### WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau

### INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7: A61K 38/26, 38/28, 47/10, 47/26, A61P 3/10 // (A61K 38/28, 38:26)

(11) International Publication Number:

**WO 00/37098** 

(43) International Publication Date:

29 June 2000 (29.06.00)

(21) International Application Number:

PCT/US99/30395

**A1** 

(22) International Filing Date:

21 December 1999 (21.12.99)

(30) Priority Data:

60/113,499

22 December 1998 (22.12.98) US

(71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BRADER, Mark, L. [NZ/US]; 6465 North Park Avenue, Indianapolis, IN 46220 (US). PEKAR, Allen, H. [US/US]; 5354 North Park Avenue, Indianapolis, IN 46220 (US).

(74) Agent: MACIAK, Ronald, S.; Eli Lilly and Company, Lilly Corporate Center, Drop Code1501, Indianapolis, IN 46285 (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

### **Published**

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SHELF-STABLE FORMULATION OF GLUCAGON-LIKE PEPTIDE-1

(57) Abstract

Glucagon-like peptide-1 (GLP-1) has been shown to be useful in the treatment of diabetes. The invention encompasses a shelf stable formulation that comprises a therapeutically effective amount of GLP-1, a pharmaceutically acceptable preservative, and a tonicity modifier, and that has a pH between about 8.2 to about 8.8.



### FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

$\mathbf{AL}$	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
ΑU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
$\mathbf{BE}$	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	ΙE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
ÐE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		



WO 00/37098 PCT/US99/30395

### SHELF-STABLE FORMULATION OF GLUCAGON-LIKE PEPTIDE-1

### **Background of the Invention**

Glucagon-like peptide-1 (7-37)-OH (GLP-1) is a 31 amino acid hormone that is produced by post-translational processing of the preglucagon gene product in the brain, stomach, intestine, and pancreas. The main physiological function of GLP-1 is to regulate insulin secretion in response to glucose, and thus it has the ability to normalize blood glucose levels. As such, there has been interest in GLP-1, its analogs and derivatives as potential therapeutic agents for the treatment of diabetes. A particular advantage to the use of GLP-1 over other drugs in the treatment of diabetes is that administration of GLP-1 at doses in the 1-5 nmole range exhibit few adverse side effects, such as hypoglycemia. Unexpectedly, GLP-1 also has been shown to work in patients that have secondary failure to sulfonylurea drugs, the most common drug type for the treatment of type II diabetes. GLP-1 also is a potent inhibitor of gastric acid secretion and gastric emptying.

In general, effective therapeutic administration of peptides can be problematic since peptides often are degraded in the gastrointestinal tract by various peptidases. Additionally, certain peptide treatment protocols require either continuous or repeated administration of the peptide agent over an extended period of time. Repeated injections cause both inconvenience and discomfort to the user. Thus, chronic use of the peptide agent, which would be required for patients afflicted with diabetes, would result in inconvenience and discomfort to the user.

The long-term stability of peptides, particularly GLP-1, as components of a pharmaceutical composition for administration to mammals, is questionable. Such a lack of stability adversely affects bioavailability. In fact, when stored at low temperatures of 4° C, by-products of GLP-1(7-37) have been found as early as eleven months after sample preparation (see Mojsov, *Int. J. Peptide Protein Res.*, Vol. 40, pages 333-343 (1992)). Additionally, the biological half-life of GLP-1 molecules, particularly those molecules affected by the activity of dipeptidyl-peptidase IV (DPPIV), is quite short. For example,



WO 00/37098 PCT/US99/30395

the biological half-life of GLP-1(7-37) is only 3 to 5 minutes (see U.S. Patent No. 5,118,666), which is further augmented by its rapid absorption following parenteral administration to a mammal.

Another factor decreasing the bioavailability of GLP-1 is the solubility of GLP-1 when incorporated into an aqueous solution. The solubility of GLP-1 is highly dependent on the environment, such as the choice of buffering system, and the treatment that the peptide has undergone. For example, conversion of a peptide into its salt form plays a role in its solubility. In this regard, synthetic GLP-1 is highly soluble in neutral phosphate buffered saline. Because the solubility of the peptide is high in such aqueous solutions, slow release of the peptide can be difficult to attain unless the peptide is incorporated into a system for slow release.

Stable formulations of therapeutic agents are particularly required for use in delivery devices that expose these agents to elevated temperatures and/or mechanical stress. For example, stable GLP-1 formulations are required for use in continuous infusion systems and pen delivery devices. Current formulations provide only limited stability in these types of delivery devices.

In continuous infusion systems, a fluid containing a therapeutic agent is pumped from a reservoir, usually to a subcutaneous, intravenous, or intraperitoneal depot. The reservoir, which must be refilled periodically, is attached to the patient's body, or is implanted in the patient's body. In either case, the patient's body heat and body motion, and turbulence in the tubing and pump impart a relatively high amount of thermomechanical energy to the formulation. In the interest of minimizing the frequency with which the reservoir is refilled, and of minimizing the size of the reservoir, formulations having a relatively high concentration of the therapeutic agent are advantageous.

Injector pens also have been developed to allow diabetic patients to accurately measure and administer controlled doses of insulinotropic agents. Generally, these pens are secured onto a cartridge having a particular quantity of liquid medication sealed therein. The cartridge includes a plunger and a mechanism for advancing the plunger in the cartridge in such a manner to dispense the medication. Injector pens may be reusable or disposable. In reusable pens, a user can change a spent cartridge and reset the leadscrew of the pen back to its initial position. In a disposable pen, the cartridge is permanently



WO 00/37098 PCT/US99/30395

embodiment, the GLP-1 molecule of the formulation is a derivative of GLP-1 and is selected from the group consisting of a peptide having the amino acid sequence: NH<sub>2</sub>-His<sup>7</sup>-Ala-Glu-Gly<sup>10</sup>-Thr-Phe-Thr-Ser-Asp<sup>15</sup>-Val-Ser-Ser-Tyr-Leu<sup>20</sup>-Glu-Gly-Gln-Ala-Ala<sup>25</sup>-Lys-Glu-Phe-Ile-Ala<sup>30</sup>-Trp-Leu-Val-X (SEQ ID NO:3) and a pharmaceutically-acceptable salt thereof, wherein X is selected from the group consisting of Lys and Lys-Gly; a pharmaceutically-acceptable lower alkylester of the peptide; and a pharmaceutically-acceptable amide of the peptide selected from the group consisting of amide, lower alkyl amide, and lower dialkyl amide. In another preferred embodiment, the formulation also comprises a long-acting insulin agent.

The present invention also provides a method of enhancing the expression of insulin in a mammalian pancreatic  $\beta$ -type islet cell in need of such enhancement, comprising administering to the cell, an effective amount of a shelf-stable pharmaceutical formulation, wherein the formulation comprises a therapeutically effective amount of a GLP-1 molecule, a pharmaceutically acceptable preservative, and a tonicity modifier, and wherein the formulation has a pH that is about 8.2 to about 8.8. In a preferred embodiment, the formulation used in the therapeutic method comprises a buffer, such as TRIS. In another preferred embodiment, the formulation used in the therapeutic method further comprises a surfactant, such as Brij-35. In an additional preferred embodiment, the GLP-1 molecule of the formulation thus administered is an analog of GLP-1 and is selected from the group consisting of a peptide having the amino acid sequence:

R<sub>1</sub>-X-Glu-Gly<sup>10</sup>-Thr-Phe-Thr-Ser-Asp<sup>15</sup>-Val-Ser-Ser-Tyr-Leu<sup>20</sup>-Y-Gly-Gln-Ala-Ala<sup>25</sup>-Lys-Z-Phe-Ile-Ala<sup>30</sup>-Trp-Leu-Val-Lys-Gly<sup>35</sup>-Arg-R<sub>2</sub> (SEQ ID NO:2) and a pharmaceutically-acceptable salt thereof, wherein R<sub>1</sub> is His or desamino-histidine, X is Ala, Gly or Val, Y is Glu or Gln, Z is Glu or Gln and R<sub>2</sub> is Gly-OH. In an especially preferred embodiment, the GLP-1 molecule administered is according to SEQ ID NO: 2, wherein R<sub>1</sub> is L-histidine, X is Val, Y is Glu, Z is Glu, and R<sub>2</sub> is Gly-OH. In an alternative preferred embodiment, the GLP-1 molecule administered is a derivative of GLP-1 and is selected from the group consisting of a peptide having the amino acid sequence:

NH<sub>2</sub>-His<sup>7</sup>-Ala-Glu-Gly<sup>10</sup>-Thr-Phe-Thr-Ser-Asp<sup>15</sup>-Val-Ser-Ser-Tyr-Leu<sup>20</sup>-Glu-Gly-Gln-Ala-Ala<sup>25</sup>-Lys-Glu-Phe-Ile-Ala<sup>30</sup>-Trp-Leu-Val-X (SEQ ID NO:3) and a pharmaceutically-acceptable salt thereof, wherein X is selected from the group consisting of Lys and Lys-Gly; a pharmaceutically-acceptable lower alkylester of the peptide;



# DOCKET

# Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

# **Real-Time Litigation Alerts**



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## **Advanced Docket Research**



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## **Analytics At Your Fingertips**



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

### API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

### **LAW FIRMS**

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

### **FINANCIAL INSTITUTIONS**

Litigation and bankruptcy checks for companies and debtors.

### **E-DISCOVERY AND LEGAL VENDORS**

Sync your system to PACER to automate legal marketing.

