IN THIS ISSUE (starts on next page)
Liraglutide (Victoza) for Type 2 Diabetes .......... p 25

Important Copyright Message

The Medical Letter® publications are protected by US and international copyright laws. Forwarding, copying or any distribution of this material is prohibited.

Sharing a password with a non-subscriber or otherwise making the contents of this site available to third parties is strictly prohibited.

By accessing and reading the attached content I agree to comply with US and international copyright laws and these terms and conditions of The Medical Letter, Inc.

For further information click: Subscriptions, Site Licenses, Reprints
or call customer service at: 800-211-2769

FORWARDING OR COPYING IS A VIOLATION OF US AND INTERNATIONAL COPYRIGHT LAWS
Liraglutide (Victoza) for Type 2 Diabetes

Liraglutide (Victoza – Novo Nordisk), a glucagon-like peptide-1 (GLP-1) receptor agonist given by subcutaneous injection, has been approved by the FDA for treatment of patients with type 2 diabetes. It can be used alone or in addition to oral antidiabetic drugs such as metformin (Glucophage, and others) or glimepiride (Amaryl, and others). Liraglutide is not recommended for first-line therapy and is not approved for use with insulin.

GLUCAGON-LIKE PEPTIDE (GLP-1) RECEPTOR AGONISTS — Liraglutide is the second GLP-1 agonist marketed in the US; exenatide (Byetta), the first, has been available since 2005.1 A long-acting formulation of exenatide (Bydureon) given only once each week may be available soon.2

MECHANISM OF ACTION — Liraglutide is structurally similar to native human GLP-1. It lowers blood glucose by potentiating glucose-mediated insulin production and by decreasing glucagon secretion. The drug may slow gastric emptying to a limited extent, but it does promote satiety and weight loss, possibly due to a central effect.

Table 1. Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Exenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>6 mg/mL in 3-mL prefilled pen</td>
<td>250 mcg/mL in 1.2-mL or 2.4-mL prefilled pen</td>
</tr>
<tr>
<td>Route</td>
<td>SC injection</td>
<td>SC injection</td>
</tr>
<tr>
<td>Dose</td>
<td>1.2 or 1.8 mg once/d</td>
<td>5 or 10 mcg bid with morning and evening meals</td>
</tr>
<tr>
<td>Tmax</td>
<td>8-13 hours</td>
<td>2.1 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>6% urine, 5% feces over 6-8 days</td>
<td>Renal</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>13 hours</td>
<td>2.4 hours</td>
</tr>
</tbody>
</table>

CLINICAL STUDIES — The approval of liraglutide was based on 5 double-blind studies in 3,978 patients with type 2 diabetes.3-7

Table 2. Liraglutide Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug (dose/d)</th>
<th>A1C Baseline Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAD-3 Mono3 52 wks</td>
<td>Liraglutide 1.2 mg 8.3%</td>
<td>-0.84%</td>
</tr>
<tr>
<td>LEAD-24 26 wks</td>
<td>Glimepiride 1.8 mg 8.3</td>
<td>-1.14</td>
</tr>
<tr>
<td>Add-on Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAD-1 SU5 26 wks</td>
<td>Liraglutide 0.6 mg 8.4</td>
<td>-0.7</td>
</tr>
<tr>
<td>LEAD-5 Met + SU6 26 wks</td>
<td>liraglutide 1.8 mg 8.3</td>
<td>-1.33</td>
</tr>
<tr>
<td>LEAD-4 Met + TZD7 26 wks</td>
<td>liraglutide 1.2 mg 8.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>vs. Exenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAD-68 26 wks</td>
<td>Metformin and/or sulfonylurea 8.2</td>
<td>-1.2</td>
</tr>
</tbody>
</table>
| Liraglutide vs. Exenatide — Like exenatide, liraglutide is injected subcutaneously (SC), but unlike exenatide, which is given twice daily with meals, liraglutide is dosed once daily without regard to meals. In a 26-week open-label trial sponsored by the manufacturer of liraglutide, 464 patients with type 2 diabetes uncontrolled with maximum tolerated doses of metformin, a sulfonylurea or both (baseline A1C 8.1-8.2%) were randomized to addition of liraglutide 1.8 mg once daily or exenatide 10 mcg twice daily. Most of the patients had had diabetes for more than 8 years; more than 60% were taking both metformin and a sulfonylurea. A1C decreased significantly more

The Medical Letter®
On Drugs and Therapeutics

Published by The Medical Letter, Inc. • 1000 Main Street, New Rochelle, NY 10801 • A Nonprofit Publication

Volume 52  (Issue 1335)
April 5, 2010

www.medicalletter.org

Liraglutide Exenatide

Formulation 6 mg/mL in 3-mL prefilled pen

Route SC injection

Dose 1.2 or 1.8 mg once/d

Tmax 8-13 hours

Excretion 6% urine, 5% feces over 6-8 days

Elimination half-life 13 hours

Table 2. Liraglutide Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug (dose/d)</th>
<th>A1C Baseline Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAD-3 Mono3 52 wks</td>
<td>Liraglutide 1.2 mg 8.3%</td>
<td>-0.84%</td>
</tr>
<tr>
<td>LEAD-24 26 wks</td>
<td>Glimepiride 1.8 mg 8.3</td>
<td>-1.14</td>
</tr>
<tr>
<td>Add-on Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAD-1 SU5 26 wks</td>
<td>Liraglutide 0.6 mg 8.4</td>
<td>-0.7</td>
</tr>
<tr>
<td>LEAD-5 Met + SU6 26 wks</td>
<td>liraglutide 1.8 mg 8.3</td>
<td>-1.33</td>
</tr>
<tr>
<td>LEAD-4 Met + TZD7 26 wks</td>
<td>liraglutide 1.2 mg 8.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>vs. Exenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAD-68 26 wks</td>
<td>Metformin and/or sulfonylurea 8.2</td>
<td>-1.2</td>
</tr>
</tbody>
</table>
| Liraglutide vs. Exenatide — Like exenatide, liraglutide is injected subcutaneously (SC), but unlike exenatide, which is given twice daily with meals, liraglutide is dosed once daily without regard to meals. In a 26-week open-label trial sponsored by the manufacturer of liraglutide, 464 patients with type 2 diabetes uncontrolled with maximum tolerated doses of metformin, a sulfonylurea or both (baseline A1C 8.1-8.2%) were randomized to addition of liraglutide 1.8 mg once daily or exenatide 10 mcg twice daily. Most of the patients had had diabetes for more than 8 years; more than 60% were taking both metformin and a sulfonylurea. A1C decreased significantly more
with liraglutide than with exenatide (1.12% vs. 0.79%). Fasting plasma glucose also decreased more with liraglutide (29 mg/dL [1.61 mmol/L]) than with exenatide (11 mg/dL [0.60 mmol/L]), but postprandial glucose increments after breakfast and dinner decreased more with exenatide. More patients reached an A1C goal of <7% with liraglutide (54%) than with exenatide (43%).

Weight loss occurred with both drugs: 3.24 kg with liraglutide and 2.87 kg with exenatide. Hypoglycemia was more common with exenatide; severe hypoglycemia occurred in 2 patients in the exenatide group who were also taking a sulfonfonyurea.8

ADVERSE EFFECTS — Hypoglycemia has been reported in patients taking liraglutide, particularly in those also taking a sulfonfonyurea. The most common adverse effects of liraglutide have been nausea (which can be severe), diarrhea, vomiting, dyspepsia and constipation. Less than 10% of patients have developed anti-liraglutide antibodies; antibody formation was not associated with decreased effectiveness. Pancreatitis, which has occurred with exenatide, has also been reported in patients taking liraglutide. Renal insufficiency and acute renal failure have occurred with exenatide, generally associated with nausea and vomiting in patients with pre-existing kidney disease or taking other drugs with a potential for nephrotoxicity. To date, renal toxicity has not been reported with liraglutide.

Thyroid C-cell carcinomas have occurred in rats given liraglutide doses 8 times higher than a patient’s usual clinical exposure. In clinical trials, thyroid C-cell hyperplasia has been reported. The FDA has required a boxed warning about the risk of thyroid cancer in the package insert.
Liraglutide is classified as category C (risk cannot be ruled out) for use during pregnancy.

**DRUG INTERACTIONS** — Hypoglycemia is a concern in patients taking liraglutide concurrently with an insulin secretagogue such as a sulfonylurea; the dose of the secretagogue may need to be lowered. Liraglutide may delay gastric emptying; it could decrease serum concentrations or increase the time to maximum concentration of oral drugs taken concurrently.

**DOSEAGE AND ADMINISTRATION** — Liraglutide is available in 3-mL prefilled pens, each containing 18 mg (6 mg/mL) of liraglutide. Each pen can deliver doses of 0.6, 1.2 or 1.8 mg. One pen can deliver a total of 15 doses of 1.2 mg or 10 doses of 1.8 mg. The drug should be injected subcutaneously in the abdomen, thigh or upper arm at any consistent time of the day; the injection site and timing can be changed without dose adjustment.

The initial dose of liraglutide is 0.6 mg once/day for one week to reduce gastrointestinal adverse effects; this is not considered an effective dose. The dose should then be increased to 1.2 mg/day for one week; if this does not lower glucose sufficiently, the dose can be increased to 1.8 mg/day.

**CONCLUSION** — Liraglutide (Victoza) is a new glucagon-like peptide-1 receptor agonist that was more effective than exenatide in one study in reducing A1C in patients not controlled on oral antidiabetic drugs. It has the advantage of requiring only one injection per day without regard to meals. Liraglutide has caused thyroid cancer in rodents and has been associated with pancreatitis in some patients. As with exenatide, its long-term safety is unknown.


**The Medical Letter**

---

**EDITOR IN CHIEF:** Mark Abramowicz, M.D.
**EXECUTIVE EDITOR:** Gianna Zuccotti, M.D., M.P.H., F.A.C.P., Harvard Medical School
**EDITOR:** Jean-Marie Pflohm, Pharm.D.

**ASSISTANT EDITORS, DRUG INFORMATION:** Susan M. Daron, Pharm.D., Blaine M. Houst, Pharm.D., Corinne E. Zanone, Pharm.D.

**CONSULTING EDITOR:** Brinda M. Shah, Pharm.D.

**ADVISORY BOARD:**
Jules Hirsch, M.D., Rockefeller University
Gerald L. Mandell, M.D., University of Virginia School of Medicine
Dan M. Roden, M.D., Vanderbilt University School of Medicine

**CONTRIBUTING EDITORS:**
Carl W. Bazil, M.D., Ph.D., Columbia University College of Physicians and Surgeons
Vanessa K. Dalton, M.D., M.P.H., University of Michigan Medical School
Etro J. Epstein, M.D., Albert Einstein College of Medicine
David N. Juurlink, B.Phm, M.D., Ph.D., Sunnybrook Health Sciences Centre
Richard B. Kim, M.D., University of Western Ontario
Hans Meinertz, M.D., University Hospital, Copenhagen
Sandip K. Mukherjee, M.D., F.A.C.C., Yale School of Medicine
F. Estelle R. Simons, M.D., University of Manitoba
Jordan W. Smoller, M.D., Sc.D., Harvard Medical School
Neal H. Steigbigel, M.D., New York University School of Medicine

**SENIOR ASSOCIATE EDITORS:** Donna Goodstein, Amy Fauscard
**ASSOCIATE EDITOR:** Cynthia Macapagal Covey
**EDITORIAL FELLOW:** Vincent Teo, B.Sc. Phm, Sunnybrook Health Sciences Centre

**MANAGING EDITOR:** Susie Wong
**ASSISTANT MANAGING EDITOR:** Liz Donohue
**PRODUCTION COORDINATOR:** Cheryl Brown

**EXECUTIVE DIRECTOR OF SALES:** Gene Carbone
**FULFILLMENT & SYSTEMS MANAGER:** Cristine Romatowski
**DIRECTOR OF MARKETING COMMUNICATIONS:** Joanne F. Valentino
**VICE PRESIDENT AND PUBLISHER:** Yosef Wissner-Levy

*The Medical Letter® On Drugs and Therapeutics*

---

**Copyright and Disclaimer:** The Medical Letter is an independent nonprofit organization that provides health care professionals with unbiased drug prescribing recommendations. The editorial process used for its publications relies on a review of published and unpublished literature, with an emphasis on controlled clinical trials, and on the opinions of its consultants. The Medical Letter is supported solely by subscription fees and accepts no advertising, grants or donations.

No part of the material may be reproduced or transmitted by any process in whole or in part without prior permission in writing. The editors do not warrant that all the material in this publication is accurate and complete in every respect. The editors shall not be held responsible for any damage resulting from any error, inaccuracy or omission.

**Subscription Services**

**Mailing Address:**
The Medical Letter Inc.
1000 Main Street
New Rochelle, NY 10801-7537

**Customer Service:**
Call: 800-211-2769 or 914-235-0500
Fax: 914-632-1733
Web Site: www.medicalletter.org
E-mail: custserv@medicalletter.org

**Permissions:**
To reproduce any portion of this issue, please e-mail your request to:
permissions@medicalletter.org

**Subscriptions:**

- **US:**
  - 1 year: $98; 2 years: $167; 3 years: $235. $49.00 per year for students, intern, residents and fellows in the US and Canada.
  - CME: $70 for 26 credits.
- **International:**
  - E-mail site license inquiries to: info@medicalletter.org or call 800-211-2769 x315.
  - Special fees for bulk subscriptions. Special classroom rates are available. Back issues are $12 each.

Major credit cards accepted.

---

Copyright 2010. ISSN 1523-2859