physiological conditions while also exhibiting sufficient solubility and chemical and physical stabilities under non-physiological conditions.

Summary

In one aspect of the present disclosure, there is provided a glucagon compound comprising the amino acid sequence of Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2).

In another aspect of the present disclosure, there is provided a glucagon compound comprising the amino acid sequence consisting of Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2).

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as described herein and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided a compound as described herein for use in a therapy.

In another aspect of the present disclosure, there is provided a compound as described herein for use in the treatment of hypoglycemia.

In yet another aspect of the present disclosure, there is provided a use of a compound as described herein in the manufacture of a medicament for the treatment of hypoglycemia.

Description

Accordingly, the present invention seeks to provide a compound which maintains wild-type glucagon activity but also exhibit sufficient solubility as well as chemical and physical stability. The present invention also provides a compound which is suitable for pump and/or emergency administration. In addition, the present invention provides a compound that can be administered in combination with a fast-acting insulin analog in a dual-chamber pump to provide closed-loop glycemic control.

The present invention provides a compound comprising the amino acid sequence Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2). The present invention also provides a compound consisting of the amino acid sequence

Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2). Unexpectedly, it has been found that the compound of the present invention exhibits increased aqueous solubility, increased chemical stability, and reduced fibrillation as compared to human glucagon in aqueous solution. In addition, the compound of the present invention demonstrates enhanced solubility at pH near 8. The compound of the present invention also provides similar activity as human glucagon – e.g., potency, time of action, and selectivity at the glucagon receptor as compared to human glucagon. Thus, the compound of the present invention is suitable to treat hypoglycemia, including severe or acute hypoglycemia. The improved properties of the compound of the present invention also allow for the preparation of glucagon in aqueous solutions for pump administration and severe hypoglycemia treatment.

The present invention further provides a method of treating hypoglycemia in a subject comprising administering a compound comprising the amino acid sequence of SEQ ID NO: 2. The present invention also provides a method of treating hypoglycemia in a subject comprising administering a compound consisting of the amino acid sequence of SEQ ID NO:2. The present invention a further provides a compound comprising the amino acid sequence of SEQ ID NO: 2 for use in therapy. The present invention also provides a compound consisting of the amino acid sequence of SEQ ID NO: 2 for use in therapy. The present invention also provides a compound comprising the amino acid

IN THE EUROPEAN PATENT OFFICE ACTING AS PRELIMINARY EXAMINATION AUTHORITY UNDER THE PCT

Applicant Docket:	X19935 WO
International Application No.:	PCT/US2014/069646
Applicant:	Eli Lilly and Company
Earliest Priority Date:	18.12.2013
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Title:	NOVEL COMPOUND FOR TREATMENT OF SEVERE HYPOGLYCEMIA

AMENDED CLAIMS PURSUANT TO ARTICLE 34 OF THE PCT

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European Patent Office
D-80298 Munich
Tel. +49 89 2399 -0
Fax+49 89 2399-4465

Attn: EPO acting as IPEA under the PCT

AMENDED CLAIMS:

1. A glucagon compound comprising the amino acid sequence of Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2).

2. The compound of Claim 1, wherein the compound consists of the amino acid sequence of Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2).

3. A compound comprising the amino acid sequence consisting of Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2).

~~3.~~ 4. A pharmaceutical composition comprising the compound of any of Claims 1-3 ~~Claim 1 or Claim 2~~ and a pharmaceutically acceptable carrier.

~~4.~~ 5. A method of treating hypoglycemia in a subject comprising administering an effective amount of a compound of any of Claims 1-3 ~~Claim 1 or Claim 2~~.

~~5.~~ 6. A compound of any of Claims 1-3 ~~Claim 1 or Claim~~ 2 for use in a therapy.

~~6.~~ 7. A compound of any of Claims 1-3 ~~Claim 1 or Claim~~ 2 for use in the treatment of hypoglycemia.

~~7.~~ 8. A compound of any of Claims 1-3 ~~Claim 1 or Claim~~ 2 for use in the manufacture of a medicament for the treatment of hypoglycemia.

WE CLAIM:

1. A glucagon compound comprising the amino acid sequence of Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2).

2. The compound of Claim 1, wherein the compound consists of the amino acid sequence of Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2).

3. A glucagon compound comprising the amino acid sequence consisting of Tyr-Ser-His-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Ala-Glu-Phe-Val-Ala-Trp-Leu-Leu-Glu-Glu (SEQ ID NO: 2).

4. A pharmaceutical composition comprising the compound of Claim 2 and a pharmaceutically acceptable carrier.

5. A compound of Claim 2 for use in a therapy.

6. A compound of Claim 2 for use in the treatment of hypoglycemia.

7. Use of a compound of Claim 2 in the manufacture of a medicament for the treatment of hypoglycemia.

8. A pharmaceutical composition comprising the compound of Claim 3 and a pharmaceutically acceptable carrier.

9. A compound of Claim 3 for use in a therapy.

10. A compound of Claim 3 for use in the treatment of hypoglycemia.

11. Use of a compound of Claim 3 in the manufacture of a medicament for the treatment of hypoglycemia.