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Coalition for Affordable Drugs II LLC v. NPS Pharmaceuticals, Inc.

IPR2015-00990 & IPR2015-01093
Patent No. 7,056,886

Counsel for Petitioner
Merchant & Gould
June 23, 2016

CFAD Exhibit 1091
CFAD v. NPS
IPR2015-00990
IPR2015-01093

Exhibit 1003
’886 patent

(12) **United States Patent**
Isaacs

(10) **Patent No.: US 7,056,886 B2**
(45) **Date of Patent: Jun. 6, 2006**

(54) **GLP-2 FORMULATIONS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 628 days.

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A61K 38/00 (2006.01)
A61K 38/26 (2006.01)
C07K 14/00 (2006.01)

(52) **U.S. Cl.** **514/12**; 530/308; 530/399; 530/324; 435/4; 435/287.1

(58) **Field of Classification Search** 514/12; 530/308, 399, 324; 435/4, 287.1
See application file for complete search history.

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(57) **ABSTRACT**

The invention is directed to formulations of GLP-2 peptides and analogs thereof exhibiting superior stability following storage and/or exposure to elevated temperatures. The GLP-2 compositions comprise a GLP-2 peptide or an analog thereof, a phosphate buffer, L-histidine, and mannitol.

75 Claims, 6 Drawing Sheets

Exhibit 1003
'886 patent

Col. 1, ll. 5-55

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GLP-2 FORMULATIONS

FIELD OF INVENTION

The present invention provides formulations for GLP-2 peptides and analogs thereof. In particular, the invention provides formulations of GLP-2 peptides and GLP-2 analogs with improved stability.

BACKGROUND OF THE INVENTION

Administration of therapeutic peptides requires peptide formulations that remain stable during storage. In general, parenteral administration is used with peptides because of their increased size and subsequent difficulty in crossing biological membranes. Peptides can be particularly difficult to formulate because of their tendency to degrade over time and/or undergo aggregation and precipitation. Degradation, aggregation, and precipitation are all indicative of an unstable formulation. Such an unstable formulation is not commercially viable, as it cannot pass U.S. Food and Drug Administration approval.

Formulation variables which affect the degradation of peptides during storage include, but are not limited to, pH, the quantity of salts present, and the type and quantity of excipients. In addition, temperatures, pressures, and time for freezing and drying cycles can affect the stability of a lyophilized peptide formulation. The role of most of these variables has been studied; however, the synergistic effect of the variables is still poorly understood.

Glucagon-like peptide-2 (GLP-2) is a 33 amino acid peptide having therapeutic applications in the treatment of diseases of the gastrointestinal tract. In particular, it has been determined that GLP-2 and analogs thereof act as trophic agents to enhance and maintain the functioning of the gastrointestinal tract and to promote growth of intestinal tissue. See e.g., U.S. Pat. Nos. 5,834,428; 5,789,379; and 5,990,077; and International Publication No. WO 98/52600.

Commercial exploitation of GLP-2 or an analog thereof requires a stable GLP-2 formulation that can be readily prepared using a commercially acceptable process. Because GLP-2 is a protein, and thus far more labile than traditional small molecular weight drugs, the formulation of GLP-2 or an analog thereof presents challenges not commonly encountered by the pharmaceutical industry. For example, methionine oxidation at position **10** and aspargine deamination at position **11**, **16**, and/or **24** of GLP-2 are potential routes of degradation. Furthermore, GLP-2 or an analog thereof may also be adsorbed to surfaces to form aggregates and/or precipitate, which would then render the formulation unstable.

There is a need in the art for stable formulations of GLP-2 peptides and analogs thereof which can be prepared using a commercially acceptable process. The present invention satisfies these needs.

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Rx" table for query on "203441."

Active Ingredient:	TEDUGLUTIDE RECOMBINANT
Dosage Form;Route:	POWDER;SUBCUTANEOUS
Proprietary Name:	GATTEX KIT
Applicant:	NPS PHARMS INC
Strength:	5MG/VIAL
Application Number:	N203441
Product Number:	001
Approval Date:	Dec 21, 2012
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Exhibit 1039
Orange Book, Gattex

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N203441	001	5789379	Apr 14, 2016	Y	Y	U - 1320	
N203441	001	7056886	Sep 18, 2022		Y	U - 1320	
N203441	001	7847061	Nov 1, 2025			U - 1320	
N203441	001	9060992	Nov 1, 2025			U - 1320	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N203441	001	ODE	Dec 21, 2019
N203441	001	NCE	Dec 21, 2017

Exhibit 1029
Drucker '379

Col. 4, ll. 26-67
Col. 5, ll. 1-55

In one aspect of the invention, the intestinotrophic analogs of GLP-2 conform to the sequence of Formula 1 (SEQ ID NO:1) as follows:

R1-(Y1)m-X1-X2-X3-X4-Ser5-Phe6-Ser7-Asp8-(P1)-Leu14-Asp15-Asn16-Leu17-Ala18-X19-X20-Asp21-Phe22-(P2)-Trp25-Leu26-Ile27-Gln-28-Thr29-Lys30-(P3)-(Y2)n-R2,

wherein

X1 is His or Tyr

X2 is Ala or an Ala-replacement amino acid conferring on said analog resistance to DPP-IV enzyme;

X3 is Asp or Glu;

X4 is Gly or Ala;

P1 is Glu-X10-Asn-Thr-Ile or Tyr-Ser-Lys-Tyr (SEQ ID NO:3);

X10 is Met or an oxidatively stable Met-replacement amino acid;

X19 is Ala or Thr;

X20 is Arg, Lys, His or Ala;

P2 is Ile-Asn, Ile-Ala or Val-Gln;

P3 is a covalent bond, or is Ile, Ile-Thr or Ile-Thr-Asp;

R1 is H or an N-terminal blocking group;

R2 is OH or a C-terminal blocking group;

Y1 is one or two basic amino acids selected from the group Arg, Lys, and His;

Y2 is one or two basic amino acids selected from the group Arg, Lys, and His; and

m and n, independently, are 0 or 1; and

wherein at least one of X1, X2, X3, X4, P1, X10, X19, X20, P2 and P3 is other than a wild type, mammalian GLP-2 residue.

Wild-type mammalian GLP-2 residues which occur at a specific position are determined by aligning the sequences of GLP-2's isolated from different mammalian species and comparing the sequence to the human sequence, reproduced below, for convenience (SEQ ID NO:2):

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His—Ala—Asp—Gly—Ser—Phe—Ser—Asp—Glu—Met—Asn—
1 5 10
Thr—Ile—Leu—Asp—Asn—Leu—Ala—Ala—Arg—Asp—Phe—
15 20
Ile—Asn—Trp—Leu—Ile—Gln—Thr—Lys—Ile—Thr—Asp (SEQ ID NO:2)
25 30

The amino acid residues which, for purposes of this application, are known to occur at specific positions in wild type mammalian GLP-2's are the following: position X13 may be Ile or Val; Position X16 may be Asn or Ser; position X19 may be Alanine or Threonine; position X20 may be Arg or Lys; position X27 may be Ile or Leu; and position X28 may be Gln or His.

The present GLP-2 analogs may incorporate desired amino acid substitutions into a "background" which is an N-terminally or C-terminally modified form of a mammalian GLP-2 peptide. Such analogs are represented in Formula 1 as those in which R1 constitutes an N-terminal blocking group, and/or when m is 1 then Y1 is one or two basic amino acids such as Arg or Lys; and/or R2 is a C-terminal blocking group; and/or when n is 1 then Y2 is independently, one or two basic amino acids such as Arg or Lys.

In preferred embodiments of the invention, the GLP-2 analog is an analog of full length GLP-2, i.e., GLP-2(1–33), and P3 is accordingly the sequence Ile-Thr-Asn. Alternatively, the GLP-2 analogs may be C-terminally truncated, to yield GLP-2(1–32) forms in which P3 is Ile-Thr, or GLP-2(1–31) forms in which P3 is Ile, or GLP-2(1–30) forms in which P3 is a covalent bond.

The "blocking groups" represented by R1 and R2 are chemical groups that are routinely used in the art of peptide chemistry to confer biochemical stability and resistance to digestion by exopeptidase. Suitable N-terminal protecting groups include, for example, C_{1-5}alkanoyl groups such as acetyl. Also suitable as N-terminal protecting groups are amino acid analogues lacking the amino function. Suitable C-terminal protecting groups include groups which form ketones or amides at the carbon atom of the C-terminal carboxyl, or groups which form esters at the oxygen atom of the carboxyl. Ketone and ester-forming groups include alkyl groups, particularly branched or unbranched C_{1-5}alkyl groups, e.g., methyl, ethyl and propyl groups, while amide-forming groups include amino functions such as primary amine, or alkylamino functions, e.g., mono-C_{1-5}alkylamino and di-C_{1-5}alkylamino groups such as methylamino, ethylamino, dimethylamino, diethylamino, methylethylamino and the like. Amino acid analogues are also suitable for protecting the C-terminal end of the present compounds, for example, decarboxylated amino acid analogues such as agmatine.

Embodiments of the invention specifically include such analogs in which m is 0 and R1 is a blocking group such as acetyl; and analogs in which m is 0 and R2 is a C-terminal blocking group such as an amine, e.g., —NH2.

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