



## **Novo Nordisk Patient Assistance Program**

**P.O. Box 181640**

**Louisville, KY 40261**

**866-310-7549 • Fax: 866-441-4190**

The Novo Nordisk Patient Assistance Program provides medication to qualifying applicants at no charge. If the applicant qualifies under the Novo Nordisk PAP guidelines, a three-month (3 month) supply of the requested medication(s) or device(s) will be shipped to the applicant's licensed practitioner for dispensing.

### **APPLYING TO THE Novo Nordisk PAP**

#### **Applicant Instructions:**

- The applicant is required to complete sections 1.0, 1.1, 1.2, and 3.1 on the application. If you are a Medicare Part D enrollee you must also sign and date section 3.2. Also, if you are 65 years of age or older, you must also (i) provide proof that you are not eligible to receive Part D benefits, (ii) [provide proof that you have applied for and been denied the Low Income Subsidy ("LIS") from the Social Security Administration], or (iii) are enrolled in a Part D Plan and have hit the donut hole. In addition, those over 65 years of age must otherwise meet the program eligibility criteria set forth below in order to receive benefits under this program... Please note that if you are eligible to receive the LIS, you are not eligible to receive product under the Novo Nordisk Patient Assistance Program.
- The applicant must print his/her legal name exactly as it appears on the Social Security card issued to the applicant.
- To apply for LIS please contact the SSA at 800-772-1213 (TTY 800-325-0778) or go to [www.socialsecurity.gov/prescriptionhelp/](http://www.socialsecurity.gov/prescriptionhelp/). Attach a photocopy of LIS denial letter to the Novo Nordisk PAP application.
- Please sign the certification sections in ink.

#### **Healthcare Practitioner Instructions:**

- The prescribing licensed healthcare practitioner is required to complete sections 2.0, 2.1, and 3.0. In addition the same licensed healthcare practitioner must complete the attached prescription sheet (Section 2.1) for a three-month supply of medication for all products except where indicated differently.
- Please include prescription for needles when applicable
- Please sign the certification section in ink.

### **DOCUMENTS TO SUBMIT TO NNI PAP**

- Application completed by the applicant and prescribing licensed healthcare practitioner
- Prescription for a three-month or 90-day supply of medication from the licensed healthcare practitioner who signed the application
- Photocopy of applicant's letter from a Part D Plan that applicant is not eligible to receive Part D benefits.
- Photocopy of applicant's LIS denial letter (Medicare Part D enrollees only)
- Photocopy of documentation demonstrating that applicant has hit the donut hole (Part D enrollees only), such as an explanation of benefits, monthly statement, or letter from Part D Plan.
- Photocopy of applicant's most recent Federal Tax Return (1040), Social Security Income (SSA 1099), Pensions, Interest, Retirement, Child Support, etc. **(NOTE: Program will accept previous years 1040 form until May 1 of the following year; If your 1040 does not reflect your current income please submit two recent paystubs for all working household members)**
- Patient currently receiving unemployment should submit:
  - Unemployment Letter
  - Last 3 months bank statements
- If patient or member of household is receiving Social Security benefits submit copy of the "Notice of Award" letter. **(NOTE: If you do not have this letter please contact your local Social Security office to request a letter stating when (date) you became eligible for benefits and what type of benefit you are receiving.)**
- Patient with zero income can submit a letter from their physician or social agency (food stamp approval) on physician or agency letterhead.

### **APPLICATION PROCESSING**

Submit the completed application with photocopies of the required proof of income to FAX 866-441-4190. Faxed requests must be sent from the healthcare practitioner's office. Please allow up to 10 business days for processing. Applications may also be mailed to the address above. Allow an additional 7 days for processing if mailed.

- Both the patient and healthcare practitioner will be advised in writing of approved and denied requests.
- If the applicant is approved, a three-month supply of the medication(s) or device(s) requested will be shipped to the licensed healthcare practitioner's office for dispensing. If you would like notification of the ship date for the requested medication, the licensed healthcare practitioner can obtain this notification by registering for the Novo Nordisk PAP free web portal at [www.diabetespap.com](http://www.diabetespap.com).
- All incomplete applications will be sent to either the patient or licensed healthcare practitioner with instructions for completion.



**PROGRAM ELIGIBILITY**

- Patient cannot have or qualify for Veteran’s Administration or any state or local programs.
- Patient cannot have or qualify for any private prescription coverage such as an HMO or PPO (with the exception of Medicare Part D).
- Patient’s total household income must be at or below 200% of the Federal Poverty Level. See Chart on the following page.
- Patient must be a US Citizen or Legal Resident

Household Size	Total Household Income 48 Contiguous States & DC	Alaska	Hawaii
1	\$21,660	\$27,060	\$24,920
2	\$29,140	\$36,420	\$33,520
3	\$36,620	\$45,780	\$42,120
4	\$44,100	\$55,140	\$50,720
5	\$51,580	\$64,500	\$59,320
6	\$59,060	\$73,860	\$67,920
7	\$66,540	\$83,220	\$76,520
8	\$74,020	\$92,580	\$85,120
	For families with more than 8 persons, add \$3,740 for each additional person.	For families with more than 8 persons, add \$4,680 for each additional person.	For families with more than 8 persons, add \$4,300 for each additional person.

Effective date: January 23, 2009

A new application must be submitted for each new product request; provided, however that Part D beneficiaries that have been accepted into the program need not only submit a new product request (not a new application) every three months to receive product for the remainder of the calendar year in which they were accepted into the program. Income documentation is only required annually.

All requests are subject to product availability and patient eligibility verification.

Novo Nordisk reserves the right to modify or cancel this program at any time without notice.



**Patient Assistance Program**  
**Novo Nordisk Inc.**  
**PO Box 181640**  
**Louisville, KY 40261**  
**Phone: 866-310-7549**  
**Fax: 866-441-4190**



**SECTION 1.0: Patient Information**

**New Application / Annual Renewal**                       **90 Day Re-order**

Patient's name: \_\_\_\_\_ Date of birth: \_\_\_/\_\_\_/\_\_\_

Patient's address: \_\_\_\_\_ Gender: Male  Female

\_\_\_\_\_

Patient's phone number \_\_\_\_\_ Social Security number: \_\_\_\_\_  
(required)

Email: \_\_\_\_\_

**SECTION 1.1: Eligibility Requirements**

- A. Annual Household adjusted gross income from most recent federal tax return \$ \_\_\_\_\_  
**(Attach a copy of the patient's most recent Federal Tax Return (1040), Social Security Income (SSA 1099), Pensions, Interest, Retirement, Child Support, etc. This information is only required annually. It is not required for 90-day reorders.)**
- B. Number of dependents in household (including self) \_\_\_\_\_
- C. Do you qualify for private, local, state or federal prescription insurance coverage? Yes  No

**Please Attach Proof of Income Documents for all New Applications and Annual Renewals**  
**Incomplete Applications will be Returned**

**SECTION 1.2: Medicare/Medicaid Information**

Are you enrolled in Medicare? <input type="checkbox"/> Yes <input type="checkbox"/> No	Are you enrolled in Medicaid? <input type="checkbox"/> Yes <input type="checkbox"/> No
Medicare ID #: _____	Are you enrolled in a Medicare Part D plan? <input type="checkbox"/> Yes <input type="checkbox"/> No

Medicare Part D enrollees: You must have (i) applied for and been denied the Low Income Subsidy ("LIS") from the Social Security Administration ("SSA"), or (ii) hit the donut hole for the relevant benefit year, before submitting this application to the NNI PAP. To apply for LIS please contact the SSA at (800)772-1213 (TTY 800-325-0778) or go to [www.socialsecurity.gov/prescriptionhelp/](http://www.socialsecurity.gov/prescriptionhelp/). Please attach (as applicable) to this application a photocopy of your LIS denial letter or documentation from your Part D Plan that you have hit the donut hole for the relevant benefit year, such as a letter from your Part D Plan, a monthly statement of benefits, or an Explanation of Benefits (EOB).



**SECTION 2.0: Licensed Healthcare Practitioner Information**

Practitioner's name: \_\_\_\_\_ State License #: \_\_\_\_\_ Exp Date: \_\_\_\_\_

Shipping Address: \_\_\_\_\_  
(no P.O.Box number)

Phone number: \_\_\_\_\_ Fax number: \_\_\_\_\_

Email: \_\_\_\_\_

I agree that, in addition to communications regarding PAP, the information I have provided may be used for Novo Nordisk business purposes, including but not limited to, providing me access to NovoMedLink™ resources and receiving facsimiles.

**SECTION 2.1: Prescription Information (Indicate Quantity Needed for a three-month (3-month) Supply)**

Patient's name: \_\_\_\_\_ Date of birth: \_\_\_\_/\_\_\_\_/\_\_\_\_

**Levemir® (insulin detemir [rDNA origin] injection)**

368712	Levemir® 10 mL vials	Max. dose per day _____ Sig _____
643910	Levemir® FlexPen® (5x3 mL) **	Max. dose per day _____ Sig _____

**NovoLog® (insulin aspart [rDNA origin] injection)**

750111	NovoLog® 10 mL vials	Max. dose per day _____ Sig _____
633910	NovoLog® FlexPen® (5x3 mL) **	Max. dose per day _____ Sig _____

**NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])**

368512	NovoLog® Mix 70/30 10 mL vials	Max. dose per day _____ Sig _____
369619	NovoLog® Mix 70/30 FlexPen® (5x3 mL) **	Max. dose per day _____ Sig _____

**Novolin® (human insulin [rDNA origin])**

183311	Novolin® R Vials	Max. dose per day _____ Sig _____
183411	Novolin® N Vials	Max. dose per day _____ Sig _____
183711	Novolin® 70/30 Vials	Max. dose per day _____ Sig _____

**NovoFine® Disposable Needles**

185250	NovoFine® 30G Disposable Needles (100/box)	Qty (boxes) _____ Use as Directed
185189	NovoFine® 32G Tip (100/box)	Qty (boxes) _____ Use as Directed

**Victoza® (liraglutide [rDNA origin] injection) Please see enclosed Important Safety Information, Prescribing Information, and Medication Guide for Victoza®**

402012	Victoza® 6mg/ml 2 x 3ml **	Max. dose per day _____ Sig _____
406013	Victoza® 6mg/ml 3 x 3ml **	Max. dose per day _____ Sig _____

**GlucaGen® HypoKit® (glucagon [rDNA origin] for injection)**

706515	GlucaGen® HypoKit®	Qty (kits) _____ Sig _____
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**\*\* This item is used with NovoFine® disposable needles. Needles will NOT be sent if not requested.**



**SECTION 3.0: Licensed Healthcare Practitioner Certification**

My signature certifies that I am a licensed practitioner eligible under state law to prescribe, receive and dispense the requested medication(s) listed on this application, shipped from Novo Nordisk. I further certify all information provided in sections 2.0 and 2.1 are correct and agree to submit appropriate verification of such information upon Novo Nordisk's reasonable request. I agree that medication(s) provided to me by Novo Nordisk pursuant to prescriptions provided by me for the applicant named in Section 1.0 will be provided by me to such eligible applicant for his or her own use without charge. I will not otherwise use any of such medications or prescribe, provide or dispense all or any portion thereof for the use of any other person. I consent that Novo Nordisk may contact the applicant named in Section 1.0 for verification of applicant status and receipt of the indicated medication(s). I further consent that Novo Nordisk may perform an on-site audit of PAP records related to the applicant named in Section 1.0 of this application. I understand that I am not eligible to seek reimbursement for any medication dispensed by Novo Nordisk PAP from any government program or third party insurer and will not apply any Novo Nordisk PAP medication towards the applicant's TrOOP. I also understand that eligibility under the PAP is subject to Novo Nordisk's discretion and the Novo Nordisk reserves the right to modify or terminate the PAP at any time.

Practitioner's signature: \_\_\_\_\_ Date: \_\_\_\_\_  
(No photocopies or stamp signature)

**SECTION 3.1: Patient Certification**

I certify that I do not have the ability to pay for the medication(s) requested by my licensed healthcare practitioner in Section 2.2 of this application and all information provided in section 1.0, 1.1, and 1.2 is correct. I understand that Novo Nordisk Patient Assistance Program is entitled at any time to request verification of any such information which I agree to provide. I consent that Novo Nordisk PAP may contact me for verification of my application status and receipt of the indicated medication(s). I understand that if approved, I am not eligible to seek reimbursement for any medication requested in Section 2.2 of this application from any government program or third party insurer. I understand eligibility under the Novo Nordisk PAP is subject to Novo Nordisk's discretion and that Novo Nordisk reserves the right to modify or terminate the PAP at any time.

**HIPAA AUTHORIZATION**

I authorize my physician to provide Protected Health Information ("PHI") (as such term is defined in the Health Insurance Portability and Accountability Act and regulations there under, "HIPAA", as well as other state or federally protected personal information), to Novo Nordisk PAP or third parties engaged, as required to assist Novo Nordisk in administering the Novo Nordisk PAP. I authorize Novo Nordisk PAP to disclose my PHI to Centers for Medicare and Medicaid Services ("CMS") for the purpose of verifying my Medicare Part D enrollment status and disclosing my enrollment in Novo Nordisk PAP to my Medicare Part D plan (if applicable). I understand that my PHI will consist of my name, address, social security number, income, prescription coverage, prescription for medication(s), financial documents and insurance records and will be used for purposes of determining my eligibility to participate in Novo Nordisk PAP and to ship appropriate medication(s) as prescribed by my licensed healthcare practitioner. I further understand that if my PHI is incomplete or completed PHI does not allow me to participate in the Novo Nordisk PAP that I may be notified of such by the Novo Nordisk PAP. I understand that upon the furnishing of my PHI to the Novo Nordisk PAP, my PHI will not be subject to all of the protections and safeguards provided by HIPAA or other federal and state privacy laws. This authorization will extend for as long as I participate in the PAP and will thereafter expire. I may revoke this authorization at any time by providing written notice to Novo Nordisk at the address set forth above. My revocation will become effective on the date my written notice is received and processed by the Novo Nordisk PAP and at such time I will no longer be qualified to receive medication assistance from the Novo Nordisk PAP. I understand that I have the right to receive a copy of this authorization from my physician. I understand that my physician will treat me even if I do not sign this form, but that I will not be able to participate in the program.

**OPT-IN**

I agree that the information I am providing may be used by Novo Nordisk, its affiliates or vendors to keep me informed about new products, services, special offers, or other opportunities that may be of interest to me, as they become available. THESE COMMUNICATIONS MAY CONTAIN MATERIAL MARKETING OR ADVERTISING NOVO NORDISK PRODUCTS, GOODS OR SERVICES. Novo Nordisk will take appropriate measures to protect my information. I can stop Novo Nordisk from sending me future communications by calling 1-877-744-2579, sending a brief note with my name and address to Novo Nordisk at 100 College Road West, Princeton, New Jersey 08540, or by clicking on the "unsubscribe" link which will be available in future email communications. By providing my information to Novo Nordisk and acknowledging below, I certify that I am at least eighteen (18) years of age.

Patient or Legal Guardian's signature: \_\_\_\_\_ Date: \_\_\_\_\_  
(No photocopies or power of attorney signature)

**SECTION 3.2: Medicare Part D Enrollee Certification**

I understand that if I am approved for the Novo Nordisk PAP, I will receive a three-month (3-month) supply of medication(s) and/or device(s) from the Novo Nordisk PAP. I understand that I will continue to be approved to receive subsequent three-month supplies of medication(s) through the end of the current calendar year by submitting a new application, regardless of whether I no longer meet the eligibility criteria for the Novo Nordisk PAP for that calendar year subsequent to my initial application. I agree that I will not seek the requested Novo Nordisk medication(s) from my Medicare Part D prescription plan while receiving the medication(s) from the Novo Nordisk PAP. I understand that I am not eligible to seek reimbursement for any medication dispensed by the Novo Nordisk PAP from any government program or third party insurer and will not apply any Novo Nordisk PAP medication(s) towards True-Out-Of-Pocket ("TrOOP) costs.

Patient or Legal Guardian's signature: \_\_\_\_\_ Date: \_\_\_\_\_  
(No photocopies or power of attorney signature)



Victoza® (liraglutide [rDNA origin] injection)  
**Important Safety Information**

**Indications and Usage:**

Victoza® is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes when used along with diet and exercise.

Victoza® is not recommended as the first medication to treat diabetes. Victoza® is not insulin and has not been studied in combination with insulin. Victoza® is not for 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.

**Important Safety Information:**

**In animal studies, Victoza® caused thyroid tumors—including thyroid cancer—in some rats and mice. It is not known whether Victoza® causes thyroid tumors or a type of thyroid cancer called medullary thyroid cancer (MTC) in people which may be fatal if not detected and treated early. Do not use Victoza® if you or any of your family members have a history of MTC or if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). While taking Victoza®, tell your doctor if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer.**

Inflammation of the pancreas (pancreatitis) may be severe and lead to death. Before taking Victoza®, tell your doctor if you have had pancreatitis, gallstones, a history of alcoholism, or high blood triglyceride levels since these medical conditions make you more likely to get pancreatitis.

Stop taking Victoza® and call your doctor right away if you have pain in your stomach area that is severe and will not go away, occurs with or without vomiting, or is felt going from your stomach area through to your back. These may be symptoms of pancreatitis.

Before using Victoza®, tell your doctor about all the medicines you take, especially sulfonylurea medicines or insulin, as taking them with Victoza® may affect how each medicine works.

Also tell your doctor if you are allergic to any of the ingredients in Victoza®; have severe stomach problems 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. Tell your doctor if you are breastfeeding or plan to breastfeed. It is unknown if Victoza® will harm your unborn baby or if Victoza® passes into your breast milk.

Your risk for getting hypoglycemia, or low blood sugar, is higher if you take Victoza® with another medicine that can cause low blood sugar, such as a sulfonylurea. The dose of your sulfonylurea medicine may need to be lowered while taking Victoza®.

The most common side effects with Victoza® include headache, nausea, diarrhea, and resistance to liraglutide (antibody formation). Nausea is most common when first starting

**Please see accompanying Prescribing Information and Medication Guide**

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Victoza® , but decreases over time in most people. Immune system related reactions, including hives, were more common in people treated with Victoza® compared to people treated with other diabetes drugs in medical studies.

**Please see accompanying Prescribing Information and Medication Guide**

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# VICTOZA<sup>®</sup>

liraglutide (rDNA origin) injection

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**Victoza<sup>®</sup> (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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, 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 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<sup>®</sup>-treated patients than among comparator-treated patients. If pancreatitis is suspected, Victoza<sup>®</sup> and other potentially suspect drugs should be discontinued. Victoza<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> or any other antidiabetic drug (5.4).

## ADVERSE REACTIONS

- The most common adverse reactions, reported in  $\geq 5\%$  of patients treated with Victoza<sup>®</sup> 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<sup>®</sup>-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](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

- Victoza<sup>®</sup> 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 FDA-Approved Medication Guide.

Revised: 1/2010

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## FULL PRESCRIBING INFORMATION

### WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications (4)*, *Warnings and Precautions (5.1)* and *Nonclinical Toxicology (13.1)*].

## 1 INDICATIONS AND USAGE

Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

### 1.1 Important Limitations of Use

- Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. Victoza® has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza®. Use with caution in patients with a history of pancreatitis.
- Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the 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-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies [see *Boxed Warning, Contraindications (4)*].

In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 patient-years). One additional case of thyroid C-cell hyperplasia in a Victoza®-treated patient and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Four of the five liraglutide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liraglutide and one non-liraglutide-treated patient developed elevated calcitonin concentrations while on treatment.

Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~ 1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo 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 pre-treatment 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 pre-treatment 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 death; however clinical causality could not be established. One additional case of pancreatitis has subsequently been reported in a Victoza®-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza® treatment. After initiation of Victoza®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Use with caution in patients with a history of pancreatitis.

## 5.3 Use with Medications Known to Cause Hypoglycemia

Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of 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 and in no comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea or other insulin secretagogues [see *Adverse Reactions (6.1)*].

## 5.4 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Victoza® was evaluated in a 52-week monotherapy trial and in four 26-week, add-on combination therapy trials. In the monotherapy trial, patients were treated with Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, or glimepiride 8 mg daily. In the add-on to metformin trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or glimepiride 4 mg. In the add-on to glimepiride trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or rosiglitazone 4 mg. In the add-on to metformin + glimepiride trial, 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
<b>Adverse Event Term</b>	(%)	(%)
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
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

**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**

<b>Add-on to Metformin Trial</b>			
	All Victoza® + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
<b>Adverse Event Term</b>	(%)	(%)	(%)
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
<b>Add-on to Glimepiride Trial</b>			
	All Victoza® + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
<b>Adverse Event Term</b>	(%)	(%)	(%)
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
<b>Add-on to Metformin + Glimepiride</b>			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
<b>Adverse Event Term</b>	(%)	(%)	(%)
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
<b>Add-on to Metformin + Rosiglitazone</b>			
	All Victoza® + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175	
<b>Adverse Event Term</b>	(%)	(%)	
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	

**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<sub>1c</sub> 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<sub>1c</sub> 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 carcinomas 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 sulfonylurea. 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).

**Table 3: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials**

	Victoza® Treatment (N = 497)	Active Comparator Glimepiride (N = 248)	Placebo Comparator None
<b>Monotherapy</b>	Victoza® (N = 497)	Glimepiride (N = 248)	None
Patient not able to self-treat	0	0	—
Patient able to self-treat	9.7 (0.24)	25.0 (1.66)	—
Not classified	1.2 (0.03)	2.4 (0.04)	—
<b>Add-on to Metformin</b>	Victoza® + Metformin (N=724)	Glimepiride + Metformin (N=242)	Placebo + Metformin (N=121)
Patient not able to self-treat	0.1 (0.001)	0	0
Patient able to self-treat	3.6 (0.05)	22.3 (0.87)	2.5 (0.06)
<b>Add-on to Glimepiride</b>	Victoza® + Glimepiride (N = 695)	Rosiglitazone + Glimepiride (N = 231)	Placebo + Glimepiride (N = 114)
Patient not able to self-treat	0.1 (0.003)	0	0
Patient able to self-treat	7.5 (0.38)	4.3 (0.12)	2.6 (0.17)
Not classified	0.9 (0.05)	0.9 (0.02)	0
<b>Add-on to Metformin + Rosiglitazone</b>	Victoza® + Metformin + Rosiglitazone (N = 355)	None	Placebo + Metformin + Rosiglitazone (N = 175)
Patient not able to self-treat	0	—	0
Patient able to self-treat	7.9 (0.49)	—	4.6 (0.15)
Not classified	0.6 (0.01)	—	1.1 (0.03)
<b>Add-on to Metformin + Glimepiride</b>	Victoza® + Metformin + Glimepiride (N = 230)	Insulin glargine + Metformin + Glimepiride (N = 232)	Placebo + Metformin + Glimepiride (N = 114)
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

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 (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established.

**Laboratory Tests**

In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

**7 DRUG INTERACTIONS**

**7.1 Oral Medications**

Victoza® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, Victoza® did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with Victoza®.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of Victoza® in pregnant women. Victoza® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Liraglutide has been shown to be teratogenic in rats at or above 0.8 times the human systemic exposures resulting from the maximum recommended human dose (MRHD) of 1.8 mg/day based on plasma area under the time-concentration curve (AUC). Liraglutide has been shown to cause reduced growth and increased total major abnormalities in rabbits at systemic exposures below human exposure at the MRHD based on plasma AUC.

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The 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),  $\geq 0.01$  mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus),  $\geq 0.025$  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. Visceral 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 24, 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<sub>2</sub> generation rats descended from liraglutide-treated rats compared to F<sub>2</sub> 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 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 overdosage, 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<sub>172</sub>H<sub>265</sub>N<sub>43</sub>O<sub>51</sub> and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:

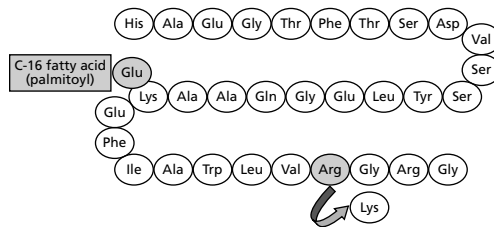


Figure 1: Structural Formula of liraglutide

Victoza® is a clear, colorless 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, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, G<sub>s</sub>, 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<sub>0-300min</sub> 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).

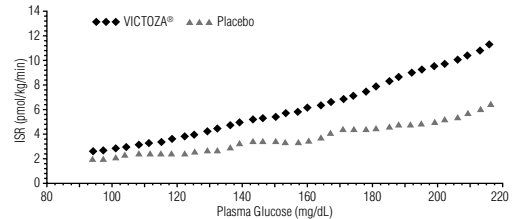


Figure 2: Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose Victoza® 7.5 mcg/kg (~0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion

#### 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.

### 12.3 Pharmacokinetics

**Absorption** - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak (C<sub>max</sub>) 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<sub>max</sub> 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<sub>0-∞</sub> was equivalent between upper arm and abdomen, and between upper arm and thigh. AUC<sub>0-∞</sub> 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 [<sup>3</sup>H]-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 [<sup>3</sup>H]-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 elimination 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 30% 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<sub>max</sub> 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<sub>max</sub> decreased by 31%. Digoxin median time to maximal concentration (T<sub>max</sub>) 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<sub>max</sub> decreased by 27%. Lisinopril median T<sub>max</sub> 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<sub>max</sub> was decreased by 38% and median T<sub>max</sub> 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<sub>max</sub> was decreased by 31% and median T<sub>max</sub> 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<sub>max</sub> increased by 37% while median T<sub>max</sub> 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<sub>max</sub> by 12% and 13%, respectively. There was no effect of Victoza® on the overall exposure (AUC) of ethinylestradiol. Victoza® increased the levonorgestrel AUC<sub>0-∞</sub> by 18%. Victoza® delayed T<sub>max</sub> for both ethinylestradiol and levonorgestrel by 1.5 h.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenicity, Mutagenicity, 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 the 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 gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1.0 mg/kg/day, a high dose yielding an estimated systemic exposure 11- times the human exposure at the MRHD, based on plasma AUC. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1.0 mg/kg/day dose.

## 14 CLINICAL STUDIES

A total of 3978 patients with type 2 diabetes participated in 5 double-blind (one of these trials had an open-label active control insulin glargine arm), randomized, controlled clinical trials, one of 52 weeks duration and four of 26 weeks duration. These multi-

national trials were conducted to evaluate the glycemic efficacy and safety of Victoza® in type 2 diabetes as monotherapy and in combination with one or two oral anti-diabetic medications. The 4 add-on combination therapy trials enrolled patients who were previously treated with anti-diabetic therapy, and approximately two-thirds of patients in the monotherapy trial also were previously treated with anti-diabetic therapy. In total, 272 (7%) of the 3978 patients in these 5 trials were new to anti-diabetic therapy. In these 5 clinical trials, patients ranged in age from 19-80 years old and 54% were men. Approximately 77% of patients were Caucasian, and 6% were Black. In the 2 trials where ethnicity was captured, 27% of patients were Hispanic/Latino and 73% were Non-Hispanic/Latino. In each of these trials, treatment with Victoza® produced clinically and statistically significant improvements in hemoglobin A<sub>1c</sub> and fasting plasma glucose (FPG) compared to placebo. Victoza® did not have adverse effects on blood pressure.

All Victoza®-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. Victoza® 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance [see Dosage and Administration (2)].

### 14.1 Monotherapy

In this 52-week trial, 746 patients were randomized to Victoza® 1.2 mg, Victoza® 1.8 mg, or glimepiride 8 mg. Patients who were randomized to glimepiride were initially treated with 2 mg daily for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily. Treatment with Victoza® 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA<sub>1c</sub> compared to glimepiride (Table 4). The percentage of patients who discontinued due to ineffective therapy was 3.6% in the Victoza® 1.8 mg treatment group, 6.0% in the Victoza® 1.2 mg treatment group, and 10.1% in the glimepiride-treatment group.

Table 4: Results of a 52-week monotherapy trial<sup>a</sup>

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

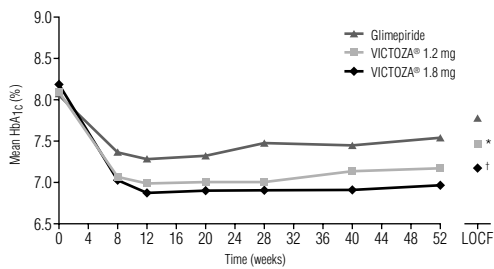
<sup>a</sup>Intent-to-treat population using last observation on study

<sup>b</sup>Least squares mean adjusted for baseline value

\*p-value < 0.05

\*\*p-value < 0.0001





\*p-value = 0.0014 for VICTOZA® 1.2 mg compared to glimepiride  
 †p-value < 0.0001 for VICTOZA® 1.8 mg compared to glimepiride  
 P values derived from change from baseline ANCOVA model.

**Figure 3: Mean HbA<sub>1c</sub> 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<sub>1c</sub> reduction relative to placebo add-on to metformin and resulted in a similar mean HbA<sub>1c</sub> 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.

**Table 5: Results of a 26-week trial of Victoza® as add-on to metformin<sup>a</sup>**

	Victoza® 1.8 mg + Metformin	Victoza® 1.2 mg + Metformin	Placebo + Metformin	Glimepiride 4 mg <sup>†</sup> + Metformin
<b>Intent-to-Treat Population (N)</b>	242	240	121	242
<b>HbA<sub>1c</sub> (%) (Mean)</b>				
Baseline	8.4	8.3	8.4	8.4
Change from baseline (adjusted mean) <sup>b</sup>	-1.0	-1.0	+0.1	-1.0
Difference from placebo + metformin arm (adjusted mean) <sup>b</sup>	-1.1**	-1.1**		
95% Confidence Interval	(-1.3, -0.9)	(-1.3, -0.9)		
Difference from glimepiride + metformin arm (adjusted mean) <sup>b</sup>	0.0	0.0		
95% Confidence Interval	(-0.2, 0.2)	(-0.2, 0.2)		
Patients (%) achieving A <sub>1c</sub> <7%	42	35	11	36
<b>Fasting Plasma Glucose (mg/dL) (Mean)</b>				
Baseline	181	179	182	180
Change from baseline (adjusted mean) <sup>b</sup>	-30	-30	+7	-24
Difference from placebo + metformin arm (adjusted mean) <sup>b</sup>	-38**	-37**		
95% Confidence Interval	(-48, -27)	(-47, -26)		
Difference from glimepiride + metformin arm (adjusted mean) <sup>b</sup>	-7	-6		
95% Confidence Interval	(-16, 2)	(-15, 3)		
<b>Body Weight (kg) (Mean)</b>				
Baseline	88.0	88.5	91.0	89.0
Change from baseline (adjusted mean) <sup>b</sup>	-2.8	-2.6	-1.5	+1.0
Difference from placebo + metformin arm (adjusted mean) <sup>b</sup>	-1.3*	-1.1*		
95% Confidence Interval	(-2.2, -0.4)	(-2.0, -0.2)		
Difference from glimepiride + metformin arm (adjusted mean) <sup>b</sup>	-3.8**	-3.5**		
95% Confidence Interval	(-4.5, -3.0)	(-4.3, -2.8)		

<sup>a</sup>Intent-to-treat population using last observation on study

<sup>b</sup>Least squares mean adjusted for baseline value

<sup>†</sup>For glimepiride, one-half of the maximal approved United States dose.

\*p-value < 0.05

\*\*p-value < 0.0001

### 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 rosiglitazone 4 mg (one-half of the maximal approved dose in the United States), 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 to 4 mg/day. The doses of glimepiride could be reduced (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<sub>1c</sub> 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.

**Table 6: Results of a 26-week trial of Victoza® as add-on to sulfonylurea<sup>a</sup>**

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

<sup>a</sup>Intent-to-treat population using last observation on study

<sup>b</sup>Least squares mean adjusted for baseline value

<sup>†</sup>For rosiglitazone, one-half of the maximal approved United States dose.

\*\*p-value < 0.0001

### 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<sub>1c</sub> 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.

**Table 7: Results of a 26-week trial of Victoza® as add-on to metformin and sulfonylurea<sup>a</sup>**

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

<sup>a</sup>Intent-to-treat population using last observation on study

<sup>b</sup>Least squares mean adjusted for baseline value

<sup>†</sup>For insulin glargine, optimal titration regimen was not achieved for 80% of patients.

\*p-value < 0.05

\*\*p-value < 0.0001

*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<sub>1c</sub> 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.

**Table 8: Results of a 26-week trial of Victoza® as add-on to metformin and thiazolidinedione<sup>a</sup>**

	Victoza® 1.8 mg + Metformin + Rosiglitazone	Victoza® 1.2 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
<b>Intent-to-Treat Population (N)</b>	178	177	175
<b>HbA<sub>1c</sub> (%) (Mean)</b>			
Baseline	8.6	8.5	8.4
Change from baseline (adjusted mean) <sup>b</sup>	-1.5	-1.5	-0.5
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) <sup>b</sup>	-0.9**	-0.9**	
95% Confidence Interval	(-1.1, -0.8)	(-1.1, -0.8)	
Patients (%) achieving A <sub>1c</sub> <7%	54	57	28
<b>Fasting Plasma Glucose (mg/dL) (Mean)</b>			
Baseline	185	181	179
Change from baseline (adjusted mean) <sup>b</sup>	-44	-40	-8
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) <sup>b</sup>	-36**	-32**	
95% Confidence Interval	(-44, -27)	(-41, -23)	
<b>Body Weight (kg) (Mean)</b>			
Baseline	94.9	95.3	98.5
Change from baseline (adjusted mean) <sup>b</sup>	-2.0	-1.0	+0.6
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) <sup>b</sup>	-2.6**	-1.6**	
95% Confidence Interval	(-3.4, -1.8)	(-2.4, -1.0)	

<sup>a</sup>Intent-to-treat population using last observation on study

<sup>b</sup>Least squares mean adjusted for baseline value

\*\*p-value < 0.0001

**16 HOW SUPPLIED/STORAGE 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 x Victoza® pen NDC 0169-4060-12

3 x 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 the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Victoza® and do not use Victoza® if it has been frozen.

After initial use of the Victoza® pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Victoza® should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Victoza® pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy.

**Table 9: Recommended Storage Conditions for the Victoza® Pen**

Prior to first use	After first use	
Refrigerated 36°F to 46°F (2°C to 8°C)	Room Temperature 59°F to 86°F (15°C to 30°C)	Refrigerated 36°F to 46°F (2°C to 8°C)
Until expiration date	30 days	

**17 PATIENT COUNSELING INFORMATION**

**17.1 Risk of Thyroid C-cell Tumors**

Patients should be informed that liraglutide causes benign and malignant thyroid C-cell tumors in mice and rats and that the human relevance of this finding is unknown. Patients should be counseled to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia or dyspnea) to their physician.

**17.2 Pancreatitis**

Patients should be informed that persistent severe abdominal pain, that may radiate to the back and which may (or may not) be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to discontinue Victoza® promptly, and to contact their physician, if persistent severe abdominal pain occurs [see Warnings and Precautions (5.2)].

**17.3 Never Share a Victoza® Pen Between Patients**

Counsel patients that they should never share a Victoza® pen with another person, even if the needle is changed. Sharing 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<sub>1c</sub> 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 reread 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<sub>1c</sub> levels, with a goal of decreasing these levels towards the normal range. A<sub>1c</sub> is especially useful for evaluating long-term glycemic control.

**17.6 FDA-Approved Medication Guide**

See separate leaflet.



**Rx only**

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.*

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140494-R1 4/2010

