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**Datasheet for the decision
of 19 December 2017**

Case Number: T 0079/15 - 3.3.07

Application Number: 10006250.4

Publication Number: 2248531

IPC: A61K38/28

Language of the proceedings: EN

Title of invention:

Antidiabetic oral insulin-biguanide combination

Applicant:

Emisphere Technologies, Inc.

Headword:

Insulin-biguanide combination/EMISPHERE

Relevant legal provisions:

EPC Art. 56

EPC R. 103(1)(a)

Keyword:

Inventive step - (no)

Reimbursement of appeal fee - (no)



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Case Number: T 0079/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 December 2017

Appellant: Emisphere Technologies, Inc.
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 28 July 2014
refusing European patent application No.
10006250.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

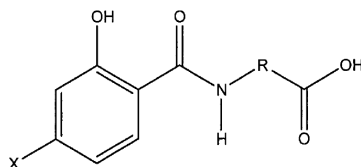
Chairman J. Riolo
Members: A. Uselli
I. Beckedorf

Summary of Facts and Submissions

- I. The appeal of the applicant (appellant) lies from the decision of the examining division to refuse European patent application No. 10006250.4, published as EP 2 248 531.
- II. The decision of the examining division was based on a single set of claims submitted on 7 March 2014.

Claim 1 of the main request read as follows:

"1. An oral dosage form comprising a therapeutically effective dose of insulin and a biguanide, further comprising a pharmaceutically acceptable delivery agent that facilitates absorption of insulin from the gastrointestinal tract, wherein said delivery agent is of the following formula or a pharmaceutically acceptable salt thereof,



wherein

X is hydrogen or halogen;

R is substituted or unsubstituted C₁-C₃ alkylene,
substituted or unsubstituted C₁-C₃ alkenylene,
substituted or unsubstituted C₁-C₃ alkyl(arylene),
substituted or unsubstituted C₁-C₃ aryl (alkylene),
wherein, preferably, X is a halogen, more preferably chlorine, wherein the insulin, biguanide and the delivery agent are combined in a single dosage form".

The following documents were among those cited in the European Search Report:

D1: WO 2004/062587

D4: Endocrine practice, 4(6), (1998), 404-412

D5: Diabetes-Metabolism Research and Reviews, 18(1), (2002), S38-S42

III. In its decision the examining division considered that the oral dosage form of the present application differed from the compositions disclosed in D1 in that they contained a biguanide such as metformin. This modification did not result in a more rapid decrease in blood glucose level and in a sustained hypoglycemic action as maintained by the appellant. The technical problem was therefore to be seen in the provision of an alternative dosage form for the treatment of diabetes. Metformin was a known anti-diabetic agent commonly used in combination with other drugs as disclosed in D4. Accordingly, it would have been obvious to the skilled person to add a biguanide such as metformin to the compositions of D1.

IV. With the statement setting out the grounds of appeal, the appellant requested that the decision under appeal be set aside and a patent be granted on the basis of a main request or on the basis of an auxiliary request.

The main request was the same request submitted during the first instance proceedings on 7 March 2014 (see point II above).

Claim 1 of auxiliary request 1 read as follows:

"1. An oral dosage form comprising a therapeutically effective dose of insulin and a biguanide selected from

metformin or a pharmaceutically acceptable salt thereof and a delivery agent selected from 4-[(4-chloro, 2-hydroxybenzoyl)amino] butanoic acid or a pharmaceutically acceptable salt thereof, wherein the insulin, biguanide and the delivery agent are combined in a single dosage form, comprising about 0.1 mg/kg insulin, about 450 mg/kg biguanide and about 200 mg/kg 4-[(4 chloro, 2-hydroxybenzoyl)amino]butanoic acid".

- V. In a communication pursuant to Article 15(1) RPBA issued on 23 October 2017, the Board observed that the compositions of the present application differed from those disclosed in the closest prior art D1, in that they contained a biguanide, such as metformin. It furthermore observed that the skilled person knew from documents D4 and D5 that metformin enhanced the effects of insulin, in particular with regard to the control of glucose levels.
- VI. Oral proceedings were held on 19 December 2018. They were not attended by the appellant as announced in its letter of 15 December 2017. For the course of the oral proceedings, reference is made to the minutes.
- VII. The appellant's arguments presented in writing can be summarised as follows:

Document D1 was the closest prior art for the assessment of inventive step. This document disclosed *inter alia* an oral composition for the treatment of diabetes comprising insulin and a delivery agent. The oral dosage form defined in the main request differed from the composition of D1 in the additional presence of a biguanide. The experiment disclosed in example 2 showed that the addition of the biguanide metformin resulted in a faster bioavailability of

insulin, a faster decrease in blood glucose level and faster onset of hypoglycemic action. The technical problem was the provision of improved formulations for treating diabetes. None of the cited documents suggested to solve this problem by the provision of a composition containing insulin, a biguanide and a delivery agent. The requirement of Article 56 EPC was therefore met.

VIII. The appellant had requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of a main request or alternatively on the basis of an auxiliary request, both submitted with the statement setting out the grounds of appeal on 5 December 2014. Furthermore, the appellant had requested that appeal fee be reimbursed.

Reasons for the Decision

Main Request

Inventive step

1. Closest prior art

1.1 The Board agrees with the appellant and with the examining division that document D1 is a suitable starting point for the assessment of inventive step. This document discloses oral dosage forms comprising insulin and a delivery agent such as 4-CNAB (i.e the sodium salt of N-[4-(4-chloro-2-hydroxybenzoyl)amino]butanoic acid, see example 3).

The compositions defined in claim 1 of the main request differs from those of D1 in that they additionally contain a biguanide, such as metformin.

2. Technical problem

2.1 Example 2 of the application describes an experiment in which two insulin compositions according to present claim 1, containing 4-CNAB as a delivery agent and metformin as biguanide, are compared *inter alia* with a composition containing only insulin and 4-CNAB. The experiment consists in the observation of the blood glucose levels in rats receiving the oral compositions.

The composition containing only insulin and 4-CNAB can be regarded as a composition according to D1. The amounts of insulin (0.25 mg/kg) and 4-CNAB (200 mg/kg) contained in this composition are identical to the amounts contained in the first of the two compositions according to present claim 1 tested in example 2 (designated in Tables 1 to 3 as "Ins(0.25)+4-CNAB(200) + metformin (450)"). Thus, the experiment of example 2 makes it possible a comparison of the effects on the blood glucose level of a composition according to the invention and of a composition according to the closest prior art.

2.2 The results disclosed in Table 2 and in Figure 2 indicate that both the composition according to D1 and the composition according to the invention provide a rapid onset of hypoglycemic action. However, the composition according to present claim 1 provides better results in terms of percentage of reduction of glucose levels in the time interval from 60 to 300 minutes after administration of the compositions.

In the Board's view, in the light of these data the technical problem can be formulated as the provision of an oral dosage form of insulin providing a rapid onset

of the hypoglycemic action and a better sustained decrease in blood glucose levels.

3. Obviousness

- 3.1 Review article D4 indicates that therapies for the treatment of diabetes based on the combination of insulin and metformin are known in the art. According to D4, metformin potentiates the action of insulin (page 405, first complete paragraph of right column). Some of the studies reviewed in D4 suggest that the addition of metformin to an insulin-based therapy results in a decrease of the mean daily plasma glucose concentration and improved glycemic control (page 408, left column, line 9 onwards; page 409 paragraph bridging left and right columns).
- 3.2 Document D5 suggests that metformin and insulin can also be administered simultaneously in separate oral formulations (paragraph "Use of Oralin in combination with metformin in patients failing on oral agents therapy", page S39). Page S40 (right column) of D5 reports that the combination metformin/insulin results in a reduction of the postprandial glucose levels.
- 3.3 Thus, documents D4 and D5 indicate that metformin can enhance the effects of insulin in particular with regard to the control of the glucose levels. It follows that on the basis of the teachings of these documents, a skilled person would expect that a therapy based on the combination of metformin and insulin would be more effective, in terms of control of blood glucose levels, than a therapy based only on the use of insulin as active ingredient. Hence, when facing the problem of improving the composition of D1 he would consider to modify this composition by the addition of metformin.

In view of the above, the Board concludes that the subject-matter of the main request does not fulfil the requirements of Article 56 EPC.

Auxiliary request

4. Claim 1 of the auxiliary request is restricted to compositions wherein the biguanide is metformin and the delivery agent is the compound 4-CNAB. Moreover, the claim recites the amounts of the ingredients in the dosage form.

4.1 As discussed above, the compositions of D1 contain 4-CNAB as delivery agent. Furthermore, in documents D4 and D5 the biguanide used in combination with insulin is metformin. Hence, the fact of specifying in claim 1 of the auxiliary request that the biguanide is metformin and the delivery agent is 4-CNAB does not alter the assessment of inventive step made above for the subject-matter of the main request.

4.2 As to the feature relating to the amounts of insulin, metformin and 4-CNAB in the dosage form, the Board notes that the appellant did not submit any argument as to its relevance for the assessment of inventive step. Nor provides the application any evidence of surprising effects arising from the specific amounts recited in claim 1.

The Board concludes therefore that these amounts represent an arbitrary choice that does not provide any inventive contribution to the subject-matter of claim 1 of the auxiliary request.

In conclusion, the auxiliary request does not meet the requirements of Article 56 EPC.

Request of reimbursement of the appeal fee

5. It follows from Rule 103(1) (a) EPC that the reimbursement of the appeal fee can only take place if the Board allows the appeal of the appellant (or if the examining division rectifies its decision by an interlocutory decision).

Since the appeal is dismissed, a reimbursement of the appeal fees, as requested by the appellant, is not possible.

Order

For these reasons it is decided that:

1. The appeal is dismissed.
2. The request for reimbursement of the appeal fee is rejected.

The Registrar:

The Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated