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Datasheet for the decision of 15 July 2021

Case Number: T 1186/19 - 3.3.04

Application Number: 12721268.6

Publication Number: 2707015

IPC: A61K38/26, A61K38/28, A61K31/155, A61P3/10, A61P3/04

Language of the proceedings: EN

Title of invention:
Lixisenatide as add-on therapy to basal insulin in type 2 diabetes

Patent Proprietor:
Sanofi-Aventis Deutschland GmbH

Opponent:
Generics [UK] Ltd

Headword:
Lixisenatide combination therapy/SANOFI

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1186/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 15 July 2021

Respondent: (Patent Proprietor)	Sanofi-Aventis Deutschland GmbH Brüningstraße 50 65929 Frankfurt am Main (DE)
Representative:	Weickmann & Weickmann PartmbB Postfach 860 820 81635 München (DE)
Appellant: (Opponent)	Generics [UK] Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 14 March 2019 concerning maintenance of the European Patent No. 2707015 in amended form**

Composition of the Board:

Chairman	A. Chakravarty
Members:	D. Luis Alves
	M. Blasi

Summary of Facts and Submissions

I. In an interlocutory decision, the opposition division held that, account being taken of the amendments in the form of auxiliary request 1, the patent and the invention to which it related met the requirements of the EPC (Article 101(3)(a) EPC).

II. The patent had been opposed under Article 100(a) EPC, on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), as well as under Article 100(b) EPC.

III. In the decision, the opposition division held that the patent as granted sufficiently disclosed the invention as claimed but that the subject-matter of claim 1 did not involve an inventive step.

IV. The opponent (appellant) filed an appeal against that decision. The patent proprietor also filed an appeal against the decision but withdrew it at the oral proceedings before the board. The patent proprietor is therefore respondent in the appeal proceedings.

V. With the statement of grounds of appeal, the appellant filed documents F22 to F24 and submitted arguments on the inventive step of the subject-matter of all claims of auxiliary request 1 as considered by the opposition division in the decision under appeal.

VI. With the reply to the appellant's statement of grounds of appeal, the respondent filed auxiliary claim requests 2 to 8 and documents F25 to F28.

VII. With a further letter the appellant submitted arguments addressing inventive step of the subject-matter of the claims as granted.

VIII. Claim 1 of auxiliary request 1 in the proceedings before the opposition division and held allowable in the decision under appeal reads:

"1. A pharmaceutical combination for use in glycemic control in diabetes type 2 patients, said combination comprising

(a) desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof,

(b) a basal insulin or/and a pharmaceutically acceptable salt thereof, and

(c) metformin or/and a pharmaceutically acceptable salt thereof,

wherein the diabetes type 2 to be treated is not adequately controlled with the basal insulin and metformin alone and the patient to be treated has a 2 hours postprandial plasma glucose concentration of at least 14 mmol/L."

IX. The following documents are referred to in this decision:

F5: Sanofi-Aventis Press Release "Once-Daily Lixisenatide in Combination with Basal Insulin Demonstrates Significant Improvement in Glucose Control", Paris, France, 30 September 2010. Retrieved from the Internet on 31 July 2017.

F7: Christensen *et al.*, IDrugs, 12(8), 2009, pages 503-513.

F8: Ratner R.E. *et al.*, Diabetic Medicine, 27(9), 2010, pages 1024-1032.

F11: Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence, International Diabetes Federation, 2011.

F21: Gerich J.E. *et al.*, Diabetologia, 53(Suppl 1), abstract 830, 2010, pages S1-S556.

F22: U.S. National Institutes of Health: "GLP-1 Agonist AVE0010 in Patients with Type 2 Diabetes for Glycemic control and Safety Evaluation, on Top of Basal Insulin", 2 March 2011, retrieved from the Internet on 26 July 2017.

X. Oral proceedings before the board were held as scheduled. The appellant did not attend these proceedings, as announced by letter dated 27 April 2021.

XI. At the oral proceedings the patent proprietor withdrew its appeal and accordingly auxiliary request 1, considered allowable by the opposition division, became its main request. At the end of the oral proceedings, the Chair announced the board's decision.

XII. The appellant's arguments as relevant to this decision are summarised as follows:

Admittance of document F22 (Article 12(4) RPBA 2007)

This document should be admitted into the appeal proceedings because it was *prima facie* relevant since it represented the closest prior art to the subject-matter of claim 1. It was filed as a legitimate reaction to the decision of the opposition division. In line with decisions T 855/96 and T 406/09, an appellant should have the opportunity to "fill the gaps in its arguments" by presenting further evidence in appeal proceedings.

Main request
Inventive step (Article 56 EPC) - claim 1

The claims were directed to a pharmaceutical combination comprising lixisenatide, basal insulin and metformin, wherein lixisenatide was administered as an add-on treatment on top of basal insulin and metformin to diabetes type 2 patients, wherein the diabetes was not adequately controlled with the combination metformin and basal insulin and the patients had a 2 hours postprandial plasma glucose (PPG) level of at least 14 mmol/L.

The claimed subject-matter lacked an inventive step when document F5 was taken to represent the closest prior art. The opposition division had correctly held that the claimed subject-matter differed from the disclosure in document F5 in the pharmaceutical combination, which additionally comprised metformin and in the patient group, which had PPG levels at least 14 mmol/L and diabetes not adequately controlled with the combination of basal insulin and metformin.

Based on these differences, the objective technical problem, solved by the claimed subject-matter, was "the provision of an alternative pharmaceutical combination for the treatment of high risk diabetes type 2 patients".

There was no evidence, from the patent or from other documents on file, that patients whose diabetes was inadequately controlled with a combination of basal insulin and metformin were any more refractory to treatment with lixisenatide than those with diabetes inadequately controlled with basal insulin alone, who were the subject of document F5.

Document F8 disclosed the treatment of patients having diabetes inadequately controlled with metformin and PPG levels close to those mentioned in claim 1. The patients' PPG levels significantly overlapped those in the example in the patent (13.1±3.3 mmol/L vs. 16.44 ±4.29 mmol/L, respectively, see table 1 of document F8 and table 14 of the patent). The patients' PPG levels mentioned in the example in the patent ranged from 5.6 to 29.3 and therefore included the PPG levels disclosed in document F8. Moreover, the patients in the study in document F8 had HbA1c levels between 7.0 and 9.0% (see abstract), which according to document F11 defined a group of patients with sub-optimal glycemic control and for whom additional therapy was suggested (see Table 1, page 54).

Document F8 thus disclosed improved glycemic control, with lixisenatide as add-on therapy to metformin, in patients very similar to those in claim 1. In view of this disclosure, the skilled person would have had a reasonable expectation that the pharmaceutical combination disclosed in document F5 would be equally

effective as an add-on treatment for patients whose diabetes was inadequately controlled with metformin.

Moreover, document F5 already disclosed that lixisenatide had comparable efficacy in two different patient populations since it stated: "*[t]he results of this second study [GETGOAL MONO] demonstrate the efficacy of lixisenatide in a different population of type 2 diabetic patients*".
As noted by the opposition division, document F5 already pointed the skilled person towards the treatment of "high risk" patients within the group of patients with diabetes inadequately controlled with basal insulin (with or without sulfonylurea). This was the case because the patients in the clinical study in that document presented HbA1c values up to 10%, which according to document F11 included "high risk" patients.

Thus, the subject-matter of claim 1 lacked an inventive step over the disclosure in document F5, alone or in combination with the disclosure in document F8.

XIII. The respondent's arguments as relevant to this decision are summarised as follows:

Admittance of document F22 (Article 12(4) RPBA 2007)

The claims of the main request had been filed in reply to the notice of opposition. Thus document F22, which was known to the appellant at the time, should have been filed in opposition proceedings. The document was also not *prima facie* relevant because it disclosed the protocol of a clinical study without disclosing any outcome, whereas there were documents on file disclosing the outcome of treatment with lixisenatide,

such as documents F5, F8 and F15. In view of the above, the document should not be admitted into the appeal proceedings.

Main request
Inventive step (Article 56 EPC) - claim 1

The claimed subject-matter differed from the disclosure in document F5 in three ways. It related (i) to patients whose diabetes was inadequately controlled with a combination of metformin and basal insulin, as opposed to patients having diabetes inadequately controlled with basal insulin alone; (ii) to a pharmaceutical combination including metformin in addition to lixisenatide and basal insulin, as opposed to lixisenatide and basal insulin alone; and (iii) to the treatment of patients having a PPG level of at least 14 mmol/L, compared to the patients in document F5, whose PPG was not known.

In view of these differences, the objective technical problem was "the provision of an improved treatment for patients with diabetes type 2 which is not adequately controlled with basal insulin and metformin and the patients have a 2 hour PPG concentration of at least 14 mmol/L".

Document F5 concerned patients whose diabetes was inadequately controlled by a combination of two agents acting via a common route, i.e. basal insulin and an insulin secretion stimulant - sulfonylurea. The patients as defined in the claim were those who did not achieve glycemic control in spite of being treated with two agents acting via different mechanisms - insulin and metformin, the latter acting by a mechanism incompletely understood which included reducing glucose

release. For this reason, the skilled person reading document F5 would not have expected that these patients could be effectively treated with lixisenatide.

Furthermore, in document F5 there was no mention of specific PPG levels. The HbA1c levels mentioned therein were mere inclusion criteria in the clinical study and from the disclosure in document F5, it could not be determined which HbA1c values the patients actually had. However, the HbA1c levels had an impact on the treatment. There were therefore significant differences between the patients as defined in the claim and those in the study in document F5.

Thus no conclusions could be drawn from document F5 as to the potential efficacy of a therapy with metformin combined with lixisenatide and basal insulin because the patients treated in document F5 differed from those treated according to the claim in terms of their baseline treatment and severity of the diabetes.

Moreover, contrary to the appellant's suggestion, a combination of the therapy disclosed in document F8 with the disclosure in document F5, was the result of hindsight because in document F8 the patients' baseline treatment was different to that in document F5. Moreover, document F8 did not relate to patients having the PPG levels required in the claim, since the authors noted that the patients in the study were mildly hyperglycaemic. This document merely disclosed average PPG values without disclosing any clinical outcome for a specific subgroup within the range of PPG values resulting in this average.

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

and that documents F22 to F24, all filed with the statement of grounds of appeal, and document F21, filed in opposition proceedings, be admitted into the appeal proceedings.

XV. The respondent requested that the appeal be dismissed, i.e. that the patent be maintained in amended form in the version as considered allowable by the opposition division.

Reasons for the Decision

Admissibility of the appeal

1. The appeal complies with the requirements Articles 106 to 108 EPC and the further provisions referred to in Rule 101(1) EPC and is admissible.

Parties not attending oral proceedings

2. The appellant was duly summoned but did not attend the oral proceedings before the board. The appellant was considered as relying on its written case, in accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020.

Admission of documents F21 and F22 (Article 12(4) RPBA 2007)

3. Document F22 was filed by the appellant with the statement of grounds of appeal and was used as a starting point for an objection of lack of inventive step against the claims of the main request. This objection had not been raised in the proceedings before the opposition division although the claim request objected to had been filed with the reply to the notice

of opposition. Thus, document F22 could and should have been filed earlier. The appellant provided no reasons for the timing of the filing of this document. The board thus holds it inadmissible pursuant to Article 12(4) RPBA 2007.

4. With the reply to the statement of grounds of appeal of the patent proprietor, the appellant requested that document F21 be admitted into the proceedings and relied on this document in the submissions in relation to the then main request of the patent proprietor. This request was subsequently withdrawn. The appellant did not rely on document F21 in its arguments relating to the claim request held allowable by the opposition division. Accordingly, there is no need for the board to decide on admission of this document.

Main request - all claims
Inventive step (Article 56 EPC)

5. The sole issue in dispute in respect of the main request is inventive step.

6. Claim 1 relates to the combination of basal insulin, lixisenatide and metformin for glycemic control in diabetes type 2 patients characterised by a level of 2 hour postprandial plasma glucose (PPG) at least 14 mmol/L and wherein the diabetes is not adequately controlled with the combination of basal insulin and metformin.

7. In view of the board's decision to not admit document F22 into the appeal proceedings (see point 3. above), only document F5 remains from those suggested by the appellant to represent the closest prior art to the claimed subject-matter.

8. This document is a press release reporting the outcome of a clinical study of lixisenatide as an add-on therapy on patients with type 2 diabetes being treated with basal insulin, with or without sulfonylurea. It discloses that lixisenatide as an add-on therapy significantly improved glycemic control in these patients. It specifically refers to "*a significant reduction in A1C*" (see page 1, second paragraph). It is silent on the patients' baseline PPG levels but discloses that the patients' baseline HbA1c levels were between 7 and 10%.

9. It is common ground that document F5 does not disclose that the patients had "a 2 hours postprandial plasma glucose concentration of at least 14 mmol/L", as set out in the claim.

10. Document F5 also does not disclose the treatment of patients who were receiving the combination of basal insulin and metformin with lixisenatide. Thus, the difference between the subject-matter of claim 1 and said disclosure in document F5 lies in the use of a different pharmaceutical combination, i.e. metformin and basal insulin with lixisenatide in the former and basal insulin with lixisenatide, with or without sulfonylurea in the latter and in a different patient group, i.e patients whose diabetes is inadequately controlled by treatment with basal insulin and metformin and wherein the PPG level is at least 14 mmol/L in the former and patients with diabetes inadequately controlled with basal insulin with or without sulfonylurea, with no indication as to PPG levels, in the latter.

11. The appellant has not disputed that the results in the patent show an effect on glycemic control of the

therapeutic combination lixisenatide, basal insulin and metformin on diabetes type 2 patients having a PPG concentration at least 14 mmol/L. Thus, the technical effect of the above mentioned differences is the attainment of glycemic control in the specified patient group.

12. In view of the above differences and the technical effects that can be attributed to them, the objective technical problem may be formulated as the provision of an alternative pharmaceutical combination for glycemic control in patients with inadequately controlled diabetes.

13. The claimed solution is the combination of lixisenatide, basal insulin and metformin for the treatment of patients having a PPG level of at least 14 mmol/L and whose diabetes was not adequately controlled by basal insulin and metformin.

14. In the board's view this solution was not obvious to a skilled person. The appellant argued that the skilled person, knowing from document F8 that lixisenatide was effective as an add-on therapy in glycaemic control in diabetes inadequately controlled with metformin, would have had the expectation that the pharmaceutical combination disclosed in document F5 (see point 8. above) would be effective as add-on treatment for improving glycemic control in patients inadequately controlled with metformin. The appellant further noted that the skilled person had this expectation since the patients in the study disclosed in document F8 had HbA1C levels which corresponded, according to document F11, to inadequately controlled diabetes requiring further therapy.

15. Document F8 discloses that lixisenatide as add-on therapy to metformin improved glycaemic control in patients with inadequately controlled diabetes, as reflected by their HbA1c and PPG levels (see abstract). The patients had average baseline PPG levels between 11.5 and 13.1 mmol/L (average PPG depending on study arm, see Table 1). However, as set out in the decision under appeal, this document does not concern diabetic patients receiving basal insulin and metformin whose diabetes is inadequately controlled. Thus, the disclosure in this document does not suggest the use of lixisenatide as an add on-therapy for patients inadequately treated with basal insulin and metformin, as claimed. In the board's view, based on the disclosure in document F8 the skilled person could not have any expectation as to the efficacy of the treatment of patients having elevated PPG levels in spite of being under treatment with two antidiabetic agents.

16. The board is of the view that the combined disclosure of lixisenatide as add-on therapy for treating diabetes inadequately controlled with basal insulin, in document F5 on the one hand, with that in document F8 as an add-on therapy for treating diabetes inadequately controlled by metformin, on the other hand, would not have led the skilled person to expect that lixisenatide could be used to efficiently treat the patients defined in the claim. The reason for this is that document F5 concerns the treatment of patients whose diabetes was inadequately controlled with basal insulin or with a combination of basal insulin and sulfonylurea, (an insulin secretagogue; see document F7), in contrast to present claim 1 which relates to diabetes patients whose diabetes is inadequately controlled in spite of being treated with two drugs with different mechanisms

of action, i.e. insulin and a biguanide, which latter acts by increasing the sensitivity to insulin (see document F11, page 26, paragraph bridging the two columns).

17. Moreover, in the board's view also the fact that the patients in the study in document F8 would require additional therapy, did not provide any motivation to treat the different diabetes patients defined in claim 1, i.e. whose diabetes were inadequately controlled with metformin and basal insulin.

18. The appellant also argued that the claimed solution was obvious because there was no evidence that the patients as defined in the claim were more refractory to treatment with lixisenatide than those treated with basal insulin alone, i.e. those concerned in the study in document F5. However, since the board has decided that the skilled person would not have arrived at the claimed solution from the disclosure in either document F5 or document F8, alone or in combination (see points 15. and 16., above), this argument is moot. Similarly, the appellant's argument that document F5 additionally mentioned the efficacy of lixisenatide in a second patient group is moot since the board considers that the skilled person would not have arrived at the patient group with diabetes inadequately controlled with basal insulin and metformin, as claimed.

19. The appellant further argued that the disclosure in either document F5 or F8 would have led the skilled person to expect that treatment with lixisenatide would be effective in patients with PPG levels of at least 14 mmol/L, as defined in the claim.

20. However, document F8, relates to a study involving patients who were "*mildly hyperglycaemic*" (see abstract, last paragraph); their average PPG level is reported as being between 11,5 and 13.1 mmol/L (see table 1, average value depending on the study arm). The study does not report on treatment efficacy for patients grouped by their PPG levels. Accordingly, this document does not allow any conclusions to be drawn about the efficacy of lixisenatide for glycaemic control, in patients whose PPG levels are above or below the above mentioned average values.

21. Moreover, document F11, referred to by the parties in the context of elevated PPG levels, provides a definition of patients whose glycaemic control is suboptimal as those whose PPG level is between 10 and 14 mmol/L. Patients at high risk for complications due to inadequate glycaemic control are defined as those who have a PPG level of above 14 mmol/L (see page 54, Table 1). Thus, the patients referred to in the claim are those with "high risk" whereas those who took part in the study reported on in document F8 are referred to as having "suboptimally controlled" glycaemia. In view of this, the board concludes that the appellant's argument, that the patients referred to in document F8 are similar to those referred to in the claim, is not convincing.

22. Finally, the appellant argued that the patients mentioned in document F5 had a baseline HbA1c range of 7 to 10% and that this range was a measure of poor glycaemic control, in the same way as the postprandial plasma glucose concentration mentioned in the claim.

23. However, the board is not convinced that the skilled person would have known that lixisenatide would be

effective for glycaemic control in patients whose PPG level was least 14 mmol/L, and also receiving a combined treatment with basal insulin and metformin, for the following reasons.

24. Firstly, the argument relies on a correspondence between the HbA1c interval in document F5 and the PPG value in the claim, based on the classification of a patient's glycaemic control as "suboptimal" or "high risk". However, whereas according to document F11 patients having PPG above 14 mmol/L or HbA1c above 9% are classified as high risk (see F11, page 54, Table 1), those with HbA1c levels between 7 and 9% have suboptimal glycaemic control. Hence, the patients mentioned in document F5, having HbA1c between 7% and 10%, do not correspond to the "high risk" classification.

25. Secondly, the actual HbA1c values presented by the patients enrolled in the study referred to in document F5 are not disclosed in the document and it can be argued, as the respondent did, that the range mentioned in the document merely represented an inclusion criterion.

26. In conclusion, the board cannot concur with the appellant that, based on the information in document F5 the skilled person would have known that treatment with lixisenatide would be effective in patients with PPG levels of at least 14 mmol/L, as defined in the claim.

27. Thus, the appellant's argument based on a combination of the disclosures in documents F5 and F8 is not persuasive. This conclusion applies equally to claims 2 to 14, all referring back to claim 1.

Reimbursement of the patent proprietor's appeal fee at 25%

28. The patent proprietor withdrew its appeal against the opposition division's decision before the decision was announced at the oral proceedings. Thus, the requirements of Rule 103(4)(a) EPC for a partial reimbursement of the patent proprietor's appeal fee are met and 25% of the appeal fee is to be reimbursed .

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The patent proprietor's appeal fee is to be reimbursed at 25%.

The Registrar: The Chairman:

I. Aperribay A. Chakravarty

Decision electronically authenticated