UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN INSTITUTIONAL LLC and PFIZER INC.,
Petitioners,

v.

NOVO NORDISK A/S,
Patent Owner.

Case IPR2020-00324[1]
Patent 8,114,833

PATENT OWNER'S DEMONSTRATIVE EXHIBITS

[1] IPR2020-01252 has been joined with this proceeding.

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IPR2020-00324*

Mylan Institutional LLC v. No

***IPR2020-01252 has been joined with this proceeding**

PATENT OWNER'S PRESENTATION

MARCH 26, 2021

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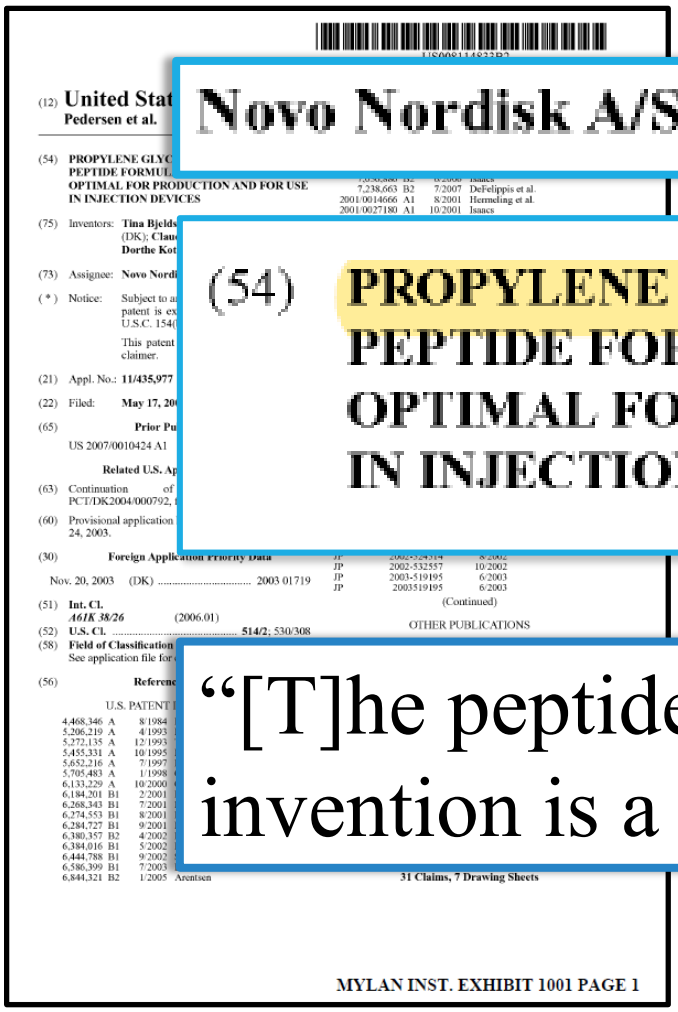
The ’833 Patent



(12) United Stat
Pedersen et al.

(54) PROPYLENE GLYC
PEPTIDE FORMUL
OPTIMAL FOR PRODUCTION AND FOR USE
IN INJECTION DEVICES

(75) Inventors: Tina Bjelds
(DK); Claud
Dorthe Kot

(73) Assignee: Novo Nordi

(*) Notice: Subject to a
patent is ex
U.S.C. 154(
This patent
claimer.

(21) Appl. No.: 11/435,977

(22) Filed: May 17, 20

(65) Prior Pu
US 2007/0010424 A1

Related U.S. Ap

(63) Continuation of
PCT/DK2004/000792,

(60) Provisional application
24, 2003.

(30) Foreign Application Priority Data
Nov. 20, 2003 (DK) 2003 01719

(51) Int. Cl.
A61K 38/26 (2006.01)

(52) U.S. Cl. 514/2; 530/308

(58) Field of Classification
See application file for

(56) Referenc

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31 Claims, 7 Drawing Sheets

MYLAN INST. EXHIBIT 1001 PAGE 1

Novo Nordisk A/S, Bagsvaerd (DK)

(54) PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

“[T]he peptide to be included in the for
invention is a **GLP-1 agonist**”

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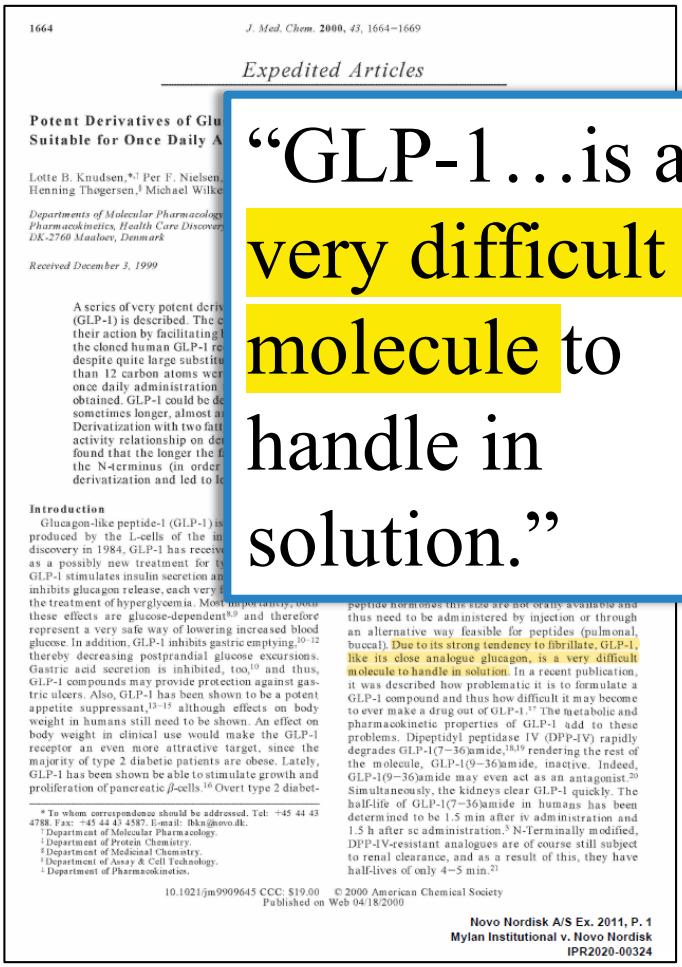
GLP-1 Was Known to Be Difficult



1664 *J. Med. Chem.* **2000**, *43*, 1664−1669

Expedited Articles

Potent Derivatives of Glu
Suitable for Once Daily A

Lotte B. Knudsen,*[,†] Per F. Nielsen,[‡] Henning Thøgersen,[§] Michael Wilke

Departments of Molecular Pharmacology, Pharmacokinetics, Health Care Discover, DK-2760 Maaloev, Denmark

Received December 3, 1999

A series of very potent deriv (GLP-1) is described. The c their action by facilitating t the cloned human GLP-1 re despite quite large substitu than 12 carbon atoms wer once daily administration obtained. GLP-1 could be de sometimes longer, almost a Derivatization with two fatt activity relationship on der found that the longer the f the N-terminus (in order derivatization and led to lo

Introduction

Glucagon-like peptide-1 (GLP-1) is produced by the L-cells of the in discovery in 1984, GLP-1 has receiv as a possibly new treatment for (t GLP-1 stimulates insulin secretion an inhibits glucagon release, each very i the treatment of hyperglycemia. Most these effects are glucose-dependent[8,9] and therefore represent a very safe way of lowering increased blood glucose. In addition, GLP-1 inhibits gastric emptying,[10−12] thereby decreasing postprandial glucose excursions. Gastric acid secretion is inhibited, too,[10] and thus, GLP-1 compounds may provide protection against gastric ulcers. Also, GLP-1 has been shown to be a potent appetite suppressant,[13−15] although effects on body weight in humans still need to be shown. An effect on body weight in clinical use would make the GLP-1 receptor an even more attractive target, since the majority of type 2 diabetic patients are obese. Lately, GLP-1 has been shown be able to stimulate growth and proliferation of pancreatic β-cells.[16] Overt type 2 diabet-

peptide hormones this size are not orally available and thus need to be administered by injection or through an alternative way feasible for peptides (pulmonal, buccal). Due to its strong tendency to fibrillate, GLP-1, like its close analogue glucagon, is a very difficult molecule to handle in solution. In a recent publication, it was described how problematic it is to formulate a GLP-1 compound and thus how difficult it may become to ever make a drug out of GLP-1.[17] The metabolic and pharmacokinetic properties of GLP-1 add to these problems. Dipeptidyl peptidase IV (DPP-IV) rapidly degrades GLP-1(7−36)amide,[18,19] rendering the rest of the molecule, GLP-1(9−36)amide, inactive. Indeed, GLP-1(9−36)amide may even act as an antagonist.[20] Simultaneously, the kidneys clear GLP-1 quickly. The half-life of GLP-1(7−36)amide in humans has been determined to be 1.5 min after iv administration and 1.5 h after sc administration.[5] N-Terminally modified, DPP-IV-resistant analogues are of course still subject to renal clearance, and as a result of this, they have half-lives of only 4−5 min.[21]

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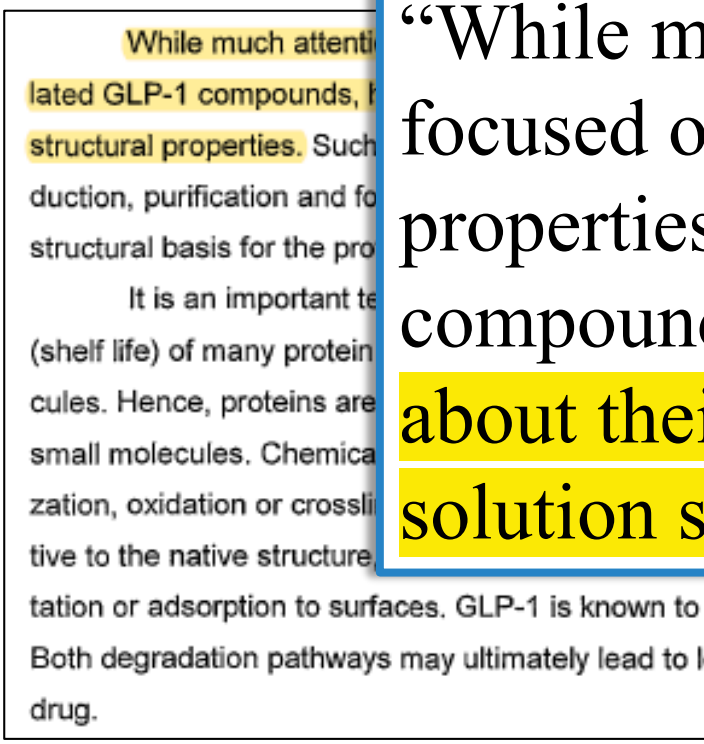
‡ Department of Protein Chemistry.
§ Department of Medicinal Chemistry.
⊥ Department of Assay & Cell Technology.
△ Department of Pharmacokinetics.

10.1021/jm9909645 CCC: $19.00 © 2000 American Chemical Society
Published on Web 04/18/2000

Novo Nordisk A/S Ex. 2011, P. 1
Mylan Institutional v. Novo Nordisk
IPR2020-00324

Ex2011 at 1

"GLP-1…is a very difficult molecule to handle in solution."



While much attenti
lated GLP-1 compounds, h
structural properties. Such
duction, purification and fo
structural basis for the pro
It is an important te
(shelf life) of many protein
cules. Hence, proteins are
small molecules. Chemica
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Both degradation pathways may ultimately lead to l
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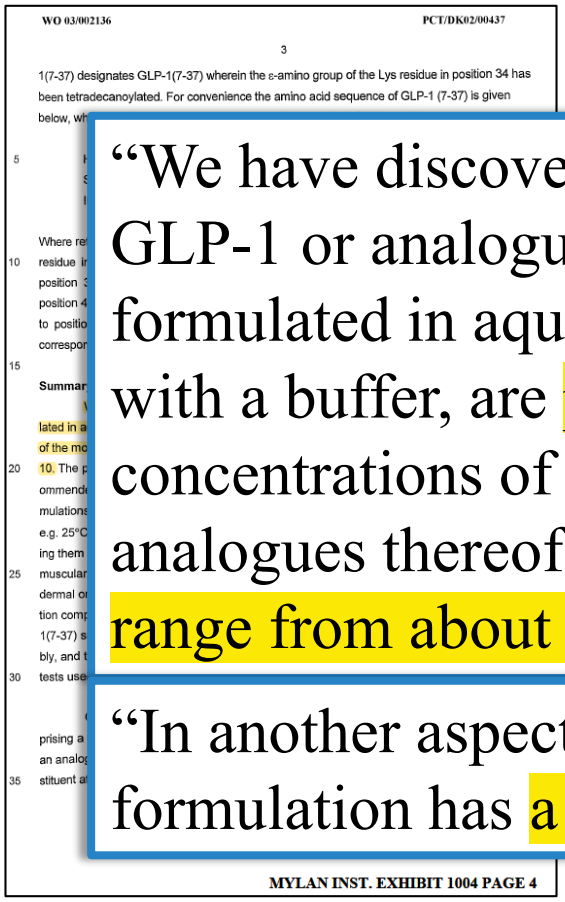
Initial Formulations Focused on Stabili



WO 03/002136 PCT/DK02/00437

3

1(7-37) designates GLP-1(7-37) wherein the ε-amino group of the Lys residue in position 34 has been tetradecanoylated. For convenience the amino acid sequence of GLP-1 (7-37) is given below, wh

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Summar

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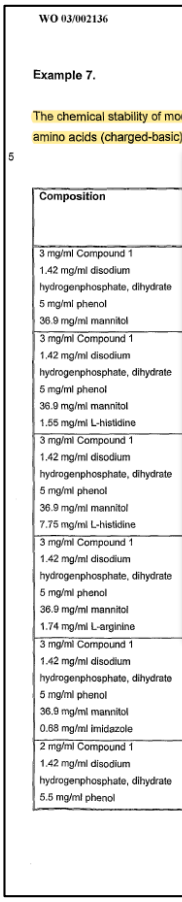
MYLAN INST. EXHIBIT 1004 PAGE 4

"We have discovered that certain modified GLP-1 or analogues thereof when formulated in aqueous solution together with a buffer, are physically stable at high concentrations of the modified GLP-1 or analogues thereof, when kept in the pH range from about 7 to about 10."

"In another aspect of the invention the formulation has a pH from 7.5 to 10."

Ex1004 at 4, ll. 17-20; 5, l. 12



WO 03/002136

Example 7.

The chemical stability of mo
amino acids (charged-basic)

Composition
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol 1.55 mg/ml L-histidine
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol 7.75 mg/ml L-histidine
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol 1.74 mg/ml L-arginine
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol 0.68 mg/ml imidazole
2 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5.5 mg/ml phenol

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