

PDR[®]
65
 EDITION
2011

PERKINS COIE

MAR 16 2011

LAW LIBRARY

PHYSICIANS' DESK REFERENCE[®]

CEO: Edward Fotsch, MD
President: David Tanzer
Chief Medical Officer: Christine Côté, MD
Chief Technology Officer: Nick Krym
Chief Financial Officer: Dawn Carfora

Vice President, Product Management & Operations: Valerie Berger
Vice President, Emerging Products: Debra Del Guidice
Vice President, Corporate Development, Copy Sales & General Counsel: Andrew Gelman
Vice President, Sales: John Loucks
Vice President, Marketing: Julie Baker
Vice President, Business Development: Tom Dieker

Director of Sales: Eileen Bruno
Business Manager: Karen Fass
Senior Account Executives: Marjorie A. Jaxel, Philip Molinaro
Account Executives: Nick W. Clark, Carlos Cornejo, Caryn Trick
Associate Account Executives: Carol Levine, Janet Wallendal
Sales Coordinator: Dawn McPartland

Senior Director, Operations & Client Services: Stephanie Struble
Senior Director, Editorial & Publishing: Bette Kennedy
Director, Clinical Services: Sylvia Nashed, PharmD
Director, Marketing: Kim Marich

Senior Manager, Client Services: Lisa Caporuscio
Manager, Clinical Services: Nermin Kerolous, PharmD
Senior Drug Information Specialist,
Database Management: Christine Sunwoo, PharmD
Senior Drug Information Specialist,
Product Development: Anila Patel, PharmD
Drug Information Specialists: Peter Leighton, PharmD;
 Kristine Mecca, PharmD; See-Won Seo, PharmD
Manager, Editorial Services: Lori Murray
Associate Editor: Jennifer Reed
Manager, Art Department: Livio Udina
Electronic Publication Designer: Carrie Spinelli Faeth

Director, PDR Production: Jeffrey D. Schaefer
Associate Director, Manufacturing & Distribution: Thomas Westburgh
Production Manager, PDR: Steven Maher
Operations Database Manager: Noel Deloughery
Senior Index Editor: Allison O'Hare
Index Editor: Julie L. Cross
Senior Production Coordinator: Yasmin Hernández
Production Coordinators: Eric Udina, Christopher Whalen
Format Editor: Dan Cappello
Fulfillment Management Specialist: Gary Lew
Manager, Customer Service: Todd Taccetta

Copyright © 2010 PDR Network, LLC. Published by PDR Network, LLC at Montvale, NJ 07645-1725. All rights reserved. None of the content of this publication may be reproduced, stored in a retrieval system, resold, redistributed, or transmitted in any form or by any means (electronic, mechanical, photocopying, recording, or otherwise) without the prior written permission of the publisher. Physicians' Desk Reference[®] and PDR[®] are registered trademarks of PDR Network, LLC. PDR[®] for Ophthalmic Medicines; PDR[®] for Nonprescription Drugs, Dietary Supplements, and Herbs; PDR[®] Pharmacopoeia; and PDR[®] Electronic Library are trademarks of PDR Network, LLC.

ISBN: 978-1-56363-780-3

Study 4: Dosing by Treatment Group

	Bolus Injection 90 micrograms/kg (n = 12)	Continuous Infusion 50 micrograms/kg/h (n = 12)
Days of dosing, median (range)	10 (4-15) ^a	10 (2-116)
No. bolus injections, median (range)	38 (36-42)	1.5 (0-7)
No. of additional bolus injections, median (range)	0 (0-3)	0 (0-4)
Mean total dose, mg	237.5	292.2

^a Includes dosing during the follow-up period after the 10-day study period.

Efficacy by Dose Group, for Patients Receiving Doses Ranging from <61 to >90 micrograms/kg NovoSeven, Compassionate Use Programs and HTRS Registry

		NovoSeven Dose (micrograms/kg)						
Outcome*	Unknown	<61	61-69	70-80	81-89	90	>90	Total
Effective N (%)	1 (33)	3 (75)	5 (63)	10 (63)	12 (57)	10 (67)	26 (58)	67
Partial N (%)	1 (33)	0 (0)	0 (0)	3 (19)	3 (14)	2 (13)	11 (24)	20
Ineffective N (%)	0 (0)	1 (25)	3 (38)	2 (13)	2 (10)	2 (13)	7 (16)	17
Unknown N (%)	1 (33)	0 (0)	0 (0)	1 (6)	4 (19)	1 (7)	1 (2)	8
No. of Bleeding Episodes [†]	3	4	8	16	21	15	45	112 [‡]

* Outcome assessed at end of treatment, last observation carried forward

[†] N (%) do not add up to 100 due to rounding

[‡] One patient in the HTRS registry was excluded from efficacy analysis since NovoSeven was used to maintain hemostasis after bleeding had been controlled

The diluent for reconstitution of NovoSeven RT is a 10 mmol solution of L-histidine in water for injection and is supplied as a clear colorless solution, and referred to as the histidine diluent. The vials are made of glass closed with a latex-free, chlorobutyl rubber disc, and covered with an aluminum cap. The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene. Prior to reconstitution, keep refrigerated or store between 2-25°C/36-77°F. Do not freeze. Store protected from light. Do not use past the expiration date.

After reconstitution, NovoSeven RT may be stored either at room temperature or refrigerated for up to 3 hours. Do not freeze reconstituted NovoSeven RT or store it in syringes.

17 PATIENT COUNSELING INFORMATION

Patients receiving NovoSeven RT should be informed of the benefits and risks associated with treatment. Patients should be warned about the early signs of hypersensitivity reactions, including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Patients should also be warned about the signs of thrombosis, including new onset swelling and pain in the limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness or speech. Patients should be told to immediately seek medical help if any of the above signs or symptoms occur.

Date of issue: August 6, 2010

Version: 4

License Number: 1261

Novo Nordisk® is a registered trademark of Novo Nordisk A/S.

NovoSeven® is a registered trademark of Novo Nordisk HealthCare AG.

© 1998-2010 Novo Nordisk A/S

For information contact:

Novo Nordisk Inc.

100 College Road West

Princeton, NJ 08540, USA

1-877-NOVO-777

www.NovoSevenRT.com

Manufactured by:

Novo Nordisk A/S

2880 Bagsvaerd, Denmark

VICTOZA®

[VIC-tou-za]

(liraglutide (rDNA origin) injection)

Solution for Subcutaneous Use

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Victoza safely and effectively. See full prescribing information for Victoza.

Victoza® (liraglutide (rDNA origin) injection)

solution for subcutaneous use
Initial U.S. Approval: 2010

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies (5.1).
- Victoza is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (5.1).

INDICATIONS AND USAGE

Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1). Important Limitations of Use (1.1):

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (5.1).
- Has not been studied sufficiently in patients with a history of pancreatitis. Use caution (5.2).
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with insulin.

DOSAGE AND ADMINISTRATION

- Administer once daily at any time of day, independently of meals (2).
- Inject subcutaneously in the abdomen, thigh or upper arm (2).
- The injection site and timing can be changed without dose adjustment (2).
- Initiate at 0.6 mg per day for one week. This dose is intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg (2).
- When initiating Victoza, consider reducing the dose of concomitantly-administered insulin secretagogues to reduce the risk of hypoglycemia (2).

DOSAGE FORMS AND STRENGTHS

- Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL) (3).

CONTRAINDICATIONS

Do not use in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).

WARNINGS AND PRECAUTIONS

- Thyroid C-cell tumors in animals: Human relevance is unknown. Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (5.1).
- Pancreatitis: In clinical trials, there were more cases of pancreatitis among Victoza-treated patients than among comparator-treated patients. If pancreatitis is suspected, Victoza and other potentially suspect drugs should be discontinued. Victoza should not be restarted if pancreatitis is confirmed. Use with caution in patients with a history of pancreatitis (5.2).
- Serious hypoglycemia: Can occur when Victoza is used with an insulin secretagogue (e.g. a sulfonylurea). Consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia (5.3).
- Macrovascular outcomes: There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza or any other antidiabetic drug (5.4).

ADVERSE REACTIONS

- The most common adverse reactions, reported in ≥5% of patients treated with Victoza and more commonly than in patients treated with placebo, are: headache, nausea, diarrhea and anti-liraglutide antibody formation (6).
- Immunogenicity-related events, including urticaria, were more common among Victoza-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials (6).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-877-484-2869 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Victoza delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use caution (7).

USE IN SPECIFIC POPULATIONS

- There are no data in patients below 18 years of age (8.4).
- Use with caution in patients with renal or hepatic impairment. Limited data (8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/2010

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: RISK OF THYROID C-CELL TUMORS

1 INDICATIONS AND USAGE

1.1 Important Limitations of Use

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

5.2 Pancreatitis

5.3 Use with Medications Known to Cause Hypoglycemia

5.4 Macrovascular Outcomes

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

7.1 Oral Medications

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

8.8 Gastroparesis

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogen cis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Monotherapy

14.2 Combination Therapy

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Recommended Storage

17 PATIENT COUNSELING INFORMATION

17.1 Risk of Thyroid C-cell Tumors

17.2 Pancreatitis

17.3 Never Share a Victoza Pen Between Patients

17.4 Instructions

17.5 Laboratory Tests

17.6 FDA-Approved Medication Guide

IMPORTANT NOTICE: Updated drug information is sent bi-monthly via the PDR® Update Insert. For monthly email updates, register at PDR.net.

treatment of diabetic ketoacidosis, as it would not be effective in these settings.

• The concurrent use of Victoza and insulin has not been studied.

2 DOSAGE AND ADMINISTRATION

Victoza can be administered once daily at any time of day, independently of meals, and can be injected subcutaneously in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment.

For all patients, Victoza should be initiated with a dose of 0.6 mg per day for one week. The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week at 0.6 mg per day, the dose should be increased to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg.

When initiating Victoza, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia (see Warnings and Precautions (5.3) and Adverse Reactions (6)).

Victoza solution should be inspected prior to each injection, and the solution should be used only if it is clear, colorless, and contains no particles.

3 DOSAGE FORMS AND STRENGTHS

Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL).

4 CONTRAINDICATIONS

Victoza is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice (see Nonclinical Toxicology (13.1)). Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-

cebo and active control, respectively.

Otherwise, Victoza did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza clinical trials, among patients with pretreatment serum calcitonin <50 ng/L, one Victoza-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza-treated patient who developed serum calcitonin >50 ng/L had an elevated pretreatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza. The clinical significance of these findings is unknown.

Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

5.2 Pancreatitis

In clinical trials of Victoza, there were 7 cases of pancreatitis among Victoza-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Five cases with Victoza were reported as acute pancreatitis and two cases with Victoza were reported as chronic pancreatitis. In one case in a Victoza-treated patient, pancreatitis, with necrosis, was observed and led to

patients were treated with victoza 1.8 mg, placebo, or insulin glargine. In the add-on to metformin + rosiglitazone trial, patients were treated with Victoza 1.2 mg, Victoza 1.8 mg or placebo (see Clinical Studies (14)).

Withdrawals

The incidence of withdrawal due to adverse events was 7.8% for Victoza-treated patients and 3.4% for comparator-treated patients in the five controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza-treated patients and 0.5% of comparator-treated patients. The most common adverse reactions leading to withdrawal for Victoza-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

Tables 1 and 2 summarize the adverse events reported in ≥5% of Victoza-treated patients in the five controlled trials of 26 weeks duration or longer.

Table 1 Adverse events reported in ≥5% of Victoza-treated patients or ≥5% of glimepiride-treated patients: 52-week monotherapy trial

	All Victoza N = 497	Glimepiride N = 248
Adverse Event Term	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Upper Respiratory Tract Infection	9.5	5.6
Headache	9.1	9.3
Influenza	7.4	3.6
Urinary Tract Infection	6.0	4.0

Visit PDR.net to register for Product Safety Alerts and to download mobilePDR® - free to U.S. prescribers

Dizziness	5.8	5.2
Sinusitis	5.6	6.0
Nasopharyngitis	5.2	5.2
Back Pain	5.0	4.4
Hypertension	3.0	6.0

(See table 2 at right)

Gastrointestinal adverse events

In the five clinical trials of 26 weeks duration or longer, gastrointestinal adverse events were reported in 41% of Victoza-treated patients and were dose-related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among Victoza-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. Approximately 13% of Victoza-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza-treated patients in the five clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza-treated patients in the 52-week monotherapy trial and in 4.8% of the Victoza-treated patients in the 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza-treated patients in the 52-week monotherapy trial and in 1.0% of the Victoza-treated patients in the 26-week add-on combination therapy trials.

Among Victoza-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza treatment.

In clinical trials of Victoza, events from a composite of adverse events potentially related to immunogenicity (e.g., urticaria, angioedema) occurred among 0.8% of Victoza-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies.

Injection site reactions

Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza-treated patients in the five clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza-treated patients discontinued due to injection site reactions.

Papillary thyroid carcinoma

In clinical trials of Victoza, there were 6 reported cases of papillary thyroid carcinoma in patients treated with Victoza and 1 case in a comparator-treated patient (1.9 vs. 0.6 cases per 1000 patient-years). Most of these papillary thyroid car-

Table 2 Adverse events reported in ≥5% of Victoza-treated patients and occurring more frequently with Victoza compared to placebo: 26-week combination therapy trials

Add-on to Metformin Trial			
	All Victoza + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Event Term	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
Adverse Event Term	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2
Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6
Add-on to Metformin + Glimepiride			
	Victoza 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Event Term	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4
Add-on to Metformin + Rosiglitazone			
	All Victoza + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175	
Adverse Event Term	(%)	(%)	
Nausea	34.6		8.6
Diarrhea	14.1		6.3
Vomiting	12.4		2.9
Decreased Appetite	9.3		1.1
Anorexia	9.0		0.0
Headache	8.2		4.6
Constipation	5.1		1.1
Fatigue	5.1		1.7

cinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

Hypoglycemia

In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza-treated patients (2.6 cases per 1000 patient-years) and in no comparator-treated patients. Six of these 7 patients treated with Victoza were also taking a sulfonylurea. One other patient was taking Victoza in combination with metformin but had another likely explanation for the hypoglycemia (this event occurred during hospitalization and after insulin infusion) (Table 3). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in patients who were not taking a concomitant sul-

fonylurea. Both patients were receiving Victoza, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

(See table 3 at top of next page)

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events (see Adverse Reactions (6.1)), no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza-treated patients

IMPORTANT NOTICE: Updated drug information is sent bi-monthly via the PDR® Update Insert. For monthly email updates, register at PDR.net.

incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Vascular abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 14, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F_2 generation rats descended from liraglutide-treated rats compared to F_2 generation rats descended from controls, but differences did not reach statistical significance for any group.

8.3 Nursing Mothers

It is not known whether Victoza is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for liraglutide in animal studies, a decision should be made whether to discontinue nursing or to discontinue Victoza, taking into account the importance of the drug to the

Patient not able to self-treat	2.2 (0.06)	0	0
Patient able to self-treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

mother. In lactating rats, liraglutide was excreted unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use

Safety and effectiveness of Victoza have not been established in pediatric patients. Victoza is not recommended for use in pediatric patients.

8.5 Geriatric Use

In the Victoza clinical trials, a total of 797 (20%) of the patients were 65 years of age and over and 113 (2.8%) were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

There is limited experience in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. Therefore, Victoza should be used with caution in this patient population. No dose adjustment of Victoza is recommended for patients with renal impairment [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, Victoza should be used with caution in this patient population. No dose adjustment of Victoza is recommended for patients with hepatic impairment [see *Clinical Pharmacology* (12.3)].

8.8 Gastroparesis

Victoza slows gastric emptying. Victoza has not been studied in patients with pre-existing gastroparesis.

10 OVERDOSAGE

In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

Victoza contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae*, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is $C_{172}H_{285}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:



Victoza is a sterile, non-preserved solution. Each 1 mL of Victoza solution contains 6 mg of liraglutide. Each pre-filled pen contains a 3 mL solution of Victoza equivalent to 18 mg liraglutide (free-base, anhydrous) and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor,

Visit PDR.net to register for Product Safety Alerts and to download mobilePDR® - free to U.S. prescribers

Table 4 Results of a 52-week monotherapy trial*

	Victoza 1.8 mg	Victoza 1.2 mg	Glimepiride 8 mg
Intent-to-Treat Population (N)	246	251	248
HbA_{1c} (%) (Mean)			
Baseline	8.2	8.2	8.2
Change from baseline (adjusted mean) [†]	-1.1	-0.8	-0.5
Difference from glimepiride arm (adjusted mean) [†]	-0.6 [‡]	-0.3 [§]	
95% Confidence Interval	(-0.8, -0.4)	(-0.5, -0.1)	
Patients (%) achieving A _{1c} <7%	51	43	28
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	172	168	172
Change from baseline (adjusted mean) [†]	-26	-15	-5
Difference from glimepiride arm (adjusted mean) [†]	-20 [‡]	-10 [§]	
95% Confidence Interval	(-29, -12)	(-19, -1)	
Body Weight (kg) (Mean)			
Baseline	92.6	92.1	93.3
Change from baseline (adjusted mean) [†]	-2.5	-2.1	+1.1
Difference from glimepiride arm (adjusted mean) [†]	-3.6 [‡]	-3.2 [§]	
95% Confidence Interval	(-4.3, -2.9)	(-3.9, -2.5)	

* Intent-to-treat population using last observation on study

† Least squares mean adjusted for baseline value

‡ p-value <0.0001

§ p-value <0.05

a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, G_s, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

GLP-1(7-37) has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

12.2 Pharmacodynamics

Victoza's pharmacodynamic profile is consistent with its pharmacokinetic profile observed after single subcutaneous administration as Victoza lowered fasting, premeal and postprandial glucose throughout the day [see Clinical Pharmacology (12.3)].

Fasting and postprandial glucose was measured before and up to 5 hours after a standardized meal after treatment to steady state with 0.6, 1.2 and 1.8 mg Victoza or placebo. Compared to placebo, the postprandial plasma glucose AUC_{0-300min} was 35% lower after Victoza 1.2 mg and 38% lower after Victoza 1.8 mg.

Glucose-dependent insulin secretion

The effect of a single dose of 7.5 mcg/kg (~0.7 mg) Victoza on insulin secretion rates (ISR) was investigated in 10 patients with type 2 diabetes during graded glucose infusion. In these patients, on average, the ISR response was increased in a glucose-dependent manner (Figure 2). [See figure at top of next column]

Glucagon secretion

Victoza lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of Victoza 7.5 mcg/kg (~0.7 mg) did not impair glucagon response to low glucose concentrations.

Gastric emptying

Victoza causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Cardiac Electrophysiology (QTc)

The effect of Victoza on cardiac repolarization was tested in a QTc study. Victoza at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

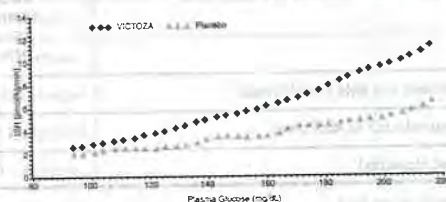


Figure 2 Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose Victoza 7.5 mcg/kg (~0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion

12.3 Pharmacokinetics

Absorption—Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak (C_{max}) and total (AUC) exposures of liraglutide were 35 ng/mL and 960 ng·h/mL, respectively, for a subcutaneous single dose of 0.6 mg. After subcutaneous single dose administrations, C_{max} and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg. At 1.8 mg Victoza, the average steady state concentration of liraglutide over 24 hours was approximately 128 ng/mL. AUC_{0-24h} was equivalent between upper arm and abdomen, and between upper arm and thigh. AUC_{0-24h} from thigh was 22% lower than that from abdomen. However, liraglutide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution—The mean apparent volume of distribution after subcutaneous administration of Victoza 0.6 mg is approximately 13 L. The mean volume of distribution after intravenous administration of Victoza is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (>98%). **Metabolism**—During the initial 24 hours following administration of a single [³H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

Elimination—Following a [³H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimi-

nation half-life of approximately 13 hours, making Victoza suitable for once daily administration.

Specific Populations

Elderly—Age had no effect on the pharmacokinetics of Victoza based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of patients 18 to 80 years of age [see Use in Specific Populations (8.5)].

Gender—Based on the results of population pharmacokinetic analyses, females have 34% lower weight-adjusted clearance of Victoza compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.

Race and Ethnicity—Race and ethnicity had no effect on the pharmacokinetics of Victoza based on the results of population pharmacokinetic analyses that included Caucasian, Black, Asian and Hispanic/Non-Hispanic subjects.

Body Weight—Body weight significantly affects the pharmacokinetics of Victoza based on results of population pharmacokinetic analyses. The exposure of liraglutide decreases with an increase in baseline body weight. However, the 1.2 mg and 1.8 mg daily doses of Victoza provided adequate systemic exposures over the body weight range of 40-160 kg evaluated in the clinical trials. Liraglutide was not studied in patients with body weight >160 kg.

Pediatric—Victoza has not been studied in pediatric patients [see Use in Specific Populations (8.4)].

Renal Impairment—The single-dose pharmacokinetics of Victoza were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 80% lower, respectively [see Use in Specific Populations (8.6)].

Hepatic Impairment—The single-dose pharmacokinetics of Victoza were evaluated in subjects with varying degrees of hepatic impairment. Subjects with mild (Child Pugh score 5-6) to severe (Child Pugh score > 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in subjects with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively [see Use in Specific Populations (8.7)].

Drug Interactions

In vitro assessment of drug-drug interactions

Victoza has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug-drug interactions

The drug-drug interaction studies were performed at steady state with Victoza 1.8 mg/day. Before administration of concomitant treatment, subjects underwent a 0.6 mg weekly dose increase to reach the maximum dose of 1.8 mg/day. Administration of the interacting drugs was timed so that C_{max} of Victoza (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Digoxin

A single dose of digoxin 1 mg was administered 7 hours after the dose of Victoza at steady state. The concomitant administration with Victoza resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median time to maximal concentration (T_{max}) was delayed from 1 h to 1.5 h.

Lisinopril

A single dose of lisinopril 20 mg was administered 5 minutes after the dose of Victoza at steady state. The co-administration with Victoza resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median T_{max} was delayed from 6 h to 8 h with Victoza.

Atorvastatin

Victoza did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg administered 5 hours after the dose of Victoza at steady state. Atorvastatin C_{max} was decreased by 38% and median T_{max} was delayed from 1 h to 3 h with Victoza.

Acetaminophen

Victoza did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1000 mg administered 8 hours after the dose of Victoza at steady state. Acetaminophen C_{max} was decreased by 31% and median T_{max} was delayed up to 15 minutes.

Griseofulvin

Victoza did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with Victoza at steady state. Griseofulvin C_{max} increased by 37% while median T_{max} did not change.

Oral Contraceptives

A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of Victoza at steady state. Victoza lowered ethinylestradiol and levonorgestrel C_{max} by 12% and 13%,

IMPORTANT NOTICE: Updated drug information is sent bi-monthly via the PDR® Update Insert. For monthly email updates, register at PDR.net.

Difference from placebo + metformin arm (adjusted mean) ^a	-1.3 ^b	-1.1 ^b	
95% Confidence Interval	(-2.2, -0.4)	(-2.0, -0.2)	
Difference from glimepiride + metformin arm (adjusted mean) ^a	-3.8 ^b	-3.5 ^b	
95% Confidence Interval	(-4.5, -3.0)	(-4.3, -2.8)	

^a Intent-to-treat population using last observation on study
^b For glimepiride, one-half of the maximal approved United States dose.
^c Least squares mean adjusted for baseline value
^d p-value <0.0001
^e p-value <0.05

respectively. There was no effect of Victoza on the overall exposure (AUC) of ethinylestradiol. Victoza increased the levonorgestrel AUC₀₋₂₄ by 18%. Victoza delayed T_{max} for both ethinylestradiol and levonorgestrel by 1.5 h.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1.0 and 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats. Human relevance of thyroid C-cell tumors in mice and rats is unknown and could not be determined by clinical studies or nonclinical studies (see Boxed Warning and Warnings and Precautions (5.1)).

Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose *in vivo* micronucleus tests in rats.

In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until ges-

due to ineffective therapy was 0.6% in the placebo treatment group, 6.0% in the Victoza 1.2 mg treatment group, and 10.1% in the glimepiride treatment group. (See table 4 at top of previous page)

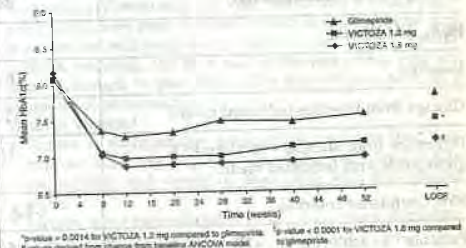


Figure 3 Mean HbA_{1c} for patients who completed the 52-week trial and for the Last Observation Carried Forward (LOCF, intent-to-treat) data at Week 52 (Monotherapy)

14.2 Combination Therapy

Add-on to Metformin

In this 26-week trial, 1091 patients were randomized to Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or glimepiride 4 mg (one-half of the maximal approved dose in the United States), all as add-on to metformin. Randomization occurred after a 6-week run-in period consisting of a 3-week initial forced metformin titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin were increased up to 2000 mg/day.

Treatment with Victoza 1.2 mg and 1.8 mg as add-on to metformin resulted in a significant mean HbA_{1c} reduction relative to placebo add-on to metformin and resulted in a similar mean HbA_{1c} reduction relative to glimepiride 4 mg add-on to metformin (Table 5). The percentage of patients who discontinued due to ineffective therapy was 5.4% in the Victoza 1.8 mg + metformin treatment group, 3.3% in the Victoza 1.2 mg + metformin treatment group, 23.8% in the placebo + metformin treatment group, and 3.7% in the glimepiride + metformin treated group.

Visit PDR.net to register for Product Safety Alerts and to download mobilePDR® - free to U.S. prescribers

Table 6 Results of a 26-week trial of Victoza as add-on to sulfonylurea*

	Victoza 1.8 mg + Glimepiride	Victoza 1.2 mg + Glimepiride	Placebo + Glimepiride	Rosiglitazone 4 mg [†] + Glimepiride
Intent-to-Treat Population (N)	234	228	114	231
HbA _{1c} (%) (Mean)				
Baseline	8.5	8.5	8.4	8.4
Change from baseline (adjusted mean) [‡]	-1.1	-1.1	+0.2	-0.4
Difference from placebo + glimepiride arm (adjusted mean) [‡]	-1.4 [§]	-1.3 [§]		
95% Confidence Interval	(-1.6, -1.1)	(-1.5, -1.1)		
Patients (%) achieving A _{1c} <7%	42	35	7	22
Fasting Plasma Glucose (mg/dL) (Mean)				
Baseline	174	177	171	179
Change from baseline (adjusted mean) [‡]	-29	-28	+18	-16
Difference from placebo + glimepiride arm (adjusted mean) [‡]	-47 [§]	-46 [§]		
95% Confidence Interval	(-58, -35)	(-58, -35)		
Body Weight (kg) (Mean)				
Baseline	83.0	80.0	81.9	80.6
Change from baseline (adjusted mean) [‡]	-0.2	+0.3	-0.1	+2.1
Difference from placebo + glimepiride arm (adjusted mean) [‡]	-0.1	0.4		
95% Confidence Interval	(-0.9, 0.6)	(-0.4, 1.2)		

* Intent-to-treat population using last observation on study

[†] For rosiglitazone, one-half of the maximal approved United States dose.[‡] Least squares mean adjusted for baseline value[§] p-value <0.0001

Table 7 Results of a 26-week trial of Victoza as add-on to metformin and sulfonylurea*

	Victoza 1.8 mg + Metformin + Glimepiride	Placebo + Metformin + Glimepiride	Insulin glargine [†] + Metformin + Glimepiride
Intent-to-Treat Population (N)	230	114	232
HbA _{1c} (%) (Mean)			
Baseline	8.3	8.3	8.1
Change from baseline (adjusted mean) [‡]	-1.3	-0.2	-1.1
Difference from placebo + metformin + glimepiride arm (adjusted mean) [‡]	-1.1 [§]		
95% Confidence Interval	(-1.3, -0.9)		
Patients (%) achieving A _{1c} <7%	53	15	46
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	165	170	164
Change from baseline (adjusted mean) [‡]	-28	+10	-32
Difference from placebo + metformin + glimepiride arm (adjusted mean) [‡]	-38 [§]		
95% Confidence Interval	(-46, -30)		
Body Weight (kg) (Mean)			
Baseline	85.8	85.4	85.2
Change from baseline (adjusted mean) [‡]	-1.8	-0.4	1.6
Difference from placebo + metformin + glimepiride arm (adjusted mean) [‡]	-1.4 [‡]		
95% Confidence Interval	(-2.1, -0.7)		

* Intent-to-treat population using last observation on study

[†] For insulin glargine, optimal titration regimen was not achieved for 80% of patients.[‡] Least squares mean adjusted for baseline value[§] p-value <0.0001[‡] p-value <0.05

[See table 5 at top of previous page]

Add-on to Sulfonylurea

In this 26-week trial, 1041 patients were randomized to Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or insulin glargine, all as add-on to glimepiride. Randomization occurred after a 4-week run-in period consisting of an initial, 2-week, forced-glimepiride titration period followed by a maintenance period of another 2 weeks. During the titration period, doses of glimepiride were increased at the discretion of the investigator from 4 mg/day to 3 mg/day or 2 mg/day (minimum) after randomization, in the event of unacceptable hypoglycemia or other adverse events.

Treatment with Victoza 1.2 mg and 1.8 mg as add-on to glimepiride resulted in a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to glimepiride (Table 6). The percentage of patients who discontinued due to ineffective therapy was 3.0% in the Victoza 1.8 mg + glimepiride treatment group, 3.5% in the Victoza 1.2 mg + glimepiride treatment group, 17.5% in the placebo + glimepiride treatment group, and 6.9% in the rosiglitazone + glimepiride treatment group.

[See table 6 at left]

Add-on to Metformin and Sulfonylurea

In this 26-week trial, 581 patients were randomized to Victoza 1.8 mg, placebo, or insulin glargine, all as add-on to metformin and glimepiride. Randomization took place after a 6-week run-in period consisting of a 3-week forced metformin and glimepiride titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin and glimepiride were to be increased up to 2000 mg/day and 4 mg/day, respectively. After randomization, patients randomized to Victoza 1.8 mg underwent a 2 week period of titration with Victoza. During the trial, the Victoza and metformin doses were fixed, although glimepiride and insulin glargine doses could be adjusted. Patients titrated glargine twice-weekly during the first 8 weeks of treatment based on self-measured fasting plasma glucose on the day of titration. After Week 8, the frequency of insulin glargine titration was left to the discretion of the investigator, but, at a minimum, the glargine dose was to be revised, if necessary, at Weeks 12 and 18. Only 20% of glargine-treated patients achieved the pre-specified target fasting plasma glucose of ≤100 mg/dL. Therefore, optimal titration of the insulin glargine dose was not achieved in most patients.

Treatment with Victoza as add-on to glimepiride and metformin resulted in a statistically significant mean reduction in HbA_{1c} compared to placebo add-on to glimepiride and metformin (Table 7). The percentage of patients who discontinued due to ineffective therapy was 0.9% in the Victoza 1.8 mg + metformin + glimepiride treatment group, 0.4% in the insulin glargine + metformin + glimepiride treatment group, and 11.3% in the placebo + metformin + glimepiride treatment group.

[See table 7 at left]

Add-on to Metformin and Thiazolidinedione

In this 26-week trial, 533 patients were randomized to Victoza 1.2 mg, Victoza 1.8 mg or placebo, all as add-on to rosiglitazone (8 mg) plus metformin (2000 mg). Patients underwent a 9 week run-in period (3-week forced dose escalation followed by a 6-week dose maintenance phase) with rosiglitazone (starting at 4 mg and increasing to 8 mg/day within 2 weeks) and metformin (starting at 500 mg with increasing weekly increments of 500 mg to a final dose of 2000 mg/day). Only patients who tolerated the final dose of rosiglitazone (8 mg/day) and metformin (2000 mg/day) and completed the 6-week dose maintenance phase were eligible for randomization into the trial.

Treatment with Victoza as add-on to metformin and rosiglitazone produced a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to metformin and rosiglitazone (Table 8). The percentage of patients who discontinued due to ineffective therapy was 1.7% in the Victoza 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the Victoza 1.2 mg + metformin + rosiglitazone treatment group, and 16.4% in the placebo + metformin + rosiglitazone treatment group.

[See table 8 at top of next page]

16 HOW SUPPLIED/STORAGE AND HANDLING**16.1 How Supplied**

Victoza is available in the following package sizes containing disposable, pre-filled, multi-dose pens. Each individual pen delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL).

2 × Victoza pen NDC 0169-4060-12

3 × Victoza pen NDC 0169-4060-13

Each Victoza pen is for use by a single patient. A Victoza pen should never be shared between patients, even if the needle is changed.

16.2 Recommended Storage

Prior to first use, Victoza should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C) (Table 9). Do not store in

IMPORTANT NOTICE: Updated drug information is sent bi-monthly via the PDR® Update Insert. For *monthly* email updates, register at PDR.net.

of the pen between patients may pose a risk of transmission of infection.

17.4 Instructions

Patients should be informed of the potential risks and benefits of Victoza and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Patients should be advised that the most common side effects of Victoza are headache, nausea and diarrhea. Nausea is most common when first starting Victoza, but decreases over time in the majority of patients and does not typically require discontinuation of Victoza.

Physicians should instruct their patients to read the Patient Medication Guide before starting Victoza therapy and to read each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

17.5 Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A_{1c} levels, with a goal of decreasing these levels towards the normal range. A_{1c} is especially useful for evaluating long-term glycemic control.

17.6 FDA-Approved Medication Guide

See separate leaflet.

Date of Issue: January 2010

Version: 1

Victoza® is a registered trademark of Novo Nordisk A/S. Victoza® is covered by US Patent Nos. 6,268,343, 6,458,924 and 7,235,627 and other patents pending.

Victoza® Pen is covered by US Patent Nos. 6,004,297, 6,235,004, 6,582,404 and other patents pending.

© 2010 Novo Nordisk A/S

Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

For information about Victoza contact:

Novo Nordisk Inc.

100 College Road West

Princeton, NJ 08540

1-877-4S4-2869

Medication Guide

Victoza® (VIC-tow-za)

(liraglutide [rDNA origin]) Injection

Read this Medication Guide and Patient Instructions for Use that come with Victoza before you start using Victoza and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have questions about Victoza after reading this information, ask your healthcare provider or pharmacist.

What is the most important information I should know about Victoza?

Serious side effects may happen in people who take Victoza, including:

- 1. Possible thyroid tumors, including cancer.** During the drug testing process, the medicine in Victoza caused rats and mice to develop tumors of the thyroid gland. Some of these tumors were cancers. It is not known if Victoza will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people. If medullary thyroid cancer occurs, it may lead to death if not detected and treated early. If you develop tumors or cancer of the thyroid, your thyroid may have to be surgically removed.
- Before you start taking Victoza, tell your healthcare provider if you or any of your family members have had thyroid cancer, especially medullary thyroid cancer, or Multiple Endocrine Neoplasia syndrome type 2. Do not take Victoza if you or any of your family members have medullary thyroid cancer, or if you have Multiple Endocrine Neoplasia syndrome type 2. People with these conditions already have a higher chance of developing medullary thyroid cancer in general and should not take Victoza.**
- While taking Victoza, tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer.**
- 2. Inflammation of the pancreas (pancreatitis), which may be severe and lead to death.**
- Before taking Victoza, tell your healthcare provider if you have had:**
 - pancreatitis
 - stones in your gallbladder (gallstones)
 - a history of alcoholism
 - high blood triglyceride levels

These medical conditions can make you more likely to get pancreatitis in general. It is not known if having these conditions will lead to a higher chance of getting pancreatitis while taking Victoza.

While taking Victoza:

Stop taking Victoza and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may happen with or without vomiting. The pain may be felt going from your abdomen through to your back. This type of pain may be a symptom of pancreatitis.

What is Victoza?

- Victoza is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes mellitus, and should be used along with diet and exercise.
- Victoza is not recommended as the first choice of medication for treating diabetes.
- Victoza is not insulin.
- It is not known if Victoza is safe and effective when used with insulin.
- Victoza is not for use in people with type 1 diabetes or people with diabetic ketoacidosis.
- It is not known if Victoza is safe and effective in children. Victoza is not recommended for use in children.

Who should not use Victoza?

Do not use Victoza if:

- you or any of your family members have a history of medullary thyroid cancer.
- you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). This is a disease where people have tumors in more than one gland in their body.

Talk with your healthcare provider if you are not sure if you have any of these conditions.

What should I tell my healthcare provider before using Victoza?

- Before taking Victoza, tell your healthcare provider if you:
- have any of the conditions listed in the section "What is the most important information I should know about Victoza?"
 - are allergic to liraglutide or any of the other ingredients in Victoza. See the end of this Medication Guide for a list of ingredients in Victoza.
 - have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.

- have or have had kidney or liver problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if Victoza will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking Victoza.
- are breastfeeding or plan to breastfeed. It is not known if Victoza passes into your breast milk. You and your healthcare provider should decide if you will take Victoza or breastfeed. You should not do both without talking with your healthcare provider first.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. Victoza slows stomach emptying and can affect medicines that need to pass through the stomach quickly. Victoza may affect the way some medicines work and some other medicines may affect the way Victoza works. Tell your healthcare provider if you take other diabetes medicines, especially sulfonylurea medicines or insulin.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist each time you get a new medicine.

How should I use Victoza?

- Use Victoza exactly as prescribed by your healthcare provider. Your dose should be increased after using Victoza for one week. After that, do not change your dose unless your healthcare provider tells you to.
- Victoza is injected 1 time each day, at any time during the day.
- You can take Victoza with or without food.
- Victoza comes in a prefilled pen.
- Your healthcare provider must teach you how to inject Victoza before you use it for the first time. If you have questions or do not understand the instructions, talk to your healthcare provider or pharmacist. See the Patient Instructions for Use that come with this Medication Guide for detailed information about the right way to use your Victoza pen.
- Pen needles are not included. You may need a prescription to get pen needles from your pharmacist. Ask your healthcare provider which needle size is best for you.
- When starting a new prefilled Victoza pen, you must follow the "First Time Use for Each New Pen" (see the detailed Patient Instructions for Use that comes with this Medication Guide). You only need to do this 1 time with each new pen. You should also do this if you drop your pen. If you do the "First Time Use for Each New Pen" before each injection, you will run out of medicine too soon.
- Inject your dose of Victoza under the skin (subcutaneous injection) in your stomach area (abdomen), upper leg (thigh), or upper arm, as instructed by your healthcare provider. Do not inject into a vein or muscle.
- If you take too much Victoza, call your healthcare provider right away. Too much Victoza may cause severe nausea and vomiting.
- Follow your healthcare provider's instructions for diet, exercise, how often to test your blood sugar, and when to get your HbA_{1c} checked. If you stop using Victoza your blood sugar levels may increase. First talk to your healthcare provider if you want to stop taking Victoza.
- Your dose of diabetes medicines may need to be changed if your body is under certain types of stress. Tell your healthcare provider if you:
 - have fever
 - have trauma
 - have an infection
 - plan to have or have had surgery
- Never share your Victoza pen or needles with another person. You may give an infection to them, or get an infection from them.

What are the possible side effects of Victoza?

Victoza may cause serious side effects, including:

- See "What is the most important information I should know about Victoza?"
- **Low blood sugar (hypoglycemia).** Your risk for getting low blood sugar is higher if you take Victoza with another medicine that can cause low blood sugar, such as a sulfonylurea. In some people, the blood sugar may get so low that they need another person to help them. The dose of your sulfonylurea medicine may need to be lowered while you use Victoza. Signs and symptoms of low blood sugar may include:
 - shakiness
 - sweating
 - headache
 - drowsiness
 - weakness
 - dizziness
 - confusion
 - irritability
 - hunger
 - fast heartbeat
 - feeling jittery

Talk to your healthcare provider about how to recognize and treat low blood sugar. Make sure that your family and other people who are around you a lot know how to recognize and treat low blood sugar.

Common side effects of Victoza include:

- headache
- nausea
- diarrhea

Nausea is most common when first starting Victoza, but decreases over time in most people as their body gets used to the medicine. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the side effects with Victoza. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Victoza?

Before use:

- Store your new, unused Victoza pen in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not freeze Victoza or use Victoza if it has been frozen.
- Do not store Victoza near the refrigerator cooling element.

Pen in use:

- Store your Victoza pen for 30 days either at 59°F to 86°F (15°C to 30°C), or in a refrigerator at 36°F to 46°F (2°C to 8°C).
- When carrying the pen away from home, store the pen at a temperature between 59°F to 86°F (15°C to 30°C) and keep it dry.
- If Victoza has been exposed to temperatures above 86°F (30°C), it should be thrown away.
- Protect your Victoza pen from heat and sunlight.
- Keep the pen cap on when your Victoza pen is not in use.
- Use your Victoza pen within 30 days after the first day it is stored outside the refrigerator. After these 30 days, throw away your Victoza pen even if some medicine is left in the pen.
- Do not use Victoza after the expiration date printed on the carton.

Do not store the Victoza pen with the needle attached. Always safely remove and safely throw away the needle after each injection. This may help prevent contamination, infection and leakage. It also helps to make sure that you get the correct dose of Victoza. See the Patient Instructions for Use for information about how to dispose of used pen needles and used Victoza pens.

Keep your Victoza pen, pen needles, and all medicines out of the reach of children.

General information about Victoza

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Victoza for a condition for which it was not prescribed. Do not give Victoza to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information you should know about using Victoza. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Victoza that is written for health professionals.

For more information, go to victoza.com or call 1-877-484-2869.

What are the ingredients in Victoza?

Active Ingredient: liraglutide

Inactive Ingredients: disodium phosphate dihydrate, propylene glycol, phenol and water for injection

Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

For information about Victoza contact:

Novo Nordisk Inc.

100 College Road West

Princeton, NJ 08540

1-877-484-2869

Issued: January 2010

Version: 1

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Victoza® is a registered trademark of Novo Nordisk A/S.

Victoza® is covered by US Patent Nos. 6,268,343, 6,458,924 and 7,235,627 and other patents pending.

Victoza® pen is covered by US Patent Nos. 6,004,297, 6,235,004, 6,582,404 and other patents pending.

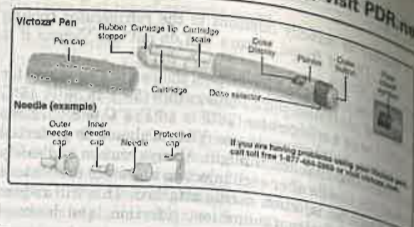
© 2010 Novo Nordisk A/S

PATIENT INSTRUCTIONS FOR USE

Victoza (liraglutide [rDNA origin]) injection

[See figure at top of next column]

First read the Medication Guide that comes with your Victoza pen and then read these Patient Instructions for Use for information about how to use your Victoza pen the right way.



These instructions do not take the place of talking with your healthcare provider about your medical condition or your treatment.

Your Victoza pen contains 3 mL of Victoza and will deliver doses of 0.6 mg, 1.2 mg or 1.8 mg. The number of doses that you can take with a Victoza pen depends on the dose of medicine that is prescribed for you. Your healthcare provider will tell you how much Victoza to take.

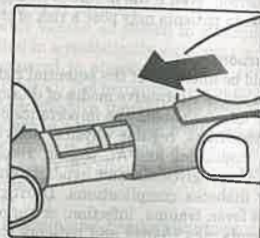
Victoza pen should be used with Novo Nordisk disposable needles. Talk to your healthcare provider or pharmacist for more information about needles for your Victoza pen.

Important Information

- Do not share your Victoza pen or needles with anyone else. You may give an infection to them or get an infection from them.
- Always use a new needle for each injection.
- Keep your Victoza pen and all medicines out of the reach of children.
- If you drop your Victoza pen, repeat "First Time Use for Each New Pen" (steps A through D).
- Be careful not to bend or damage the needle.
- Do not use the cartridge scale to measure how much Victoza to inject.
- Be careful when handling used needles to avoid needle stick injuries.
- You can use your Victoza pen for up to 30 days after you use it the first time.

Caring for your Victoza pen

- After removing the needle, put the pen cap on your Victoza pen and store your Victoza pen without the needle attached.



- Do not try to refill your Victoza pen - it is prefilled and is disposable.
- Do not try to repair your pen or pull it apart.
- Keep your Victoza pen away from dust, dirt and liquids.
- If cleaning is needed, wipe the outside of the pen with a clean, damp cloth.

How should I store Victoza?

Before use:

- Store your new, unused Victoza pen in the refrigerator at 36°F to 46°F (2°C to 8°C).
- If Victoza is stored outside of refrigeration (by mistake) prior to first use, it should be used or thrown away within 30 days.
- Do not freeze Victoza or use Victoza if it has been frozen.

Do not store Victoza near the refrigerator cooling element.

Pen in use:

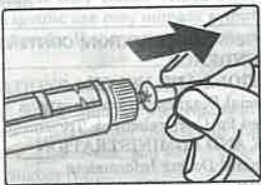
- Store your Victoza pen for 30 days at 59°F to 86°F (15°C to 30°C), or in a refrigerator at 36°F to 46°F (2°C to 8°C).
- When carrying the pen away from home, store the pen at a temperature between 59°F to 86°F (15°C to 30°C).
- If Victoza has been exposed to temperatures above 86°F (30°C), it should be thrown away.
- Protect your Victoza pen from heat and sunlight.
- Keep the pen cap on when your Victoza pen is not in use.
- Use a Victoza pen for only 30 days. Throw away a used Victoza pen after 30 days, even if some medicine is left in the pen.

First Time Use for Each New Pen

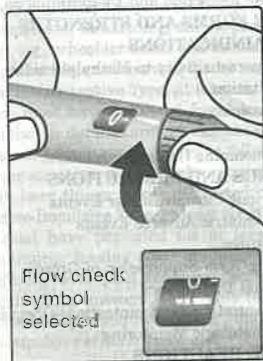
Step A. Check the Pen

- Take your new Victoza pen out of the refrigerator.
- Wash hands with soap and water before use.
- Check pen label before each use to make sure it is your Victoza pen.

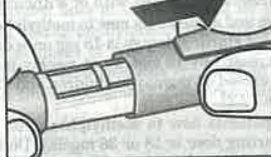
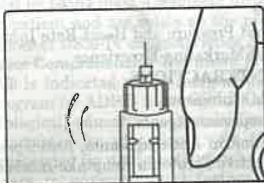
IMPORTANT NOTICE: Updated drug information is sent bi-monthly via the PDR® Update Insert. For monthly email updates, register at PDR.net.



Step C. Dial to the Flow Check Symbol
 Turn dose selector until flow check symbol (--) lines up with pointer.



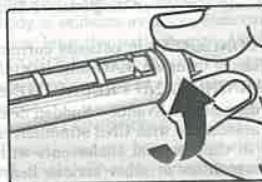
Step D. Prepare the Pen
 Hold pen with needle pointing up.
 Tap cartridge gently with your finger a few times to bring any air bubbles to the top of the cartridge.



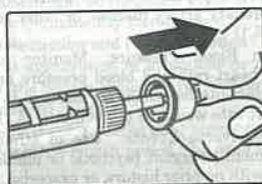
- Check Victoza in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
- Wipe the rubber stopper with an alcohol swab.

Step F. Attach the Needle

- Remove protective tab from outer needle cap.
- Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure.



- Pull off outer needle cap. Do not throw away.

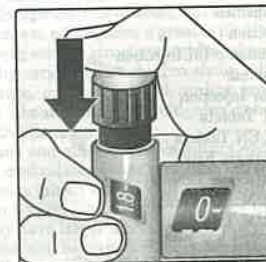


- Pull off inner needle cap and throw away. A small drop of liquid may appear. This is normal.

- You will hear a "click" every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear.
- If you select a wrong dose, change it by turning the dose selector backwards or forwards until the correct dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector. This may cause Victoza to come out.

Step H. Injecting the Dose

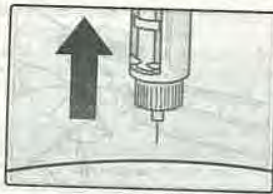
- Insert needle into your skin in the stomach, thigh or upper arm. Use the injection technique shown to you by your healthcare provider. **Do not inject Victoza into a vein or muscle.**
- Press down on the center of the dose button to inject until 0 mg lines up with the pointer.
- Be careful not to touch the dose display with your other fingers. **This may block the injection.**
- Keep the dose button pressed down and make sure that you keep the needle under the skin for a full count of 6 seconds to make sure the full dose is injected. Keep your thumb on the injection button until you remove the needle from your skin.



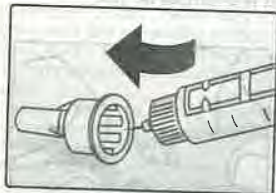
Step I. Withdraw Needle

- You may see a drop of Victoza at the needle tip. **This is normal and it does not affect the dose you just received.** If blood appears after you take the needle out of your skin, apply light pressure, but **do not rub the area.**

Visit PDR.net to register for Product Safety Alerts and to download *mobilePDR* - free to U.S. prescribers

**Step J. Remove and Dispose of the Needle**

- Carefully put the outer needle cap over the needle. Unscrew the needle.



- Safely remove the needle from your Victoza pen after each use.
- Place used needles in a closable, puncture-resistant container. If your Victoza pen is empty or if you have been using it for 30 days (even if it is not empty), throw away the used pen. You may use a sharps container (such as a red biohazard container), a hard plastic container (such as an empty detergent bottle), or metal container with a screw top (such as an empty coffee can).
- Ask your healthcare provider for instructions on the right way to dispose of your used needles, pens, and the container. Do not throw the disposal container in the household trash. Do not recycle.

Shown in Product Identification Guide, page 316

**Ortho-McNeil-Janssen
Pharmaceuticals, Inc.**
RARITAN, NJ 08869-0602 and
TITUSVILLE, NJ 08560-0200

www.ortho-mcneil.com
www.pricara.com
www.janssen.com
www.mcneilpediatrics.net
www.ortho-mcneilneurologics.com
For Medical Information Contact:

(800) 682-6532
In Emergencies:
(908) 218-7325

For Patient Education Materials Contact:
877-323-2200

For Customer Service (Sales and Ordering):
800-631-5273

To obtain Prescribing Information on the following products, please contact:

Ortho-McNeil-Janssen Pharmaceuticals, Inc.
1000 Route 202 South
PO Box 300
Raritan, NJ 08869-0602

AXERT Tablets
DORIBAX Injection
ELMIRON Capsules
HALDOL Injection
HALDOL Decanoate IM Injection
MODICON Tablets
NATRECOR for Injection
ORTHO-CEPT Tablets
ORTHO-CYCLEN Tablets
ORTHO Diaphragm Kits
ORTHO MICRONOR Tablets
ORTHO-NOVUM 1/50 Tablets
ORTHO-NOVUM Tablets
ORTHO TRI-CYCLEN Tablets
ORTHO TRI-CYCLEN LO Tablets
PARAFON FORTE DSC
RAZADYNE Oral Solution
RAZADYNE Tablets
RAZADYNE ER Extended-Release Capsules
RISPERDAL Tablets, Oral Solution, M-Tab
TERAZOL 3 Vaginal Cream

TERAZOL 3 Vaginal Suppositories
TERAZOL 7 Vaginal Cream
TOLECTIN 200/400/600
TOPAMAX Sprinkle Capsules
TOPAMAX Tablets
TYLOX Capsules
ULTRACET Tablets
ULTRAM Tablets
ULTRAM ER Extended-Release Tablets

CONCERTA®

(methylphenidate HCl)

Extended-Release Tablets (C)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CONCERTA® safely and effectively. See full prescribing information for CONCERTA®.

CONCERTA® (methylphenidate HCl) Extended-Release Tablets CII

Initial U.S. Approval: 2000

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning.

CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior.

INDICATIONS AND USAGE

CONCERTA® is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. (1)

DOSAGE AND ADMINISTRATION

- CONCERTA® should be taken once daily in the morning and swallowed whole with the aid of liquids. CONCERTA® should not be chewed or crushed. CONCERTA® may be taken with or without food. (2.1)
- For children and adolescents new to methylphenidate, the recommended starting dosage is 18 mg once daily. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 54 mg/day in children and 72 mg/day in adolescents. (2.2)
- For adult patients new to methylphenidate, the recommended starting dose is 18 or 36 mg/day. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 72 mg/day for adults. (2.2)
- For patients currently using methylphenidate, dosing is based on current dose regimen and clinical judgment. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 18, 27, 36, and 54 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to the product (4.1)
- Marked anxiety, tension, or agitation (4.2)
- Glaucoma (4.3)
- Tics or a family history or diagnosis of Tourette's syndrome (4.4)
- Do not use CONCERTA® in patients currently using or within 2 weeks of using an MAO inhibitor (4.5)

WARNINGS AND PRECAUTIONS

- **Serious Cardiovascular Events:** Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. (5.1)
- **Increase in Blood Pressure:** Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic. (5.1)
- **Psychiatric Adverse Events:** Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Clinical evaluation for Bipolar Disorder is recommended prior to stimulant use. Monitor for aggressive behavior. (5.2)

- **Seizures:** Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. (5.3)
- **Visual Disturbance:** Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. (5.5)
- **Long-Term Suppression of Growth:** monitor height and weight at appropriate intervals in pediatric patients. (5.4)
- **Gastrointestinal obstruction** with pre-existing GI narrowing. (5.6)
- **Hematologic monitoring:** Periodic CBC, differential and platelet counts are advised during prolonged therapy. (5.7)

ADVERSE REACTIONS

The most common adverse reaction in double-blind clinical trials (>5%) in children and adolescents was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis. (5.1 and 6.2)

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased. (6.3)

To report SUSPECTED ADVERSE REACTIONS, contact McNeil Pediatrics at 1-888-440-7903 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Do not use CONCERTA® in patients currently using or within 2 weeks of using an MAO inhibitor (7.1)
- CONCERTA® may increase blood pressure; use cautiously with vasopressors (7.2)
- Inhibition of metabolism of coumarin anticoagulants, anticonvulsants, and some antidepressants (7.3)
- Serious adverse events when using methylphenidate in combination with clonidine (7.4)

USE IN SPECIFIC POPULATIONS

Caution should be exercised if administered to nursing mothers (8.3)

- Safety and efficacy has not been established in children less than six years old or elderly patients greater than 65 years of age (8.4 and 8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2010

FULL PRESCRIBING INFORMATION: CONTENTS**DRUG DEPENDENCE****1 INDICATIONS AND USAGE**

- 1.1 Special Diagnostic Considerations
- 1.2 Need for Comprehensive Treatment Program

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Patients New to Methylphenidate
- 2.3 Patients Currently Using Methylphenidate
- 2.4 Dose Titration
- 2.5 Maintenance/Extended Treatment
- 2.6 Dose Reduction and Discontinuation

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS**

- 4.1 Hypersensitivity to Methylphenidate
- 4.2 Agitation
- 4.3 Glaucoma
- 4.4 Tics
- 4.5 Monoamine Oxidase Inhibitors

5 WARNINGS AND PRECAUTIONS

- 5.1 Serious Cardiovascular Events
- 5.2 Psychiatric Adverse Events
- 5.3 Seizures
- 5.4 Long-Term Suppression of Growth
- 5.5 Visual Disturbance
- 5.6 Potential for Gastrointestinal Obstruction
- 5.7 Hematologic Monitoring

6 ADVERSE REACTIONS

- 6.1 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials
- 6.2 Other Adverse Reactions Observed in CONCERTA® Clinical Trials
- 6.3 Discontinuation Due to Adverse Reactions
- 6.4 Tics
- 6.5 Blood Pressure and Heart Rate Increases
- 6.6 Post-Marketing Experience

7 DRUG INTERACTIONS

- 7.1 MAO Inhibitors
- 7.2 Vasopressor Agents
- 7.3 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors
- 7.4 Clonidine

IMPORTANT NOTICE: Updated drug information is sent bi-monthly via the PDR® Update Insert. For monthly email updates, register at PDR.net.