

Request for permission for oral testimony at Idaho
Medicaid's P&T Committee meeting on 05-11-2012

Submission # 2

As of April 26, 2012, this request has been:

- Approved
- Denied

Request for permission for oral testimony at Idaho
Medicaid's P&T Committee meeting on 05-11-2012

Submission # 2

As of April 23, 2012, this request has not been
reviewed yet.

Gennrich, Jane - Medicaid

From: Eide, Tamara J. - Medicaid
Sent: Thursday, April 19, 2012 3:32 PM
To: Gennrich, Jane - Medicaid
Subject: FW: Your Request for Medical Information from Novo Nordisk Inc. is Attached
Attachments: Your Novo Nordisk Response #2012-003866.pdf; 19145.pdf; 19032.pdf

Tami Eide, Pharm.D., BCPS

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Idaho Department of Health and Welfare
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From: NNI Medical Information [<mailto:NNIDrugInformation@novonordisk.com>]
Sent: Thursday, April 19, 2012 2:49 PM
To: Eide, Tamara J. - Medicaid
Subject: Your Request for Medical Information from Novo Nordisk Inc. is Attached

Thank you for contacting Novo Nordisk Inc. Attached is the product information you requested. If you have further questions, call toll free 800-727-6500. THIS MAILBOX IS NOT MONITORED SO REPLIES WILL NOT BE PROCESSED.

Medical Information Department
Novo Nordisk Inc.

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E-MAIL TRANSMISSION

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TO: Tami Eide, PharmD

FROM: Medical Information, Novo Nordisk Inc.

DATE: April 19, 2012



April 19, 2012

Tami Eide, PharmD
3232 Elder Street
Boise, ID 83701

Dear Dr. Eide:

Our Novo Nordisk Medical Liaison, Coleen Fong, PharmD, has asked me to submit additional information about Victoza® (liraglutide [rDNA origin] injection) for consideration by the Idaho State Medicaid Pharmacy & Therapeutics Committee. Please pass the enclosed information along to the Chair of the Medicaid Pharmacy unit.

These data were recently added to the Victoza® prescribing information on April 6, 2012.

Adding-on Levemir® to Victoza® and Metformin: 26-Week Data

Novo Nordisk sponsored a Phase 3b study evaluating the efficacy and safety of adding-on Levemir® to Victoza® and metformin in insulin-naïve adult patients with type 2 diabetes. The trial consisted of a 12-week run-in period with Victoza® 1.8 mg and metformin followed by a 26-week randomized, parallel-group period for patients not achieving A1C<7%. At the end of the run-in period, patients with an A1C \geq 7% were randomized to continue Victoza® in combination with metformin (n=161) or intensified with Levemir® starting at 10 units/day (n=162). Those patients achieving an A1C of <7% at the end of the run-in period could continue on Victoza® plus metformin for an additional 26 weeks as the observational (non-randomized) group to assess durability of response and safety. The primary endpoint was the change in A1C from randomization (Week 0) to Week 26.¹

Randomized Period (Weeks 0 to 26)¹

- Mean prescribed doses of Levemir® increased from 10 units to 39.5 units/day by Week 26.
- Addition of Levemir® further reduced mean A1C following randomization compared to continued treatment with Victoza® and metformin (-0.5% vs 0%; $P<.0001$) from baselines of 7.6%.
- More than twice as many patients achieved A1C <7% following the addition of Levemir® compared to the control group (43% vs 17%).
- Mean FPG also decreased more in the group of patients treated with Levemir® compared to the control group (-39 mg/dL vs -9 mg/dL; $P<.0001$).
- From a mean baseline body weight of 211.2 lb after randomization, there was a mean reduction of 0.7 lb in the patients who received Levemir® add-on therapy compared to a mean reduction of 2.4 lb in the patients who continued on unchanged treatment with Victoza® 1.8 mg +metformin alone.

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- There were no major hypoglycemic events during the randomized portion of the trial.
- Excluding one outlier with 25 minor hypoglycemic episodes in the Victoza® plus metformin group, rates of minor hypoglycemia per patient-year were 0.29 and 0.03 in the randomized treatment groups with or without insulin, respectively.
- During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with Victoza® 1.8 mg and Levemir® (11.7%) and greater than in patients treated with Victoza® 1.8 mg and metformin alone (6.9%).

The above information is supplied to you as a professional service in response to your specific request. A copy of the prescribing information for Victoza®, which includes a boxed warning, is enclosed for your convenience. Novo Nordisk does not recommend use of its products in any manner other than as described in the prescribing information.

About Victoza®

Victoza® is a once-daily human glucagon-like peptide-1 (GLP-1) analog with 97% homology to native GLP-1. The differences in the structure of Victoza® compared to native GLP-1 are substitution of arginine for lysine, at position 34, and addition of palmitic acid, a 16-carbon (C16) fatty acid, via a glutamic acid spacer at position 26. Victoza® activates the GLP-1 receptor on pancreatic beta-cells, stimulating insulin secretion in a glucose-dependent manner. Victoza® also decreases glucagon secretion in a glucose-dependent manner. The mechanism of postprandial blood glucose lowering also involves a delay in gastric emptying.

Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Victoza® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).** Enclosed please see the Important Limitations of Use Section in the prescribing information and the attached Medication Guide. The most common adverse effects of Victoza® are gastrointestinal related, including nausea, vomiting, and diarrhea. Additional information may be found at victoza.com.

If you did not request this information from your Novo Nordisk representative or the information provided does not address your specific question, please contact Novo Nordisk Medical Information at (800) 727-6500.

Sincerely,

Jane S. Oreper, PharmD
Principal Medical Information Scientist

JVOR/rbrr 3866

cc: Coleen Fong, PharmD

Enc: Package Insert - Victoza®
Package Insert - Levemir®

Tami Eide, PharmD
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Page 3

References

1. Victoza® [package insert]. Princeton, NJ: Novo Nordisk Inc.; April 2012.

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).

.....**RECENT MAJOR CHANGES**.....

Indications and Usage: Important Limitations of Use (1.1)	04/2012
Dosage and Administration	04/2012
Contraindications	04/2012
Warnings and Precautions: Serious hypersensitivity (5.5)	04/2012
Warnings and Precautions: Renal Impairment (5.4)	05/2011

.....**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).
- Limited data in patients with a history of pancreatitis. (5.2).
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with prandial 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).

.....**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).

Do not use if history of serious hypersensitivity to Victoza or any product components (4).

.....**WARNINGS AND PRECAUTIONS**.....

- Thyroid C-cell tumors in animals: 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) or insulin. Consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia (5.3).
- Renal Impairment: Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza in patients with renal impairment (5.4).
- Hypersensitivity: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). The patient should discontinue Victoza and other suspect medications and promptly seek medical advice (5.5).
- Macrovascular outcomes: There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza or any other antidiabetic drug (5.6).

.....**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**.....

- Limited data in patients with renal or hepatic impairment. (8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.

Revised: 04/2012

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

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*Sections or subsections omitted from the full prescribing information are not listed.

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 prandial 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)*].

When using Victoza with insulin, administer as separate injections. Never mix. It is acceptable to inject Victoza and insulin in the same body region but the injections should not be adjacent to each other.

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.

If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. An extra dose or increase in dose should not be taken to make-up for the missed dose.

Based on the elimination half-life, patients should be advised to reinitiate Victoza at 0.6 mg if more than 3 days have elapsed since the last Victoza dose. This approach will mitigate any gastrointestinal symptoms associated with reinitiation of treatment. Upon reinitiation, Victoza should be titrated at the discretion of the prescribing healthcare provider.

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

Do not use 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).

Do not use in patients with a prior serious hypersensitivity reaction to Victoza or to any of the product components.

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 6 reported cases of thyroid C-cell hyperplasia among Victoza-treated patients and 2 cases in comparator-treated patients (1.3 vs. 1.0 cases per 1000 patient-years). One 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. Five of

the six Victoza-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One Victoza and one non-Victoza-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 have been 13 cases of pancreatitis among Victoza-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with Victoza were reported as acute pancreatitis and four 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. 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) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin [see *Adverse Reactions (6.1)*].

5.4 Renal Impairment

Victoza has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza-treated patients [see *Adverse Reactions (6.2)*]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration [see *Adverse Reactions (6.1)*]. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza. Use caution when initiating or escalating doses of Victoza in patients with renal impairment [see *Use in Specific Populations (8.6)*].

5.5 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza. If a hypersensitivity reaction occurs, the patient should discontinue Victoza and other suspect medications and promptly seek medical advice.

Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza.

5.6 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 has been evaluated in 8 clinical trials [see *Clinical Studies (14)*]:

- A double-blind 52-week monotherapy trial compared Victoza 1.2 mg daily, Victoza 1.8 mg daily, and glimepiride 8 mg daily.
- A double-blind 26 week add-on to metformin trial compared Victoza 0.6 mg once-daily, Victoza 1.2 mg once-daily, Victoza 1.8 mg once-daily, placebo, and glimepiride 4 mg once-daily.
- A double-blind 26 week add-on to glimepiride trial compared Victoza 0.6 mg daily, Victoza 1.2 mg once-daily, Victoza 1.8 mg once-daily, placebo, and rosiglitazone 4 mg once-daily.
- A 26 week add-on to metformin + glimepiride trial, compared double-blind Victoza 1.8 mg once-daily, double-blind placebo, and open-label insulin glargine once-daily.
- A double-blind 26-week add-on to metformin + rosiglitazone trial compared Victoza 1.2 mg once-daily, Victoza 1.8 mg once-daily and placebo.
- An open-label 26-week add-on to metformin and/or sulfonylurea trial compared Victoza 1.8 mg once-daily and exenatide 10 mcg twice-daily.
- An open-label 26-week add-on to metformin trial compared Victoza 1.2 mg once-daily, Victoza 1.8 mg once-daily, and sitagliptin 100 mg once-daily.
- An open-label 26-week trial compared insulin detemir as add-on to Victoza 1.8 mg + metformin to continued treatment with Victoza + metformin alone.

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 double-blind 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. In these five trials, 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.

Common adverse reactions

Tables 1, 2, 3 and 4 summarize common adverse reactions (hypoglycemia is discussed separately) reported in seven of the eight controlled trials of 26 weeks duration or longer. Most of these adverse reactions were gastrointestinal in nature.

In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred at a higher incidence among Victoza-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation.

In the five double-blind and three open-label clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. In the five double-blind trials approximately 13% of Victoza-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment.

In the 26-week open-label trial comparing Victoza to exenatide, both in combination with metformin and/or sulfonylurea, gastrointestinal adverse reactions were reported at a similar incidence in the Victoza and exenatide treatment groups (Table 3).

In the 26-week open-label trial comparing Victoza 1.2 mg, Victoza 1.8 mg and sitagliptin 100 mg, all in combination with metformin, gastrointestinal adverse reactions were reported at a higher incidence with Victoza than sitagliptin (Table 4).

In the remaining 26-week trial, all patients received Victoza 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with insulin detemir or continued, unchanged treatment with Victoza 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in $\geq 5\%$ of patients treated with Victoza 1.8 mg + metformin + insulin detemir (11.7%) and greater than in patients treated with Victoza 1.8 mg and metformin alone (6.9%).

Table 1 Adverse reactions reported in $\geq 5\%$ of Victoza-treated patients in a 52-week monotherapy trial

	All Victoza N = 497	Glimepiride N = 248
Adverse Reaction	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Headache	9.1	9.3

Table 2 Adverse reactions reported in $\geq 5\%$ 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 Reaction	(%)	(%)	(%)
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 Reaction	(%)	(%)	(%)
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 Reaction	(%)	(%)	(%)
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 Reaction	(%)	(%)	
Nausea	34.6	8.6	
Diarrhea	14.1	6.3	
Vomiting	12.4	2.9	
Headache	8.2	4.6	
Constipation	5.1	1.1	

Table 3 Adverse Reactions reported in $\geq 5\%$ of Victoza-treated patients in a 26-Week Open-Label Trial versus Exenatide

	Victoza 1.8 mg once daily + metformin and/or sulfonylurea N = 235	Exenatide 10 mcg twice daily + metformin and/or sulfonylurea N = 232
Adverse Reaction	(%)	(%)
Nausea	25.5	28.0
Diarrhea	12.3	12.1
Headache	8.9	10.3
Dyspepsia	8.9	4.7
Vomiting	6.0	9.9
Constipation	5.1	2.6

Table 4 Adverse Reactions in $\geq 5\%$ of Victoza-treated patients in a 26-Week Open-Label Trial versus Sitagliptin

	All Victoza + metformin N = 439	Sitagliptin 100 mg/day + metformin N = 219
Adverse Reaction	(%)	(%)
Nausea	23.9	4.6
Headache	10.3	10.0
Diarrhea	9.3	4.6
Vomiting	8.7	4.1

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 double-blind 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 double-blind 52-week monotherapy trial and in 4.8% of the Victoza-treated patients in the double-blind 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 double-blind 52-week monotherapy trial and in 1.0% of the Victoza-treated patients in the double-blind 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 the five double-blind 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 double-blind 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 7 reported cases of papillary thyroid carcinoma in patients treated with Victoza and 1 case in a comparator-treated patient (1.5 vs. 0.5 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 eight clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 Victoza-treated patients (2.3 cases per 1000 patient-years) and in two exenatide-treated patients. Of these 11 Victoza-treated patients, six patients were concomitantly using metformin and a sulfonylurea, one was concomitantly using a sulfonylurea, two were concomitantly using metformin (blood glucose values were 65 and 94 mg/dL) and two were using Victoza as monotherapy (one of these patients was undergoing an intravenous glucose tolerance test and the other was receiving insulin as treatment during a hospital stay). For these two patients on Victoza monotherapy, the insulin treatment was the likely explanation for the hypoglycemia.

In the 26-week open-label trial comparing Victoza to sitagliptin, the incidence of hypoglycemic events defined as symptoms accompanied by a fingerstick glucose <56 mg/dL was comparable among the treatment groups (approximately 5%).

Table 5 Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza Treatment	Active Comparator	Placebo Comparator
Monotherapy	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)	-
Add-on to Metformin	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)
Add-on to Victoza + Metformin	Insulin detemir + Victoza + Metformin (N = 163)	Continued Victoza + Metformin alone (N = 158*)	None
Patient not able to self-treat	0	0	-
Patient able to self-treat	9.2 (0.29)	1.3 (0.03)	-
Add-on to Glimepiride	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
Add-on to Metformin + Rosiglitazone	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)
Add-on to Metformin + Glimepiride	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

* One patient is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study.

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.

Vital signs

Victoza did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established [see *Warnings and Precautions (5.6)*].

6.2 Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of Victoza. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Dehydration resulting from nausea, vomiting and diarrhea. [see *Warnings and Precautions (5.4) and Patient Counseling Information (17.3)*]
- Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis. [see *Warnings and Precautions (5.4) and Patient Counseling Information (17.3)*]
- Angioedema and anaphylactic reactions. [see *Contraindications (4), Warnings and Precautions (5.5), Patient counseling Information (17.5)*]

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), ≥ 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. 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 F₂ generation rats descended from liraglutide-treated rats compared to F₂ 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 with Victoza in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. However, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis [*see Warnings and Precautions (5.4) and Adverse Reactions (6.2)*]. 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 $C_{172}H_{265}N_{43}O_{51}$ 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, Gs, 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).

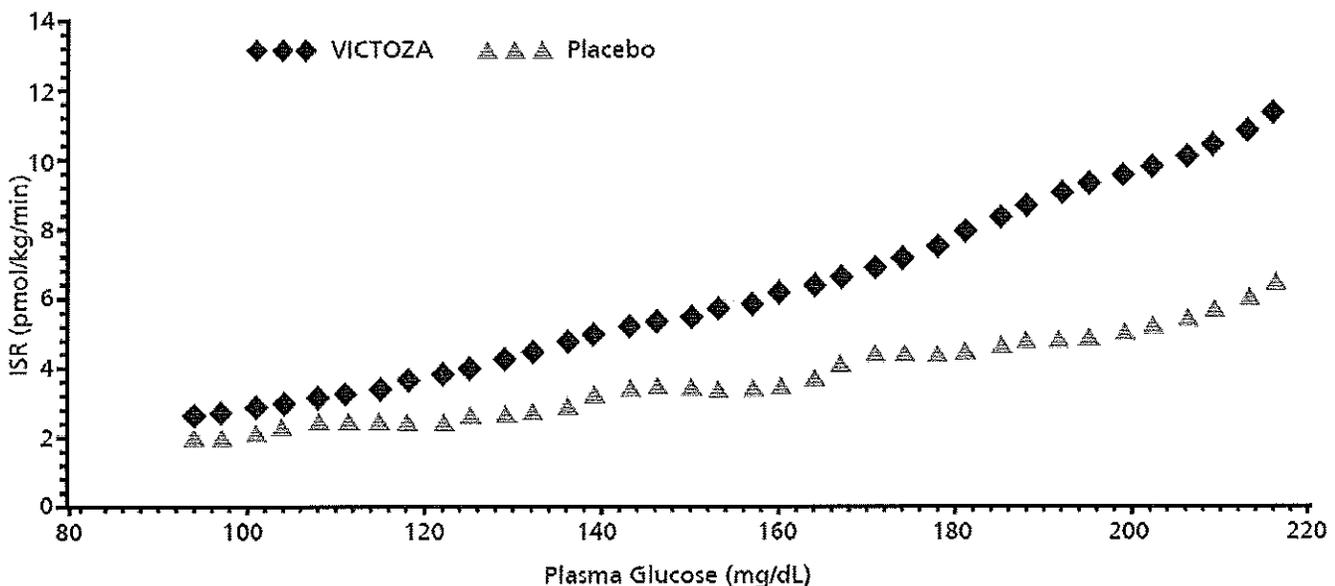


Figure 2 Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose Victoza 7.5 mcg/kg (~ 0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion

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_{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. $AUC_{0-\infty}$ was equivalent between upper arm and abdomen, and between upper arm and thigh. $AUC_{0-\infty}$ 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 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_{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%, respectively. There was no effect of Victoza on the overall exposure (AUC) of ethinylestradiol. Victoza increased the levonorgestrel $AUC_{0-\infty}$ by 18%. Victoza delayed T_{max} for both ethinylestradiol and levonorgestrel by 1.5 h.

Insulin Detemir

No pharmacokinetic interaction was observed between Victoza and insulin detemir when separate subcutaneous injections of insulin detemir 0.5 Unit/kg (single-dose) and Victoza 1.8 mg (steady state) were administered in patients with type 2 diabetes.

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 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 6090 patients with type 2 diabetes participated in 8 phase 3 trials. There were 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. There were also three 26 week open-label trials; one comparing Victoza to twice-daily exenatide, one comparing Victoza to sitagliptin and one comparing Victoza+metformin+insulin detemir to Victoza+metformin alone. These multinational 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 or insulin detemir. The 7 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 (4%) of the 6090 patients in these 8 trials were new to anti-diabetic therapy. In these 8 clinical trials, patients ranged in age from 18-80 years old and 54% were men. Approximately 82% of patients were Caucasian, and 6% were Black. In the 5 trials where ethnicity was captured, 10% of patients were Hispanic/Latino (n=630).

In each of the placebo controlled trials, treatment with Victoza produced clinically and statistically significant improvements in hemoglobin A_{1c} and fasting plasma glucose (FPG) compared to placebo.

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_{1c} compared to glimepiride (Table 6). 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 6 Results of a 52-week monotherapy trial^a

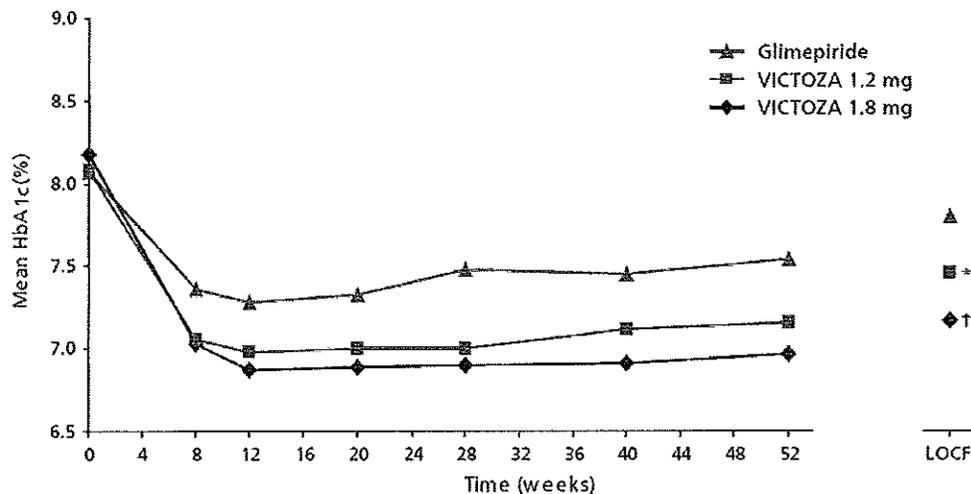
	Victoza 1.8 mg	Victoza 1.2 mg	Glimepiride 8 mg
Intent-to-Treat Population (N)	246	251	248
HbA_{1c} (%) (Mean)			
Baseline	8.2	8.2	8.2
Change from baseline (adjusted mean) ^b	-1.1	-0.8	-0.5
Difference from glimepiride arm (adjusted mean) ^b	-0.6**	-0.3*	
95% Confidence Interval	(-0.8, -0.4)	(-0.5, -0.1)	
Percentage of patients achieving A _{1c} <7%	51	43	28
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	172	168	172
Change from baseline (adjusted mean) ^b	-26	-15	-5
Difference from glimepiride arm (adjusted mean) ^b	-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) ^b	-2.5	-2.1	+1.1
Difference from glimepiride arm (adjusted mean) ^b	-3.6**	-3.2**	
95% Confidence Interval	(-4.3, -2.9)	(-3.9, -2.5)	

^aIntent-to-treat population using last observation on study

^bLeast 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_{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 7). 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 7 Results of a 26-week trial of Victoza as add-on to metformin^a

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

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

[†] For glimepiride, one-half of the maximal approved United States dose.

*p-value <0.05

**p-value <0.0001

Victoza Compared to Sitagliptin, Both as Add-on to Metformin

In this 26-week, open-label trial, 665 patients on a background of metformin ≥1500 mg per day were randomized to Victoza 1.2 mg once-daily, Victoza 1.8 mg once-daily or sitagliptin 100 mg once-daily, all dosed according to approved labeling. Patients were to continue their current treatment on metformin at a stable, pre-trial dose level and dosing frequency.

The primary endpoint was the change in HbA_{1c} from baseline to Week 26. Treatment with Victoza 1.2 mg and Victoza 1.8 mg resulted in statistically significant reductions in HbA_{1c} relative to sitagliptin 100 mg (Table 8). The percentage of patients who discontinued due to ineffective therapy was 3.1% in the Victoza 1.2 mg group, 0.5% in the Victoza 1.8 mg treatment group, and 4.1% in the sitagliptin 100 mg treatment group. From a mean baseline body weight of 94 kg, there was a mean reduction of 2.7 kg for Victoza 1.2 mg, 3.3 kg for Victoza 1.8 mg, and 0.8 kg for sitagliptin 100 mg.

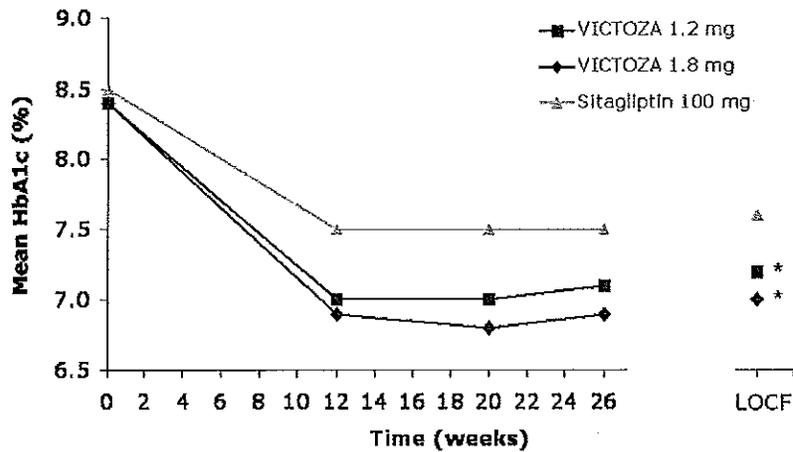
Table 8 Results of a 26-week open-label trial of Victoza Compared to Sitagliptin (both in combination with metformin)^a

	Victoza 1.8 mg + Metformin	Victoza 1.2 mg + Metformin	Sitagliptin 100 mg + Metformin
Intent-to-Treat Population (N)	218	221	219
HbA_{1c} (%) (Mean)			
Baseline	8.4	8.4	8.5
Change from baseline (adjusted mean)	-1.5	-1.2	-0.9
Difference from sitagliptin arm (adjusted mean) ^b	-0.6**	-0.3**	
95% Confidence Interval	(-0.8, -0.4)	(-0.5, -0.2)	
Percentage of patients achieving A _{1c} <7%	56	44	22
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	179	182	180
Change from baseline (adjusted mean)	-39	-34	-15
Difference from sitagliptin arm (adjusted mean) ^b	-24**	-19**	
95% Confidence Interval	(-31, -16)	(-26, -12)	

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

**p-value <0.0001



*p-value <0.0001 for Victoza compared with sitagliptin

P values derived from change from baseline ANCOVA model

Figure 4 Mean HbA_{1c} for patients who completed the 26-week trial and for the Last Observation Carried Forward (LOCF, intent-to-treat) data at Week 26

Combination Therapy with Metformin and Insulin

This 26-week open-label trial enrolled 988 patients with inadequate glycemic control (HbA_{1c} 7-10%) on metformin (≥ 1500 mg/day) alone or inadequate glycemic control (HbA_{1c} 7-8.5%) on metformin (≥ 1500 mg/day) and a sulfonylurea. Patients who were on metformin and a sulfonylurea discontinued the sulfonylurea then all patients entered a 12-week run-in period during which they received add-on therapy with Victoza titrated to 1.8 mg once-daily. At the end of the run-in period, 498 patients (50%) achieved HbA_{1c} <7% with Victoza 1.8 mg and metformin and continued treatment in a non-randomized, observational arm. Another 167 patients (17%) withdrew from the trial during the run-in period with approximately one-half of these patients doing so because of gastrointestinal adverse reactions [see *Adverse Reactions* (6.1)]. The remaining 323 patients with HbA_{1c} $\geq 7\%$ (33% of those who entered the run-in period) were randomized to 26 weeks of once-daily insulin detemir administered in the evening as add-on therapy (N=162) or to continued, unchanged treatment with Victoza 1.8 mg and metformin (N=161). The starting dose of insulin detemir was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26 week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with Victoza 1.8 mg and metformin and 1.2% in the group randomized to add-on therapy with insulin detemir.

Treatment with insulin detemir as add-on to Victoza 1.8 mg + metformin resulted in statistically significant reductions in HbA_{1c} and FPG compared to continued, unchanged treatment with Victoza 1.8 mg + metformin alone (Table 9). From a mean baseline body weight of 96 kg after randomization, there was a mean reduction of 0.3 kg in the patients who received insulin detemir add-on therapy compared to a mean reduction of 1.1 kg in the patients who continued on unchanged treatment with Victoza 1.8 mg + metformin alone.

Table 9 Results of a 26-week open label trial of Insulin detemir as add on to Victoza + metformin compared to continued treatment with Victoza + metformin alone in patients not achieving HbA_{1c} < 7% after 12 weeks of Metformin and Victoza^a

	Insulin detemir + Victoza + Metformin	Victoza + Metformin
Intent-to-Treat Population (N)	162	157
HbA_{1c} (%) (Mean)		
Baseline (week 0)	7.6	7.6
Change from baseline (adjusted mean)	-0.5	0
Difference from Victoza + metformin arm (LS mean) ^b	-0.5**	
95% Confidence Interval	(-0.7, -0.4)	
Percentage of patients achieving A _{1c} <7%	43	17
Fasting Plasma Glucose (mg/dL) (Mean)		
Baseline (week 0)	166	159
Change from baseline (adjusted mean)	-39	-9
Difference from Victoza + metformin arm (LS mean) ^b	-31**	
95% Confidence Interval	(-39, -23)	

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

**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_{1c} compared to placebo add-on to glimepiride (Table 10). 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 10 Results of a 26-week trial of Victoza as add-on to sulfonylurea^a

	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) ^b	-1.1	-1.1	+0.2	-0.4
Difference from placebo + glimepiride arm (adjusted mean) ^b	-1.4**	-1.3**		
95% Confidence Interval	(-1.6, -1.1)	(-1.5, -1.1)		
Percentage of 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) ^b	-29	-28	+18	-16
Difference from placebo + glimepiride arm (adjusted mean) ^b	-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) ^b	-0.2	+0.3	-0.1	+2.1
Difference from placebo + glimepiride arm (adjusted mean) ^b	-0.1	0.4		
95% Confidence Interval	(-0.9, 0.6)	(-0.4, 1.2)		

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

[†] 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_{1c} compared to placebo add-on to glimepiride and metformin (Table 11). 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 11 Results of a 26-week trial of Victoza as add-on to metformin and sulfonylurea^a

	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) ^b	-1.3	-0.2	-1.1
Difference from placebo + metformin + glimepiride arm (adjusted mean) ^b	-1.1**		
95% Confidence Interval	(-1.3, -0.9)		
Percentage of patients achieving A _{1c} <7%	53	15	46
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	165	170	164
Change from baseline (adjusted mean) ^b	-28	+10	-32
Difference from placebo + metformin + glimepiride arm (adjusted mean) ^b	-38**		
95% Confidence Interval	(-46, -30)		
Body Weight (kg) (Mean)			
Baseline	85.8	85.4	85.2
Change from baseline (adjusted mean) ^b	-1.8	-0.4	1.6
Difference from placebo + metformin + glimepiride arm (adjusted mean) ^b	-1.4*		
95% Confidence Interval	(-2.1, -0.7)		

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

[†] For insulin glargine, optimal titration regimen was not achieved for 80% of patients.

*p-value <0.05

**p-value <0.0001

Victoza Compared to Exenatide, Both as Add-on to Metformin and/or Sulfonylurea Therapy

In this 26-week, open-label trial, 464 patients on a background of metformin monotherapy, sulfonylurea monotherapy or a combination of metformin and sulfonylurea were randomized to once daily Victoza 1.8 mg or exenatide 10 mcg twice daily. Maximally tolerated doses of background therapy were to remain unchanged for the duration of the trial. Patients randomized to exenatide started on a dose of 5 mcg twice-daily for 4 weeks and then were escalated to 10 mcg twice daily.

Treatment with Victoza 1.8 mg resulted in statistically significant reductions in HbA_{1c} and FPG relative to exenatide (Table 12). The percentage of patients who discontinued for ineffective therapy was 0.4% in the Victoza treatment group and 0% in the exenatide treatment group. Both treatment groups had a mean decrease from baseline in body weight of approximately 3 kg.

Table 12 Results of a 26-week open-label trial of Victoza versus Exenatide (both in combination with metformin and/or sulfonylurea)^a

	Victoza 1.8 mg once daily + metformin and/or sulfonylurea	Exenatide 10 mcg twice daily + metformin and/or sulfonylurea
Intent-to-Treat Population (N)	233	231
HbA_{1c} (%) (Mean)		
Baseline	8.2	8.1
Change from baseline (adjusted mean) ^b	-1.1	-0.8
Difference from exenatide arm (adjusted mean) ^b	-0.3**	
95% Confidence Interval	(-0.5, -0.2)	
Percentage of patients achieving A_{1c} <7%	54	43
Fasting Plasma Glucose (mg/dL) (Mean)		
Baseline	176	171
Change from baseline (adjusted mean) ^b	-29	-11
Difference from exenatide arm (adjusted mean) ^b	-18**	
95% Confidence Interval	(-25, -12)	

^aIntent-to-treat population using last observation carried forward

^bLeast squares mean adjusted for baseline value

**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_{1c} compared to placebo add-on to metformin and rosiglitazone (Table 13). 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 13 Results of a 26-week trial of Victoza as add-on to metformin and thiazolidinedione^a

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

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

**p-value <0.0001

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 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 14). 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 14 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 FDA-Approved Medication Guide

See separate leaflet.

17.2 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.

17.3 Dehydration and Renal Failure

Patients treated with Victoza should be advised of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Patients should be informed of the potential risk for worsening renal function, which in some cases may require dialysis.

17.4 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)*].

17.5 Hypersensitivity Reactions

Patients should be informed that serious hypersensitivity reactions have been reported during postmarketing use of Victoza. If symptoms of hypersensitivity reactions occur, patients must stop taking Victoza and seek medical advice promptly [*see Warnings and Precautions (5.5)*].

17.6 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.

17.7 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 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.

Inform patients not to take an extra dose of Victoza to make up for a missed dose. If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose.

If more than 3 days have elapsed since the last dose, the patient should be advised to reinitiate Victoza at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. Victoza should be titrated at the discretion of the prescribing physician [*see Dosage and Administration (2)*]

17.8 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.

Date of Issue: April 6, 2012

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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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Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

For information about Victoza contact:

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100 College Road West

Princeton, NJ 08540

1-877-484-2869

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 a substitute for 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.
- you are allergic to liraglutide or any of the ingredients in Victoza. See the end of this Medication Guide for a complete list of ingredients in Victoza. Symptoms of a serious allergic reaction may include:

- o swelling of your face, lips, tongue, or throat
- o fainting or feeling dizzy
- o very rapid heartbeat
- o problems breathing or swallowing
- o severe rash or itching

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. Use the Victoza pen with Novo Nordisk disposable needles. 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 also give yourself insulin injections in addition to Victoza, **never mix insulin and Victoza together.** Give yourself 2 separate injections. You may give both injections in the same body area (for example, your stomach area), but you should not give the injections right next to each other.
- If you take too much Victoza, call your healthcare provider right away. Too much Victoza may cause severe nausea and vomiting.
- If you miss your daily dose of Victoza, use Victoza as soon as you remember. Then take your next daily dose as usual on the following day. Do not take an extra dose of Victoza or increase your dose on the following day to make up for your missed dose. If you miss your dose of Victoza for **3 days or more**, call your healthcare provider to talk about how to restart your treatment.
- 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 or insulin. In some people, the blood sugar may get so low that they need another person to help them. The dose of your

sulfonylurea medicine or insulin 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.

- **Kidney problems (kidney failure).** Victoza may cause nausea, vomiting or diarrhea leading to loss of fluids (dehydration). Dehydration may cause kidney failure which can lead to the need for dialysis. This can happen in people who have never had kidney problems before. Drinking plenty of fluids may reduce your chance of dehydration.

Call your healthcare provider right away if you have nausea, vomiting, or diarrhea that does not go away, or if you cannot drink liquids by mouth.

- **Serious allergic reactions.** Serious allergic reactions can happen with Victoza. Stop using Victoza, and get medical help right away if you have any symptom of a serious allergic reaction **See “Who should not use Victoza?”**

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: April 6, 2012
Version: 3

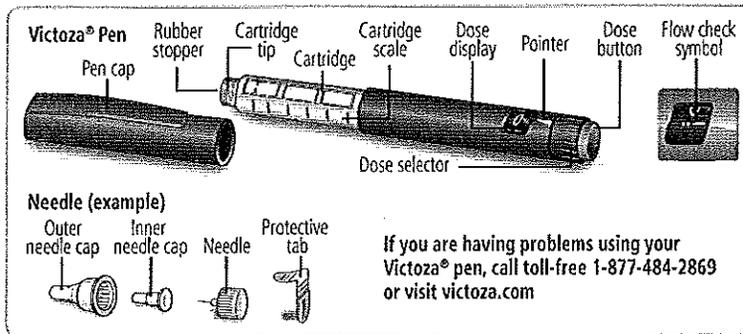
This Medication Guide has been approved by the U.S. Food and Drug Administration.

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.

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Patient Instructions for Use**Victoza® (liraglutide [rDNA origin]) injection**

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.

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.
- Pull off pen cap.
- 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 B. 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.

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.
- Keep needle pointing up and press dose button until 0 mg lines up with pointer. Repeat steps C and D, up to 6 times, until a drop of Victoza® appears at the needle tip.

If you still see no drop of Victoza®, use a new pen and contact Novo Nordisk at 1-877-484-2869.

Continue to Step G under "Routine Use" ⇌

Routine Use**Step E. Check the Pen**

- Take your Victoza® pen from where it is stored.
- Wash hands with soap and water before use.
- Check pen label before each use to make sure it is your Victoza® pen.
- Pull off pen cap.
- 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.

Step G. Dial the Dose

- Victoza® pen can give a dose of 0.6 mg (starting dose), 1.2 mg or 1.8 mg. Be sure that you know the dose of Victoza® that is prescribed for you.
- Turn the dose selector until your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg).
- 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.**

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 closeable, 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.

Caring for your Victoza® pen

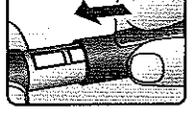
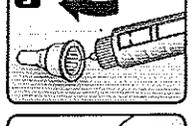
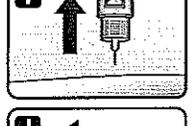
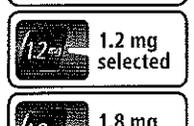
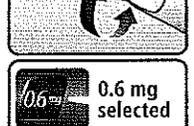
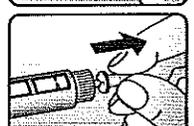
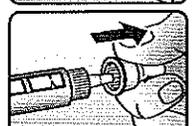
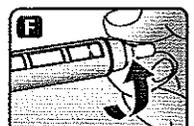
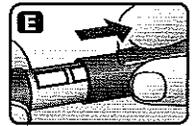
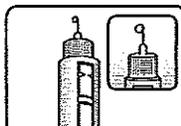
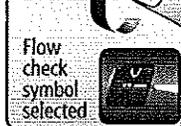
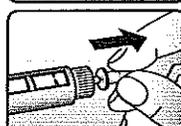
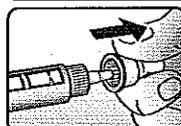
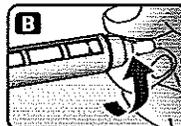
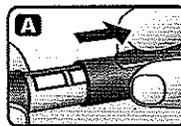
- After removing the needle, put the pen cap on your Victoza® pen and store your Victoza® pen without the needle attached.
- Do not try to refill your Victoza® pen – it is pre-filled and is disposable.
- Do not try to repair your pen or pull it apart.
- Keep your Victoza® pen away from dust, dirt and 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.



HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LEVEMIR[®] (insulin detemir [rDNA origin] injection) solution for subcutaneous injection
Initial U.S. Approval: 2005

INDICATIONS AND USAGE

LEVEMIR is a long-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. (1)

Important Limitations of Use:

- Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid-acting or short-acting insulin instead.

DOSAGE AND ADMINISTRATION

- The starting dose should be individualized based on the type of diabetes and whether the patient is insulin-naïve (2.1, 2.2, 2.3)
- Administer subcutaneously once daily or in divided doses twice daily. Once daily administration should be given with the evening meal or at bedtime (2.1)
- Rotate injection sites within an injection area (abdomen, thigh, or deltoid) to reduce the risk of lipodystrophy (2.1)
- Converting from other insulin therapies may require adjustment of timing and dose of LEVEMIR. Closely monitor glucoses especially upon converting to LEVEMIR and during the initial weeks thereafter (2.3)

DOSAGE FORMS AND STRENGTHS

Solution for injection 100 Units/mL (U-100) in

- 3 mL LEVEMIR FlexPen[®]
- 10 mL vial (3)

CONTRAINDICATIONS

- Do not use in patients with hypersensitivity to LEVEMIR or any of its excipients (4)

WARNINGS AND PRECAUTIONS

- Dose adjustment and monitoring: Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision (5.1)
- Administration: Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump, intramuscularly, or intravenously because severe hypoglycemia can occur (5.2)
- Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening (5.3, 6.1)
- Allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur (5.4)
- Renal or hepatic impairment: May require adjustment of the LEVEMIR dose (5.5, 5.6)

ADVERSE REACTIONS

Adverse reactions associated with LEVEMIR include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, rash and pruritus (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Certain drugs may affect glucose metabolism requiring insulin dose adjustment and close monitoring of blood glucose (7)
- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine) (7)

USE IN SPECIFIC POPULATIONS

Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes < 6 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LEVEMIR is indicated to improve glycemic control in adults and children with diabetes mellitus.

Important Limitations of Use:

- LEVEMIR is not recommended for the treatment of diabetic ketoacidosis. Intravenous rapid-acting or short-acting insulin is the preferred treatment for this condition.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

LEVEMIR is a recombinant human insulin analog for once- or twice-daily subcutaneous administration.

Patients treated with LEVEMIR once-daily should administer the dose with the evening meal or at bedtime.

Patients who require twice-daily dosing can administer the evening dose with the evening meal, at bedtime, or 12 hours after the morning dose.

The dose of LEVEMIR must be individualized based on clinical response. Blood glucose monitoring is essential in all patients receiving insulin therapy.

Patients adjusting the amount or timing of dosing with LEVEMIR should only do so under medical supervision with appropriate glucose monitoring [*see Warnings and Precautions (5.1)*].

In patients with type 1 diabetes, LEVEMIR must be used in a regimen with rapid-acting or short-acting insulin.

As with all insulins, injection sites should be rotated within the same region (abdomen, thigh, or deltoid) from one injection to the next to reduce the risk of lipodystrophy [*see Adverse Reactions (6.1)*].

LEVEMIR can be injected subcutaneously in the thigh, abdominal wall, or upper arm. As with all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables, such as stress, intercurrent illness, or changes in co-administered medications or meal patterns.

2.2 Initiation of LEVEMIR Therapy

The recommended starting dose of LEVEMIR in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Rapid-acting or short-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirements.

The recommended starting dose of LEVEMIR in patients with type 2 diabetes who are not currently treated with insulin is 10 Units (or 0.1-0.2 Units/kg) given once daily in the evening or divided into a twice daily regimen.

LEVEMIR doses should subsequently be adjusted based on blood glucose measurements. The dosages of LEVEMIR should be individualized under the supervision of a healthcare provider.

2.3 Converting to LEVEMIR from other insulin therapies

If converting from insulin glargine to LEVEMIR, the change can be done on a unit-to-unit basis.

If converting from NPH insulin, the change can be done on a unit-to-unit basis. However, some patients with type 2 diabetes may require more LEVEMIR than NPH insulin, as observed in one trial [*see Clinical Studies (14)*].

As with all insulins, close glucose monitoring is recommended during the transition and in the initial weeks thereafter. Doses and timing of concurrent rapid-acting or short-acting insulins or other concomitant antidiabetic treatment may need to be adjusted.

3 DOSAGE FORMS AND STRENGTHS

LEVEMIR solution for injection 100 Unit per mL is available as:

- 3 mL LEVEMIR FlexPen[®]
- 10 mL vial

4 CONTRAINDICATIONS

LEVEMIR is contraindicated in patients with hypersensitivity to LEVEMIR or any of its excipients. Reactions have included anaphylaxis [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Dosage adjustment and monitoring

Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision.

Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in the insulin dose or an adjustment of concomitant anti-diabetic treatment.

As with all insulin preparations, the time course of action for LEVEMIR may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity.

5.2 Administration

LEVEMIR should only be administered subcutaneously.

Do not administer LEVEMIR intravenously or intramuscularly. The intended duration of activity of LEVEMIR is dependent on injection into subcutaneous tissue. Intravenous or intramuscular

administration of the usual subcutaneous dose could result in severe hypoglycemia [*see Warnings and Precautions (5.3)*].

Do not use LEVEMIR in insulin infusion pumps.

Do not dilute or mix LEVEMIR with any other insulin or solution. If LEVEMIR is diluted or mixed, the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LEVEMIR and the mixed insulin may be altered in an unpredictable manner.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin therapy, including LEVEMIR. The risk of hypoglycemia increases with intensive glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion, or glucagon administration has been observed in clinical trials with insulin, including trials with LEVEMIR.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia [*see Drug Interactions (7)*].

The prolonged effect of subcutaneous LEVEMIR may delay recovery from hypoglycemia.

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as beta-blockers, or intensified glycemic control [*see Drug Interactions (7)*]. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

5.4 Hypersensitivity and allergic reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LEVEMIR.

5.5 Renal Impairment

No difference was observed in the pharmacokinetics of insulin detemir between non-diabetic individuals with renal impairment and healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with renal impairment [*see Clinical Pharmacology (12.3)*].

5.6 Hepatic Impairment

Non-diabetic individuals with severe hepatic impairment had lower systemic exposures to insulin detemir compared to healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with hepatic impairment [see *Clinical Pharmacology (12.3)*].

5.7 Drug interactions

Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia [see *Drug Interactions (7)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [see *Warnings and Precautions (5.3)*]
- Hypersensitivity and allergic reactions [see *Warnings and Precautions (5.4)*]

6.1 Clinical trial experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of adverse reactions (excluding hypoglycemia) reported during LEVEMIR clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Tables 1-4 below. See Tables 5 and 6 for the hypoglycemia findings.

Table 1: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 16 weeks and 24 weeks duration in adults with type 1 diabetes (adverse reactions with incidence \geq 5%)

	LEVEMIR, % (n = 767)	NPH, % (n = 388)
Upper respiratory tract infection	26.1	21.4
Headache	22.6	22.7
Pharyngitis	9.5	8.0
Influenza-like illness	7.8	7.0
Abdominal Pain	6.0	2.6

Table 2: Adverse reactions (excluding hypoglycemia) in a 26-week trial comparing insulin aspart + LEVEMIR to insulin aspart + insulin glargine in adults with type 1 diabetes (adverse reactions with incidence \geq 5%)

	LEVEMIR, % (n = 161)	Glargine, % (n = 159)
Upper respiratory tract infection	26.7	32.1
Headache	14.3	19.5
Back pain	8.1	6.3
Influenza-like illness	6.2	8.2
Gastroenteritis	5.6	4.4
Bronchitis	5.0	1.9

Table 3: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 22 weeks and 24 weeks duration in adults with type 2 diabetes (adverse reactions with incidence \geq 5%)

	LEVEMIR, % (n = 432)	NPH, % (n = 437)
Upper respiratory tract infection	12.5	11.2
Headache	6.5	5.3

Table 4: Adverse reactions (excluding hypoglycemia) in a 26-week clinical trial of children and adolescents with type 1 diabetes (adverse reactions with incidence \geq 5%)

	LEVEMIR, % (n = 232)	NPH, % (n = 115)
Upper respiratory tract infection	35.8	42.6
Headache	31.0	32.2
Pharyngitis	17.2	20.9
Gastroenteritis	16.8	11.3
Influenza-like illness	13.8	20.9
Abdominal pain	13.4	13.0
Pyrexia	10.3	6.1
Cough	8.2	4.3
Viral infection	7.3	7.8
Nausea	6.5	7.0
Rhinitis	6.5	3.5
Vomiting	6.5	10.4

Pregnancy

A randomized, open-label, controlled clinical trial has been conducted in pregnant women with type 1 diabetes. [*see Use in Specific Populations (8.1)*]

- ***Hypoglycemia***

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LEVEMIR [*see Warnings and Precautions (5.3)*].

Tables 5 and 6 summarize the incidence of severe and non-severe hypoglycemia in the LEVEMIR clinical trials. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring assistance of another person and associated with either a plasma glucose value below 56 mg/dL (blood glucose below 50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. Non-severe hypoglycemia was defined as an asymptomatic or symptomatic plasma glucose < 56 mg/dL (or equivalently blood glucose <50 mg/dL as used in Study A and C) that was self-treated by the patient.

The rates of hypoglycemia in the LEVEMIR clinical trials (see Section 14 for a description of the study designs) were comparable between LEVEMIR-treated patients and non-LEVEMIR-treated patients (see Tables 5 and 6).

Table 5: Hypoglycemia in Patients with Type 1 Diabetes

		Study A Type 1 Diabetes Adults 16 weeks In combination with insulin aspart		Study B Type 1 Diabetes Adults 26 weeks In combination with insulin aspart		Study C Type 1 Diabetes Adults 24 weeks In combination with regular insulin		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with insulin aspart	
		Twice-Daily LEVEMIR	Twice-Daily NPH	Twice-Daily LEVEMIR	Once-Daily Glargine	Once-Daily LEVEMIR	Once-Daily NPH	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH
Severe hypoglycemia	Percent of patients with at least 1 event (n/total N)	8.7 (24/276)	10.6 (14/132)	5.0 (8/161)	10.1 (16/159)	7.5 (37/491)	10.2 (26/256)	15.9 (37/232)	20.0 (23/115)
	Event/patient/year	0.52	0.43	0.13	0.31	0.35	0.32	0.91	0.99
Non-severe hypoglycemia	Percent of patients (n/total N)	88.0 (243/276)	89.4 (118/132)	82.0 (132/161)	77.4 (123/159)	88.4 (434/491)	87.9 (225/256)	93.1 (216/232)	95.7 (110/115)
	Event/patient/year	26.4	37.5	20.2	21.8	31.1	33.4	31.6	37.0

Table 6: Hypoglycemia in Patients with Type 2 Diabetes

		Study E Type 2 Diabetes Adults 24 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 22 weeks In combination with insulin aspart	
		Twice-Daily LEVEMIR	Twice-Daily NPH	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH
Severe hypoglycemia	Percent of patients with at least 1 event (n/total N)	0.4 (1/237)	2.5 (6/238)	1.5 (3/195)	4.0 (8/199)
	Event/patient/year	0.01	0.08	0.04	0.13
Non-severe hypoglycemia	Percent of patients (n/total N)	40.5 (96/237)	64.3 (153/238)	32.3 (63/195)	32.2 (64/199)
	Event/patient/year	3.5	6.9	1.6	2.0

- *Insulin Initiation and Intensification of Glucose Control*

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

- *Lipodystrophy*

Long-term use of insulin, including LEVEMIR, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin adsorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy [see *Dosage and Administration (2.1)*].

- Weight Gain

Weight gain can occur with insulin therapy, including LEVEMIR, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

- Peripheral Edema

Insulin, including LEVEMIR, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

- Allergic Reactions

Local Allergy

As with any insulin therapy, patients taking LEVEMIR may experience injection site reactions, including localized erythema, pain, pruritis, urticaria, edema, and inflammation. In clinical studies in adults, three patients treated with LEVEMIR reported injection site pain (0.25%) compared to one patient treated with NPH insulin (0.12%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LEVEMIR, and may be life-threatening [see *Warnings and Precautions (5.4)*].

- Antibody Production

All insulin products can elicit the formation of insulin antibodies. These insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LEVEMIR, antibody development has been observed with no apparent impact on glycemic control.

6.2 Postmarketing experience

The following adverse reactions have been identified during post approval use of LEVEMIR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported during post-approval use of LEVEMIR in which other insulins, particularly rapid-acting or short-acting insulins, have been accidentally administered instead of LEVEMIR [see *Patient Counseling Information (17)*]. To avoid medication errors between LEVEMIR and other insulins, patients should be instructed always to verify the insulin label before each injection.

7 DRUG INTERACTIONS

A number of medications affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of medications that may increase the blood-glucose-lowering effect of insulins including LEVEMIR and, therefore, increase the susceptibility to hypoglycemia: oral antidiabetic medications, pramlintide acetate, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of medications that may reduce the blood-glucose-lowering effect of insulins including LEVEMIR: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either increase or decrease the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

The background risk of birth defects, pregnancy loss, or other adverse events that exists for all pregnancies is increased in pregnancies complicated by hyperglycemia. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant while taking LEVEMIR. A randomized controlled clinical trial of pregnant women with type I diabetes using LEVEMIR during pregnancy did not show an increase in the risk of fetal abnormalities. Reproductive toxicology studies in non-diabetic rats and rabbits that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity that were attributed to maternal hypoglycemia.

Clinical Considerations

The increased risk of adverse events in pregnancies complicated by hyperglycemia may be decreased with good glucose control before conception and throughout pregnancy. Because insulin requirements vary throughout pregnancy and in the post-partum period, careful monitoring of glucose control is essential in pregnant women.

Human Data

In an, open-label, clinical study, women with type 1 diabetes who were (between weeks 8 and 12 of gestation) or intended to become pregnant were randomized 1:1 to LEVEMIR (once or twice daily) or NPH insulin (once, twice or thrice daily). Insulin aspart was administered before each meal. 152 women in the LEVEMIR arm and 158 women in the NPH arm were or became pregnant during the

study (Total pregnant women = 310). Approximately one half of the study participants in each arm were randomized as pregnant and were exposed to NPH or to other insulins prior to conception and in the first 8 weeks of gestation. In the 310 pregnant women, the mean glycosylated hemoglobin (HbA_{1c}) was < 7% at 10, 12, and 24 weeks of gestation in both arms. In the intent-to-treat population, the adjusted mean HbA_{1c} (standard error) at gestational week 36 was 6.27% (0.053) in LEVEMIR-treated patient (n=138) and 6.33% (0.052) in NPH-treated patients (n=145); the difference was not clinically significant.

Adverse reactions in pregnant patients occurring at an incidence of $\geq 5\%$ are shown in Table 7. The two most common adverse reactions were nasopharyngitis and headache. These are consistent with findings from other type 1 diabetes trials (see Table 1, Section 6.1.), and are not repeated in Table 7.

The incidence of adverse reactions of pre-eclampsia was 10.5% (16 cases) and 7.0% (11 cases) in the Levemir and NPH insulin groups respectively. Out of the total number of cases of pre-eclampsia, eight (8) cases in the LEVEMIR group and 1 case in the NPH insulin group required hospitalization. The rates of pre-eclampsia observed in the study are within expected rates for pregnancy complicated by diabetes. Pre-eclampsia is a syndrome defined by symptoms, hypertension and proteinuria; the definition of pre-eclampsia was not standardized in the trial making it difficult to establish a link between a given treatment and an increased risk of pre-eclampsia. All events were considered unlikely related to trial treatment. In all nine (9) cases requiring hospitalization the women had healthy infants. Events of hypertension, proteinuria and edema were reported less frequently in the LEVEMIR group than in the NPH insulin group as a whole. There was no difference between the treatment groups in mean blood pressure during pregnancy and there was no indication of a general increase in blood pressure.

In the NPH insulin group there were 6 serious adverse reactions in four mothers of the following placental disorders, 'Placenta previa', 'Placenta previa hemorrhage', and 'Premature separation of placenta' and 1 serious adverse reaction of 'Antepartum haemorrhage'. There were none reported in the LEVEMIR group.

The incidence of early fetal death (abortions) was similar in LEVEMIR and NPH treated patients; 6.6% and 5.1%, respectively. The abortions were reported under the following terms: 'Abortion spontaneous', 'Abortion missed', 'Blighted ovum', 'Cervical incompetence' and 'Abortion incomplete'.

Table 7: Adverse reactions during pregnancy in a trial comparing insulin aspart + LEVEMIR to insulin aspart + NPH insulin in pregnant women with type 1 diabetes (adverse reactions with incidence $\geq 5\%$)*

	LEVEMIR, % (n = 152)	NPH, % (n = 158)
Anaemia	13.2	10.8
Diarrhoea	11.8	5.1
Pre-eclampsia	10.5	7.0
Urinary tract infection	9.9	5.7
Gastroenteritis	8.6	5.1
Abdominal pain upper	5.9	3.8
Vomiting	5.3	4.4
Abortion spontaneous	5.3	2.5

Abdominal pain	5.3	6.3
Oropharyngeal pain	5.3	6.3

*Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The proportion of subjects experiencing severe hypoglycemia was 16.4% and 20.9% in LEVEMIR and NPH treated patients respectively. The rate of severe hypoglycemia was 1.1 and 1.2 events per patient-year in LEVEMIR and NPH treated patients respectively. Proportion and incidence rates for non-severe episodes of hypoglycemia were similar in both treatment groups (Table 8).

Table 8: Hypoglycemia in Pregnant Women with Type 1 Diabetes

		Study G Type 1 Diabetes Pregnancy In combination with insulin aspart	
		LEVEMIR	NPH
Severe hypoglycemia*	Percent of patients with at least 1 event (n/total N)	16.4 (25/152)	20.9 (33/158)
	Events/patient/year	1.1	1.2
Non-severe hypoglycemia*	Percent of patients with at least 1 event (n/total N)	94.7 (144/152)	92.4 (146/158)
	Events/patient/year	114.2	108.4

* For definition regarding severe and non-severe hypoglycemia see section 6, Hypoglycemia.

In about a quarter of infants,, LEVEMIR was detected in the infant cord blood at levels above the lower level of quantification (<25 pmol/L).

No differences in pregnancy outcomes or the health of the fetus and newborn were seen with LEVEMIR use.

Animal Data

In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times a human dose of 0.5 Units/kg/day, based on plasma area under the curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times a human dose of 0.5 Units/kg/day based on AUC ratio) were given to rabbits during organogenesis. Drug and dose related increases in the incidence of fetuses with gallbladder abnormalities such as small, bilobed, bifurcated, and missing gallbladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity suggesting that the effects seen were the result of hypoglycemia resulting from insulin exposure in normal animals.

8.3 Nursing Mothers

It is unknown whether LEVEMIR is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, use caution when administering LEVEMIR to a nursing woman. Women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The pharmacokinetics, safety and effectiveness of subcutaneous injections of LEVEMIR have been established in pediatric patients (age 6 to 17 years) with type 1 diabetes [*see Clinical Pharmacology (12.3) and Clinical Studies (14)*]. LEVEMIR has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LEVEMIR has not been studied in pediatric patients with type 2 diabetes.

The dose recommendation when converting to LEVEMIR is the same as that described for adults [*see Dosage and Administration (2) and Clinical Studies (14)*]. As in adults, the dosage of LEVEMIR must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In controlled clinical trials comparing LEVEMIR to NPH insulin or insulin glargine, 64 of 1624 patients (3.9%) in the type 1 diabetes trials and 309 of 1082 patients (28.6%) in the type 2 diabetes trials were ≥ 65 years of age. A total of 52 (7 type 1 and 45 type 2) patients (1.9%) were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, but small sample sizes, particularly for patients ≥ 65 years of age in the type 1 diabetes trials and for patients ≥ 75 years of age in all trials limits conclusions. Greater sensitivity of some older individuals cannot be ruled out. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be difficult to recognize in the elderly.

10 OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed.

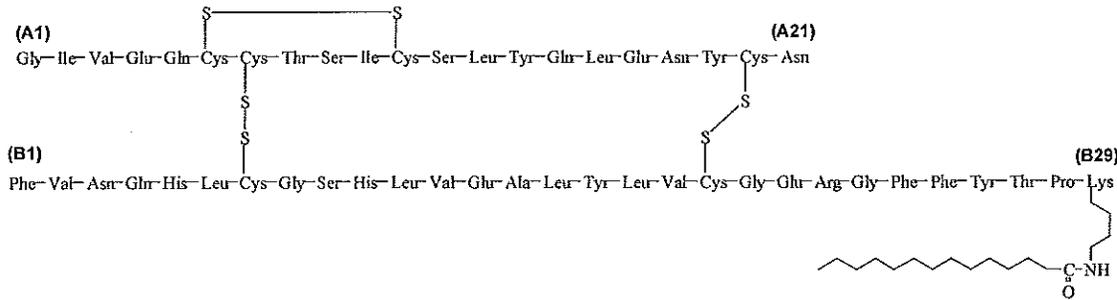
More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia [*see Warnings and Precautions (5.3)*].

11 DESCRIPTION

LEVEMIR (insulin detemir [rDNA origin] injection) is a sterile solution of insulin detemir for use as a subcutaneous injection. Insulin detemir is a long-acting (up to 24-hour duration of action) recombinant human insulin analog. LEVEMIR is produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

Insulin detemir differs from human insulin in that the amino acid threonine in position B30 has been omitted, and a C14 fatty acid chain has been attached to the amino acid B29. Insulin detemir has a molecular formula of $C_{267}H_{402}O_{76}N_{64}S_6$ and a molecular weight of 5916.9. It has the following structure:

Figure 1: Structural Formula of insulin detemir



LEVEMIR is a clear, colorless, aqueous, neutral sterile solution. Each milliliter of LEVEMIR contains 100 units (14.2 mg/mL) insulin detemir, 65.4 mcg zinc, 2.06 mg m-cresol, 16.0 mg glycerol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride, and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. LEVEMIR has a pH of approximately 7.4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of insulin detemir is the regulation of glucose metabolism. Insulins, including insulin detemir, exert their specific action through binding to insulin receptors. Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and adipose tissue and by inhibiting the output of glucose from the liver. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

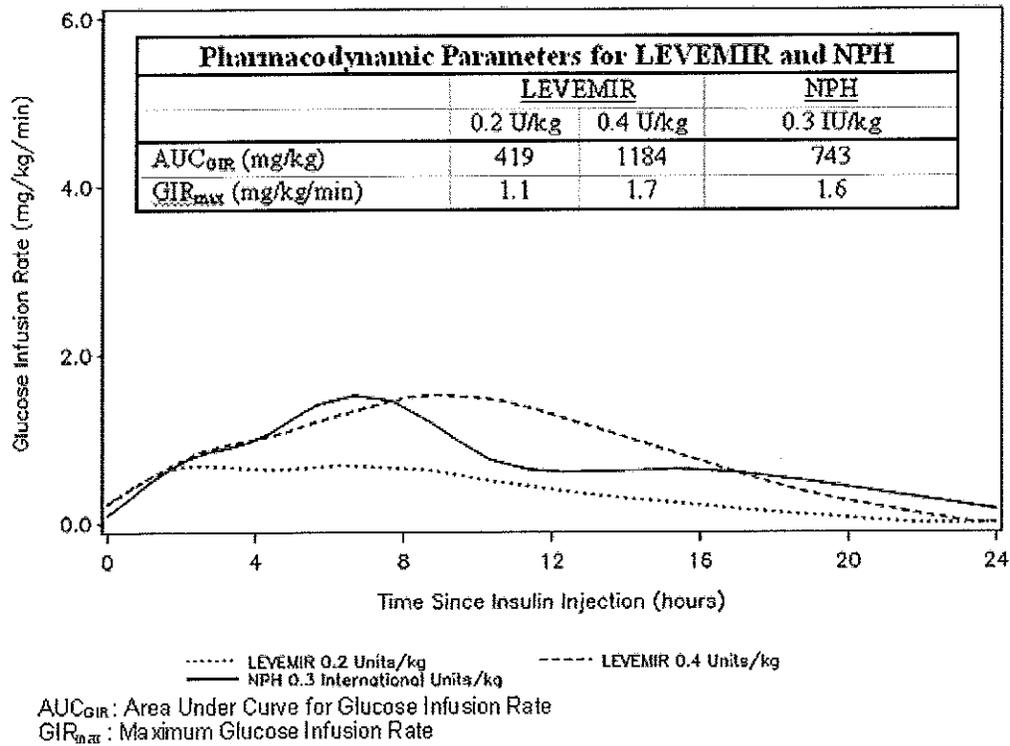
12.2 Pharmacodynamics

Insulin detemir is a soluble, long-acting basal human insulin analog with up to a 24-hour duration of action. The pharmacodynamic profile of LEVEMIR is relatively constant with no pronounced peak.

The duration of action of LEVEMIR is mediated by slowed systemic absorption of insulin detemir molecules from the injection site due to self-association of the drug molecules. In addition, the distribution of insulin detemir to peripheral target tissues is slowed because of binding to albumin.

Figure 2 shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after the subcutaneous injection of LEVEMIR or NPH insulin. The mean time between injection and the end of pharmacological effect for insulin detemir ranged from 7.6 hours to > 24 hours (24 hours was the end of the observation period).

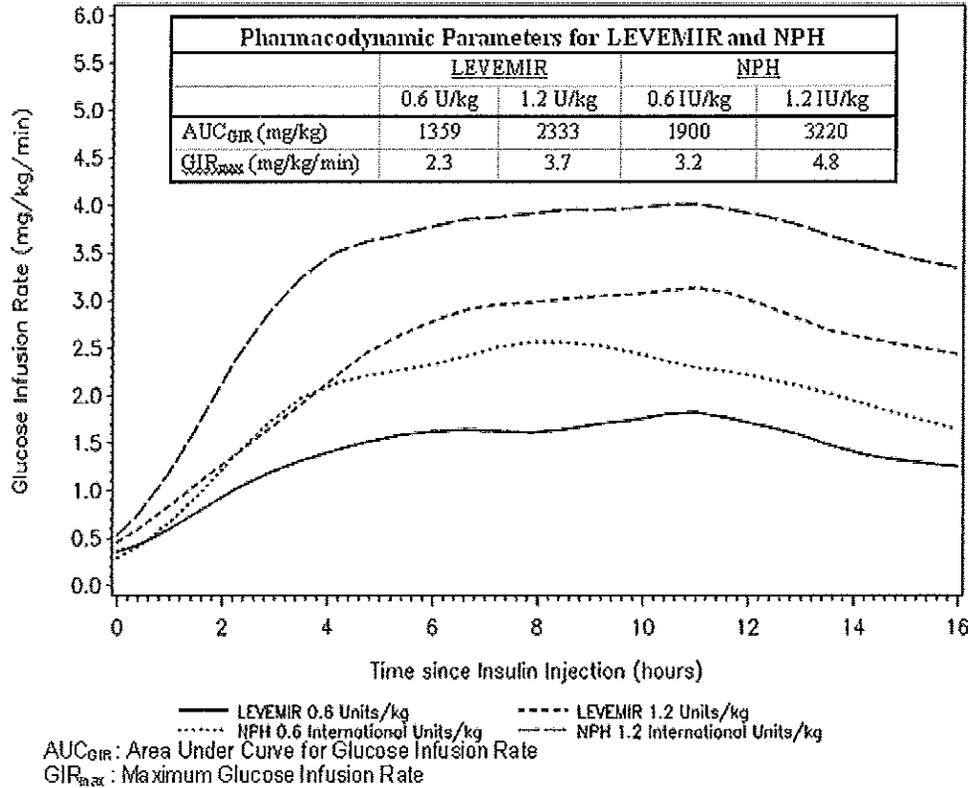
Figure 2: Activity Profiles in Patients with Type 1 Diabetes in a 24-hour Glucose Clamp Study



For doses in the interval of 0.2 to 0.4 Units/kg, insulin detemir exerts more than 50% of its maximum effect from 3 to 4 hours up to approximately 14 hours after dose administration.

Figure 3 shows glucose infusion rate results from a 16-hour glucose clamp study in patients with type 2 diabetes. The clamp study was terminated at 16 hours according to protocol.

Figure 3: Activity Profiles in Patients with Type 2 Diabetes in a 16-hour Glucose Clamp Study



12.3 Pharmacokinetics

Absorption and Bioavailability

After subcutaneous injection of LEVEMIR in healthy subjects and in patients with diabetes, insulin detemir serum concentrations had a relatively constant concentration/time profile over 24 hours with the maximum serum concentration (C_{max}) reached between 6-8 hours post-dose. Insulin detemir was more slowly absorbed after subcutaneous administration to the thigh where AUC_{0-5h} was 30-40% lower and AUC_{0-inf} was 10% lower than the corresponding AUCs with subcutaneous injections to the deltoid and abdominal regions.

The absolute bioavailability of insulin detemir is approximately 60%.

Distribution and Elimination

More than 98% of insulin detemir in the bloodstream is bound to albumin. The results of *in vitro* and *in vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein-bound drugs.

Insulin detemir has an apparent volume of distribution of approximately 0.1 L/kg. After subcutaneous administration in patients with type 1 diabetes, insulin detemir has a terminal half-life of 5 to 7 hours depending on dose.

Specific Populations

Children and Adolescents- The pharmacokinetic properties of LEVEMIR were investigated in children (6-12 years), adolescents (13-17 years), and adults with type 1 diabetes. In children, the insulin detemir

plasma area under the curve (AUC) and C_{max} were increased by 10% and 24%, respectively, as compared to adults. There was no difference in pharmacokinetics between adolescents and adults.

Geriatrics- In a clinical trial investigating differences in pharmacokinetics of a single subcutaneous dose of LEVEMIR in young (20 to 35 years) versus elderly (≥ 68 years) healthy subjects, the insulin detemir AUC was up to 35% higher among the elderly subjects due to reduced clearance. As with other insulin preparations, LEVEMIR should always be titrated according to individual requirements.

Gender- No clinically relevant differences in pharmacokinetic parameters of LEVEMIR are observed between males and females.

Race- In two clinical pharmacology studies conducted in healthy Japanese and Caucasian subjects, there were no clinically relevant differences seen in pharmacokinetic parameters. The pharmacokinetics and pharmacodynamics of LEVEMIR were investigated in a clamp study comparing patients with type 2 diabetes of Caucasian, African-American, and Latino origin. Dose-response relationships for LEVEMIR were comparable in these three populations.

Renal impairment- A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR was administered to healthy subjects and those with varying degrees of renal impairment (mild, moderate, severe, and hemodialysis-dependent). In this study, there were no differences in the pharmacokinetics of LEVEMIR between healthy subjects and those with renal impairment. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with renal impairment [*see Warnings and Precautions (5.5)*].

Hepatic impairment- A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR was administered to healthy subjects and those with varying degrees of hepatic impairment (mild, moderate and severe). LEVEMIR exposure as estimated by AUC decreased with increasing degrees of hepatic impairment with a corresponding increase in apparent clearance. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with hepatic impairment [*see Warnings and Precautions (5.6)*].

Pregnancy- The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LEVEMIR has not been studied [*see Use in Specific Populations (8.1)*].

Smoking- The effect of smoking on the pharmacokinetics and pharmacodynamics of LEVEMIR has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in vitro* reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the *in vivo* mouse micronucleus test.

In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times a human dose of 0.5 Units/kg/day, based on plasma AUC ratio). There were no effects on fertility in the rat.

14 CLINICAL STUDIES

The efficacy and safety of LEVEMIR given once-daily at bedtime or twice-daily (before breakfast and at bedtime, before breakfast and with the evening meal, or at 12-hour intervals) was compared to that of once-daily or twice-daily NPH insulin in open-label, randomized, parallel studies of 1155 adults with type 1 diabetes mellitus, 347 pediatric patients with type 1 diabetes mellitus, and 869 adults with type 2 diabetes mellitus. The efficacy and safety of LEVEMIR given twice-daily was compared to once-daily insulin glargine in an open-label, randomized, parallel study of 320 patients with type 1 diabetes. The evening LEVEMIR dose was titrated in all trials according to pre-defined targets for fasting blood glucose. The pre-dinner blood glucose was used to titrate the morning LEVEMIR dose in those trials that also administered LEVEMIR in the morning. In general, the reduction in glycosylated hemoglobin (HbA_{1c}) with LEVEMIR was similar to that with NPH insulin or insulin glargine.

Type 1 Diabetes – Adult

In a 16-week open-label clinical study (Study A, n=409), adults with type 1 diabetes were randomized to treatment with either LEVEMIR at 12-hour intervals, LEVEMIR administered in the morning and bedtime or NPH insulin administered in the morning and bedtime. Insulin aspart was also administered before each meal. At 16 weeks of treatment, the combined LEVEMIR-treated patients had similar HbA_{1c} and fasting plasma glucose (FPG) reductions compared to the NPH-treated patients (Table 9). Differences in timing of LEVEMIR administration had no effect on HbA_{1c}, fasting plasma glucose (FPG), or body weight.

In a 26-week, open-label clinical study (Study B, n=320), adults with type 1 diabetes were randomized to twice-daily LEVEMIR (administered in the morning and bedtime) or once-daily insulin glargine (administered at bedtime). Insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA_{1c} similar to that of insulin glargine-treated patients.

In a 24-week, non-blinded clinical study (Study C, n=749), adults with type 1 diabetes were randomized to once-daily LEVEMIR or once-daily NPH insulin, both administered at bedtime and in combination with regular human insulin before each meal. LEVEMIR and NPH insulin had a similar effect on HbA_{1c}.

Table 9: Type 1 Diabetes Mellitus – Adult

Treatment duration Treatment in combination with	Study A 16 weeks NovoLog [®] (insulin aspart)		Study B 26 weeks NovoLog [®] (insulin aspart)		Study C 24 weeks Human Soluble Insulin (regular insulin)	
	<u>Twice-daily</u> <u>LEVEMIR</u>	<u>Twice-daily</u> <u>NPH</u>	<u>Twice-daily</u> <u>LEVEMIR</u>	<u>Once-</u> <u>daily</u> <u>insulin</u> <u>glargine</u>	<u>Once-daily</u> <u>LEVEMIR</u>	<u>Once-</u> <u>daily</u> <u>NPH</u>
	Number of patients treated	276	133	161	159	492
HbA _{1c} (%)						
Baseline HbA _{1c}	8.6	8.5	8.9	8.8	8.4	8.3
Adj. mean change from baseline	-0.8	-0.7	-0.6	-0.5	-0.1	0.0

LEVEMIR – NPH	-0.2 (-0.3, -0.0)		-0.0 (-0.2, 0.2)		-0.1 (-0.3, 0.0)	
95% CI for Treatment difference						
Basal insulin dose (units/day)						
Baseline mean	21	24	27	23	12	24
Mean change from baseline	16	10	10	4	9	2
Total insulin dose (units/day)						
Baseline mean	48	54	56	51	46	57
Mean change from baseline	17	10	9	6	11	3
Fasting blood glucose (mg/dL)						
Baseline mean	209	220	153	150	213	206
Adj. mean change from baseline	-44	-9	-38	-41	-30	-9
Body weight (kg)						
Baseline mean	74.6	75.5	77.5	75.1	76.5	76.9
Mean change from baseline	0.2	0.8	0.5	1.0	-0.3	0.3

Baseline values were included as covariates in an ANCOVA analysis.

Type 1 Diabetes – Pediatric

In an open-label clinical study (Study D, n=347), pediatric patients (age range 6 to 17) with type 1 diabetes were randomized to 26 weeks of treatment with LEVEMIR or NPH insulin both of which were administered either once- or twice-daily (bedtime or morning and bedtime), at a dosing frequency consistent with the number of daily basal insulin injections a patient was taking prior to trial entry. Insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA_{1c} similar to that of NPH insulin (Table 10).

Table 10: Type 1 Diabetes Mellitus – Pediatric

Treatment duration Treatment in combination with	Study D 26 weeks NovoLog [®] (insulin aspart)	
	Once- or Twice Daily <u>LEVEMIR</u>	Once- or Twice Daily <u>NPH</u>
Number of subjects treated	232	115
HbA _{1c} (%)		
Baseline HbA _{1c}	8.8	8.8
Adj. mean change from baseline	-0.7	-0.8
LEVEMIR – NPH	0.1	
95% CI for Treatment difference	(-0.1, 0.3)	
Basal insulin dose (units/day)		
Baseline mean	24	26
Mean change from baseline	8	6
Total insulin dose (units/day)		
Baseline mean	48	50
Mean change from baseline	9	7
Fasting blood glucose (mg/dL)		
Baseline mean	181	181
Adj. mean change from baseline	-39	-21
Body weight (kg)		
Baseline mean	46.3	46.2
Mean change from baseline	1.6	2.7

Type 2 Diabetes – Adult

In a 24-week, open-label, randomized, clinical study (Study E, n=476), LEVEMIR administered twice-daily (before breakfast and evening) was compared to NPH insulin administered twice-daily (before breakfast and evening) as part of a regimen of stable combination therapy with one or two of the following oral antidiabetic medications: metformin, an insulin secretagogue, or an alpha-glucosidase inhibitor. All patients were insulin-naïve at the time of randomization. LEVEMIR and NPH insulin similarly lowered HbA_{1c} from baseline (Table 11).

In a 22-week, open-label, randomized, clinical study (Study F, n=395) in adults with type 2 diabetes, LEVEMIR and NPH insulin were given once- or twice-daily as part of a basal-bolus regimen with insulin aspart. As measured by HbA_{1c} or FPG, LEVEMIR had efficacy similar to that of NPH insulin.

Table 11: Type 2 Diabetes Mellitus – Adult

Treatment duration Treatment in combination with	Study E 24 weeks oral agents		Study F 22 weeks insulin aspart	
	Twice-daily LEVEMIR	Twice-daily NPH	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH
Number of subjects treated	237	239	195	200
HbA _{1c} (%)				
Baseline HbA _{1c}	8.6	8.5	8.2	8.1
Adj. mean change from baseline	-2.0	-2.1	-0.6	-0.6
LEVEMIR – NPH	0.1		-0.1	
95% CI for Treatment difference	(-0.0, 0.3)		(-0.2, 0.1)	
Basal insulin dose (units/day)				
Baseline mean	18	17	22	22
Mean change from baseline	48	28	26	15
Total insulin dose ¹ (units/day)				
Baseline mean	-	-	22	22
Mean change from baseline	-	-	57	42
Fasting blood glucose ² (mg/dL)				
Baseline mean	179	173	-	-
Adj. mean change from baseline	-69	-74	-	-
Body weight (kg)				
Baseline mean	82.7	82.5	82.0	79.6
Mean change from baseline	1.2	2.7	0.5	1.2

¹Study E – Conducted in insulin-naïve patients

²Study F - Fasting blood glucose data not collected

Pregnancy

A randomized, open-label, controlled clinical trial has been conducted in pregnant women with type 1 diabetes. [see *Use in Specific Populations (8.1)*]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LEVEMIR is available in the following package sizes: each presentation containing 100 Units of insulin detemir per mL (U-100).

3 mL LEVEMIR FlexPen® NDC 0169-6439-10
10 mL vial NDC 0169-3687-12

FlexPen is for use with NovoFine® disposable needles. Each FlexPen is for use by a single patient. LEVEMIR FlexPen should never be shared between patients, even if the needle is changed.

16.2 Storage:

Unused (unopened) LEVEMIR should be stored in the refrigerator between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use LEVEMIR if it has been frozen.

Unused (unopened) LEVEMIR can be kept until the expiration date printed on the label if it is stored in a refrigerator. Keep unused LEVEMIR in the carton so that it stays clean and protected from light.

If refrigeration is not possible, unused (unopened) LEVEMIR can be kept unrefrigerated at room temperature, below 30°C (86°F) as long as it is kept as cool as possible and away from direct heat and light. Unrefrigerated LEVEMIR should be discarded 42 days after it is first kept out of the refrigerator, even if the FlexPen or vial still contains insulin.

Vials:

After initial use, vials should be stored in a refrigerator, never in a freezer. If refrigeration is not possible, the in-use vial can be kept unrefrigerated at room temperature, below 30°C (86°F) as long as it is kept as cool as possible and away from direct heat and light. Refrigerated LEVEMIR vials should be discarded 42 days after initial use. Unrefrigerated LEVEMIR vials should be discarded 42 days after they are first kept out of the refrigerator.

LEVEMIR FlexPen:

After initial use, the LEVEMIR FlexPen must NOT be stored in a refrigerator and must NOT be stored with the needle in place. Keep the opened (in use) LEVEMIR FlexPen away from direct heat and light at room temperature, below 30°C (86°F). Unrefrigerated LEVEMIR FlexPens should be discarded 42 days after they are first kept out of the refrigerator.

The storage conditions are summarized in Table 12:

Table 12: Storage Conditions for LEVEMIR FlexPen and vial

	Not in-use (unopened) Refrigerated	Not in-use (unopened) Room Temperature (below 30°C)	In-use (opened)
3 mL LEVEMIR FlexPen	Until expiration date	42 days*	42 days* Room Temperature (below 30°C) (Do not refrigerate)
10 mL vial	Until expiration date	42 days*	42 days* Refrigerated or Room Temperature (below 30°C)

*The total time allowed at room temperature (below 30°C) is 42 days regardless of whether the product is in-use or not in-use.

16.3 Preparation and handling

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. LEVEMIR should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.

Mixing and diluting: LEVEMIR must NOT be mixed or diluted with any other insulin or solution [See *Warnings and Precautions* (5.2)].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information and Instructions for Use)

17.1 Instructions for Patients

Patients should be informed that changes to insulin regimens must be made cautiously and only under medical supervision. Patients should be informed about the potential side effects of insulin therapy, including hypoglycemia, weight gain, lipodystrophy (and the need to rotate injection sites within the same body region), and allergic reactions. Patients should be informed that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

Accidental mix-ups between LEVEMIR and other insulins, particularly short-acting insulins, have been reported. To avoid medication errors between LEVEMIR and other insulins, patients should be instructed to always check the insulin label before each injection.

LEVEMIR must only be used if the solution is clear and colorless with no particles visible. Patients must be advised that LEVEMIR must NOT be diluted or mixed with any other insulin or solution.

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Patients should be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals.

Patients with diabetes should be advised to inform their healthcare professional if they are pregnant or are contemplating pregnancy. Refer patients to the LEVEMIR "Patient Information" for additional information.

17.2 Never Share a LEVEMIR FlexPen Between Patients

Counsel patients that they should never share a LEVEMIR FlexPen with another person, even if the needle is changed. Sharing of the FlexPen between patients may pose a risk of transmission of infection.

Novo Nordisk[®], *Levemir*[®], *NovoLog*[®], *FlexPen*[®], and *NovoFine*[®] are registered trademarks of Novo Nordisk A/S.

LEVEMIR is covered by US Patent Nos. 5,750,497, 5,866,538, 6,011,007, 6,869,930 and other patents pending.

FlexPen is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,400 and other patents pending.

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