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Oberursel, 20/08/2018

Opposition against European Patent EP 1 687 019 B1

Title: Propylene glycol-containing peptide formulations which are optimal for production and for use in injection devices

Proprietor: NOVO NORDISK A/S

Our Ref.: FKE18087

1. General matters

The patent is opposed in its entirety. As will be shown below, none of claims 1-17 meets the requirements of the EPC. The patent is opposed on the grounds of Article 100(a) and (c) EPC in conjunction with Articles 54, 56, and 123(2) EPC.

The opposition fee (EUR 785,00) is to be debited from our account no. 28002213.

Full revocation of the patent is requested. Should the Opposition Division be minded to maintain the patent in any form, oral proceedings under Article 116 EPC are requested.

2. List of documents

Reference is made to the following documents:

D1 WO 03/002136 A2 – published: 9 January 2003

D2 WO 2005/046716 A1 – published: 26 May 2005

D3 Pharmaceuticals and Medical Devices Agency Japan: Victoza Subcutaneous Injection 18 mg - Report on the Deliberation Results. Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare – published: 2009

D4 Powell et al.: Parenteral Peptide Formulations: Chemical and Physical Properties of Native Luteinizing Hormone-Releasing Hormone (LHRH) and Hydrophobic Analogues in Aqueous Solution. Pharmaceutical Research, Vol. 8, No. 10, 1991

D5 WO 03/033671 A2 – published: 24 April 2003

D6 WO 95/22560 A1 – published: 1995

D7 Board of Appeal Decision T 0235/97 - 3.3.2, 10 January 2002

3. Added subject-matter, Article 123(2) EPC

The subject-matter of claim 7 is not found in the application as filed. Claim 1 refers to a pharmaceutical formulation comprising the peptide Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37), wherein claim 7 further requires that "*said peptide consists of Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)*". It is not apparent how this would further qualify the subject-matter of claim 1, which already specifies the exact same peptide. In any event such combination of features and terms is nowhere found in the original disclosure.

In addition, the subject-matter of claim 10 extends beyond the content of the application as filed, which is silent on a pH range of 8.0 to 8.3.

For these reasons, the requirements of Article 123(2) EPC are not met.

4. Lack of novelty, Article 54 EPC

4.1 Claim 1 lacks novelty over **D1**

D1 discloses pharmaceutical formulations of GLP-1 compounds and methods for preparation thereof (see abstract). Claim 1 of **D1** relates to a pharmaceutical formulation comprising a GLP-1 compound and a buffer, the formulation having a pH from 7.0 to 10. According to claim 25 of **D1**, the GLP-1 compound is Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37). The formulation of **D1** further comprises an isotonic agent which is present in a concentration from 1 mg/ml to 50 mg/ml (claims 13 and 14; p19, lines 10-11), which falls within the range of 1 to 100 mg/ml of claim 1 of the opposed patent.

The isotonic agent may be propylene glycol (**D1**, p18, lines 34-35). While propylene glycol is disclosed as part of a list of possible isotonic agents (**D1**, p18, line 34 – p19, line 4), a selection from a single list of specifically disclosed elements does not confer novelty (GL G-VI 8(i)). In addition, **D1** notes that "*each*

one of these specific isotonic agents constitutes an alternative embodiment of the invention" (p19, lines 7-8).

Thus, **D1** discloses all features of claim 1 of the opposed patent, which consequently lacks novelty.

4.2 Claim 1 lacks novelty over **D2**

Document **D2** (WO 2005/046716) has a priority date of 13 November 2003 and a filing date of 12 November 2004. It was published on 26 May 2005. It has been supplied to the European Patent Office in one of its official languages and the national fee provided for in Article 22(1) or Article 39(1) PCT has been paid. **D2** thus constitutes state of the art pursuant to Articles 54(3) EPC and 54(4) EPC 1973.

In the examination phase of the application leading to the opposed patent, the patentee argued that the priority claim of **D2** was invalid as far as the disclosure of propylene glycol was concerned, since its priority application (Danish patent application PA 2003 01689) did not mention propylene glycol. According to the applicant, **D2** thus had an effective date of 12 November 2004, i.e. its filing date.

However, the priority claim of the opposed patent is also invalid pursuant to Article 87(4) EPC.

As discussed above in section 4.1, **D1** discloses the same subject-matter as claimed in the opposed patent. Importantly, **D1** is an earlier patent application of the present patentee which precedes the filing of the priority application of the opposed patent. **D1** has a filing date of 27 June 2002, whereas the priority application of the opposed patent has a filing date of 20 November 2003. Consequently, the priority application of the opposed patent is not the first application of the patentee for this subject-matter in the sense of Article 87(4) EPC. The priority claim is therefore invalid. The effective date of all claims is the filing date of the application leading to the opposed patent, i.e. 18 November 2004, which is later than the filing date of **D2** (12 November 2014). Therefore, **D2** constitutes prior art under Article 54(3) EPC for all claims.

D2 discloses soluble pharmaceutical composition for parenteral administration with a pH of 7-9, comprising Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) and propylene glycol (claims 1, 2, 28, 56-58). Examples of such pharmaceutical formulations comprise liraglutide (Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)) and 14 mg/ml propylene glycol, wherein the formulations have a pH of 7.7 (**D2**, p3, lines 15-26, p21-22, Examples 2-4). Such compositions fall within the respective ranges of claim 1 of the opposed patent and are therefore novelty-destroying for the same.

4.3 Dependent claims

Claim 2 further requires that the formulation is suitable for parenteral administration performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. This requirement is also met by the respective compositions of **D1** (see p16, lines 22-25) and **D2** (see p17, lines 23-25).

Claims 3, 4 and 5 further require that the concentration of propylene glycol is from 1-50, 5-25, and 8-16 mg/ml, respectively. The range of claim 3 is disclosed in **D1** (claims 13 and 14; p19, lines 10-11). In addition, **D1** discloses the range of claim 5 (p19, lines 12-13), which is also novelty-destroying for the range of claim 4. Furthermore, the value of 14 mg/ml propylene glycol as disclosed in **D2** (see above) also falls within the respective ranges of claims 3, 4 and 5.

Claim 6 requires that the pH of the formulation is 7.0 to 9.5. The same range is disclosed in **D1** (p17, lines 22-23). Also, the compositions of **D2** have a pH of 7.7 (p3, lines 15-26, p21-22, Examples 2-4), which falls within the range of claim 6.

Claim 7 requires that the peptide consists of Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37). As discussed above, it is not apparent how this would further limit the subject-matter of claim 1. In any event, the compositions of **D1** and **D2** comprise a peptide consisting of Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37); see above.

Claims 8-10 recite pH ranges of 7.0 to 8.3, 7.3 to 8.3, and 8.0 to 8.3, respectively. **D1** teaches a preferred pH range of 7.5 to 8.0 (p17, lines 24-25), which falls within the respective ranges of claims 8 and 9. Also, the upper limit of pH 8.0 in **D1** is novelty destroying for the range of claim 10. Having a pH of 7.7, the compositions of **D2** fall within the ranges of claims 8 and 9 (see above). Also, claim 3 of **D2** discloses a pH range of 7.0 to 8.0, the upper limit of which falls within the range of claim 10.

Claim 11 further requires that the formulation comprises a preservative. The same subject-matter is found in **D1** (p18, lines 16-17; claim 11) and **D2** (claim 1).

Claim 12 further requires that the preservative is present in a concentration from 0.1 mg/ml to 20 mg/ml. **D1** discloses the same range for its preservative (see p18, lines 23-24; claim 12). The compositions of **D2** contain 40 mM phenol (p3, lines 15-26). With a molecular weight of phenol of 94.11 g/mol (see https://en.wikipedia.org/wiki/Phenol), this corresponds to a phenol concentration of about 3.8 mg/ml (40*94.11/1000), which also falls within the range of claim 12.

Claim 13 further requires that the preservative is phenol. The same subject-matter is disclosed in **D1** (p18, lines 21-22) and **D2** (p3, lines 15-26; p5, lines 5-6).

Claim 14 further requires that the formulation comprises a buffer. According to

claim 15, the buffer is selected from the group consisting of glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate or mixtures thereof. According to claim 16, the buffer is disodium phosphate dihydrate. The compositions of **D1** also comprise a buffer (see claim 1). The buffers of claims 15 and 16 are also disclosed in **D1** (p17, lines 27-33). The same applies to **D2** (p3, lines 15-26; p14, lines 21-23).

Claim 17 further requires that the concentration of liraglutide is from 0.1 mg/ml to 50 mg/ml, or from 0.1 mg/ml to 10 mg/ml. Claim 1 of **D1** requires that the GLP-1 compound is present in a concentration of 0.1-100 mg/ml, the lower limit of which falls within both ranges of claim 17. In addition, claim 9 of **D1** discloses the same ranges of 0.1-50 and 0.1-10 mg/ml. The example compositions of **D2** contain 1.2 mM liraglutide (p3, lines 15-26). With a molar mass of 3751.2 g/mol (https://en.wikipedia.org/wiki/Liraglutide), this corresponds to a liraglutide concentration of about 4.5 mg/ml (1.2*3751.2/1000), which falls into the range of claim 17. **D2** also discloses a concentration range for its peptide of 1-25 mg/ml (see claim 30), which also falls within in the range of claim 17.

In summary, all dependent claims lack novelty over **D1** and **D2**, respectively.

5. Lack of inventive step, Article 56 EPC

Irrespective of the foregoing, it is submitted that none of the claims involves an inventive step.

5.1 No technical effect over the whole range of the claim

Claim 1 of the opposed patent relates to pharmaceutical formulations of liraglutide comprising 1-100 mg/ml of propylene glycol, at a pH of 7-10. The alleged technical effects associated with these features are specified in paragraph [0004] of the opposed patent, as reproduced below (emphasis added):

> **[0004]** The present inventors have discovered that peptide formulations containing propylene glycol at certain concentrations exhibit reduced deposits in production equipment and in the final product and also exhibit reduced clogging of injection devices. The present compositions may be formulated with any peptide and are also physically and chemically stable thus rendering them shelf-stable and suitable for invasive (eg. injection, subcutaneous injection, intramuscular, intraveneous or infusion) as well as non-invasive (eg nasal, oral, pulmonary, transdermal or transmucosal e.g. buccal) means of administration.

When examining the experimental data allegedly supporting the reduction in the formation of deposits, clogging and/or impurities, it is apparent that all experiments were conducted with compositions comprising several non-claimed components. All tested formulations contain a preservative (5.5 mg/ml phenol) and a buffer (1.42 mg/ml disodium hydrogen phosphate, dihydrate); see Example 1, paragraph [0044]; Example 2, paragraph [0057]; Example 3, paragraph [0060].

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