PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A01N 37/18	A1	(11) International Publication Number: WO 99/40788
		(43) International Publication Date: 19 August 1999 (19.08.99)

(21) International Application Number: PCT/US99/02554

(22) International Filing Date: 5 February 1999 (05.02.99)

(30) Priority Data:
60/075,122 13 February 1998 (13.02.98) US

(71) Applicant *(for all designated States except US)*: AMYLIN PHARMACEUTICALS, INC. [US/US]; 9373 Towne Centre Drive, San Diego, CA 92121 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: YOUNG, Andrew, A. [US/US]; 9514 Easter Way, San Diego, CA 92121 (US). VINE, Will [US/US]; 14537 Crestline Drive, Poway, CA 92064 (US). BEELEY, Nigel, R., A. [US/US]; 227 Loma Corta Drive, Solana Beach, CA 92075 (US). PRICKETT, Kathryn [US/US]; 7612 Trailbrush Terrace, San Diego, CA 92126 (US).

(74) Agents: MUNSON, Peter, R. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071–2066 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, 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.

(54) Title: INOTROPIC AND DIURETIC EFFECTS OF EXENDIN AND GLP–1

(57) Abstract

Methods for increasing urine flow are disclosed, comprising administration of an effective amount of GLP–1, an exendin, or an exendin or GLP–1 agonist. Methods for increasing urinary sodium excretion and decreasing urinary potassium concentration are also disclosed. The methods are useful for treating conditions or disorders associated with toxic hypervolemia, such as renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, and hypertension. The present invention also relates to methods for inducing an inotropic response comprising administration of an effective amount of GLP–1, an exendin, or an exendin or GLP–1 agonist. These methods are useful for treating conditions or disorders that can be alleviated by an increase in cardiac contractility such as congestive heart failure. Pharmaceutical compositions for use in the methods of the invention are also disclosed.

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.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	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
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	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 Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**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		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

DESCRIPTION

INOTROPIC AND DIURETIC EFFECTS OF EXENDIN AND GLP-1

FIELD OF THE INVENTION

The present invention relates to methods for increasing urine flow comprising administration of an effective amount of glucagon-like peptide-1[7-36] amide (abbreviated "GLP-[7-36]NH_2" or simply "GLP-1"), an exendin, or an exendin or GLP-1 agonist. Methods for increasing urinary sodium excretion and decreasing urinary potassium concentration are also disclosed. The methods are useful for treating conditions or disorders associated with toxic hypervolemia, such as renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, and hypertension. Pharmaceutical compositions for use in the methods of the invention are also disclosed.

The present invention also relates to methods for inducing an inotropic response comprising administration of an effective amount of an exendin, GLP-1, or an exendin or GLP-1 agonist. These methods are useful for treating conditions or disorders that can be alleviated by an increase in cardiac contractility, such as congestive heart failure.

The following description summarizes information relevant to the present invention. It is not an admission that any of the information provided herein is prior art to the presently claimed invention, nor that any of the publications specifically or implicitly referenced are prior art to that invention.

GLP-1

Glucagon-like peptide-1 [7-36] amide (also referred to as GLP-1[7-36]NH_2 or GLP-1) is a product of the proglucagon gene. It is secreted into plasma mainly from the gut and produces a variety of biological effects related to pancreatic and gastrointestinal function. The parent peptide, proglucagon (PG), has numerous cleavage sites that produce other peptide products dependent on the tissue of origin including glucagon (PG[32-62]) and GLP-1[7-36]NH_2 (PG[72-107]) in the pancreas, and GLP-1[7-37] (PG[78-108]) and GLP-1[7-36]NH_2 (PG [78-107]) in the L cells of the intestine where GLP-1[7-36]NH_2 (78-107 PG) is the major product.

GLP-1[7-36]NH_2, also known as proglucagon [78-107], or commonly, just GLP-1," as used herein, has an insulinotropic effect, stimulating insulin secretion from pancreatic -cells; GLP-1 also inhibits glucagon secretion from pancreatic -cells (Orskov, et al., Diabetes, 42:658-61, 1993; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). GLP-1 is reported to inhibit gastric emptying (Williams B, et al., J Clin Endocrinol Metab 81 (1): 327-32, 1996; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993), and gastric acid secretion. (Schjoldager BT, et al., Dig Dis Sci 34 (5): 703-8, 1989; O'Halloran DJ, et al., J Endocrinol 126 (1): 169-73, 1990; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993). A diuretic, antidypsogenic effect of intracerebroventricular administration of GLP-1 has been reported, however, this report claims that a peripheral, intraperitoneal injection of GLP-1 did not have this effect. (Tand-Christensen et al., Am. J. Physiol., 271:R848-56, 1996). GLP-1[7-37], which has an additional glycine residue at its carboxy terminus, also stimulates insulin secretion in humans (Orskov, et al., Diabetes, 42:658-61, 1993). A transmembrane G-protein adenylate-cyclase-coupled receptor believed to be responsible for the insulinotropic effect of GLP-1 has been cloned from a -cell line (Thorens, Proc. Natl. Acad. Sci., USA 89:8641-45, 1992).

Glucagon and glucagon-like peptides have been found to have different cardiovascular effects. Glucagon has been reported to have positive inotropic and chronotropic effects, produce a slight increase in arterial blood pressure in normal individuals, and affect regional blood circulation. GLP-1 has been found to produce a moderate increase in both systolic and diastolic blood pressure, while GLP-2 has no effect on those parameters. GLP-1, administered through the jugular vein, has been reported to induce an increase in systolic and diastolic blood pressure and heart rate. (Reviewed in Barragán, J.M., et al., Regul. Peptides, 67:63-68, 1996).

EXENDIN

Exendins are peptides that are found in the venom of the Gila-monster, a lizard endogenous to Arizona, and the Mexican Beaded Lizard. Exendin-3 is present in the venom of *Heloderma horridum*, and exendin-4 is present in the venom of *Heloderma suspectum* (Eng, J., et al., J. Biol. Chem., 265:20259-62, 1990; Eng., J., et al., J. Biol. Chem., 267:7402-05, 1992). The exendins have some sequence similarity to several

members of the glucagon-like peptide family, with the highest homology, 53%, being to GLP-1 (Goke, et al., J. Biol. Chem., 268:19650-55, 1993).

Exendin-4 is a potent agonist at GLP-1 receptors on insulin-secreting TC1 cells, at dispersed acinar cells from guinea pig pancreas, and at parietal cells from stomach; the peptide also stimulates somatostatin release and inhibits gastrin release in isolated stomachs (Goke, et al., J. Biol. Chem. 268:19650-55, 1993; Schepp, et al., Eur. J. Pharmacol., 69:183-91, 1994; Eissele, et al., Life Sci., 55:629-34, 1994). Exendin-3 and exendin-4 were found to be GLP-1 agonists in stimulating cAMP production in, and amylase release from, pancreatic acinar cells (Malhotra, R., et al., Regulatory Peptides, 41:149-56, 1992; Raufman, et al., J. Biol. Chem. 267:21432-37, 1992; Singh, et al., Regul. Pept. 53:47-59, 1994). The use of the insulinotropic activities of exendin-3 and exendin-4 for the treatment of diabetes mellitus and the prevention of hyperglycemia has been proposed (Eng, U.S. Patent No. 5,424,286).

Truncated exendin peptides such as exendin[9-39], a carboxyamidated molecule, and fragments 3-39 through 9-39 have been reported to be potent and selective antagonists of GLP-1 (Goke, et al., J. Biol. Chem., 268:19650-55, 1993; Raufman, J.P., et al., J. Biol. Chem. 266:2897-902, 1991; Schepp, W., et al., Eur. J. Pharm. 269:183-91, 1994; Montrose-Rafizadeh, et al., Diabetes, 45(Suppl. 2):152A, 1996). Exendin[9-39] blocks endogenous GLP-1 in vivo, resulting in reduced insulin secretion. Wang, et al., J. Clin. Invest., 95:417-21, 1995; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). The receptor apparently responsible for the insulinotropic effect of GLP-1 has been cloned from rat pancreatic islet cells (Thorens, B., Proc. Natl. Acad. Sci. USA 89:8641-8645, 1992). Exendins and exendin[9-39] bind to the cloned GLP-1 receptor (rat pancreatic -cell GLP-1 receptor: Fehmann HC, et al., Peptides 15 (3): 453-6, 1994; human GLP-1 receptor: Thorens B, et al., Diabetes 42 (11): 1678-82, 1993). In cells transfected with the cloned GLP-1 receptor, exendin-4 is an agonist, i.e., it increases cAMP, while exendin[9-39] is an antagonist, i.e., it blocks the stimulatory actions of exendin-4 and GLP-1. Id.

Exendin[9-39] also acts as an antagonist of the full length exendins, inhibiting stimulation of pancreatic acinar cells by exendin-3 and exendin-4 (Raufman, et al., J. Biol. Chem. 266:2897-902, 1991; Raufman, et al., J. Biol. Chem., 266:21432-37, 1992). Exendin[9-39] inhibits the stimulation of plasma insulin levels by exendin-4, and inhibits

DOCKET ALARM

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.