagliptin by lixisenatide.

The opposition division stated that the technical problem underlying the patent in suit is the same as the one found in document (3), i.e. to provide an improved therapeutic regimen for diabetes mellitus type 2 patients receiving insulin glargine and metformin. The terms "alternative triple therapy" were also employed. It was found that document (3) did not



show better control of glycaemia by triple therapy than by the combination of insulin glargine. Having in mind the fact that the triple therapy with exenatide, working via the same mechanism as lixisenatide, had the most adverse effects, a skilled person would turn to the other study arm, the arm employing sitagliptin, which acted via a completely different mechanism than lixisenatide. The disclosure of document (8) was found not to provide an incentive to replace exenatide by lixisenatide since it related to in vitro data of a very specific effect. The opposition division further acknowledged that the data of document (13) provided evidence that an effective treatment was achieved by the triple combination of insulin glargine, metformin and lixisenatide. Concerning the provision of a solution over the whole scope of the claims, the opposition division came to the conclusion that a skilled person would not try to administer the actives via unsuitable routes.

In the absence of any arguments to the contrary, the board concurs with the opposition division that starting from document (3) as the closest prior art, the technical problem can be seen as an alternative add-on therapy for the treatment of diabetes mellitus type 2. The replacement of exenatide or sitagliptin would not be obvious to the skilled person since the data provided in document (3) points away from the use of a GLP-1 agonist in view of the side effects due to exenatide, or does not suggest a GLP-1 agonist in the first place, having in mind that sitagliptin works by a completely different mechanism (as DPP-4 inhibitor).

6.6 The subject-matter of the independent claims of the main request involves an inventive step.

## Order

### For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the opposition division with the order to maintain the patent as amended in the following version:

Description: pages 1-7 of the patent specification;

Claims: 1-11 of the main request, received during the oral proceedings on 8 October 2018.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated