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 us Initial U.S. Approval: 2010

WARNING: RISK OF THYROID C-CELL TUMORS

- WARNING: RISK OF THYROID C-CELL TUMORS See full prescribing information for complete boxed warning. Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies (5.1). Victoza is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (5.1).
- -----INDICATIONS AND USAGE -----

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

Important Limitations of Use (1.1):

Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (5.1). Has not been studied sufficiently in patients with a history of pancreatitis. Use caution (5.2).

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with insulin.

......DOSAGE AND ADMINISTRATION-

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

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

FULL PRESCRIBING INFORMATION: CONTENTS

BOXED WARNING: RISK OF THYROID C-CELL TUMORS

1 INDICATIONS AND USAGE Important Limitations of Use

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- DOSAGE FORMS AND STRENGTHS 3
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FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza is contraindicated in patients with a personal or family history of MTC studies. Victoza is contraindicated in patients with a personal or tamily history of MIC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (NHEN 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 unnecessar 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 classed by the discontence of thereid tumore free Categoria discontence for the categoria the science of thereid tumore free Categoria discontence for the categoria the science of the science for the science of the science of the science for the science of the sci counseled regarding the risk and symptoms of thyroid tumors [see Contraindications (4), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)].

INDICATIONS AND USAGE

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

- 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
- The concurrent use of Victoza and insulin has not been studied

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 insulir secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia (see Warnings and Precautions (5.3) and Adverse Reactions (6)]

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

DOSAGE FORMS AND STRENGTHS ution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg 12 mg or 18 mg (6 mg/ml 3 ml)

4 CONTRAINDICATIONS

Victoza is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) 5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

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

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

---WARNINGS AND PRECAUTIONS -

Thyroid C-cell tumors in animals: Human relevance unknown. Coursel 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. sulfonylurea). Consider lowering the dose of the insulin secretagogue to reduce the risk of ia (5.3).
- nypogycemia (5.3). Macrovascular outcomes: There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza or any other antidiabetic drug (5.4).
- --- ADVERSE REACTIONS The most common adverse reactions, reported in ≥5% of patients treated with Victoza and more commonly than in patients treated with placebo, are: headache, nausea,
- and more commonly than in patients treated with placebo, are needed in haddea, diarrhea and anti-liragutide 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 nedications. Use caution (7)

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

10 OVERDOSAGE

11 DESCRIPTION

12.2

12.3

16.1 16.2

17.5

17.6

in serum calcitonin.

endocrinologist for further evaluation.

5.2 Pancreatitis

are not listed.

12

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Risk of Thyroid C-cell Tumors

FDA-Approved Medication Guide

Sections or subsections omitted from the full prescribing information

Pancreatitis Never Share a Victoza Pen Between Patients

will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as

the human relevance of liragilutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies *[see Boxed Warning, Contraindications (4)]*. In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among Victoza-treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 patient-years). One additional case of thyroid C-cell hyperplasia in a Victoza-treated patient and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations 11000 pdf (ungesting are origined fictors). All of there, caser using dispected fitters

the human relevance of liradutide-induced rodent thyroid C-cell tumors could not be

>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 Invitioeccomy, which was prompted by adminimistration of mounts, protocol-specified measurements of serum calcitonin. Four of the five liragluide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liragluide and one non-liragluide-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 Victora clinical trials had a lower limit of quantification of UOD of 0.7 and and the unpress limit of the reference range up to 0.0 and file material trials had a lower limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and file the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the reference range up to 0.0 and the unpress limit of the range up to 0.0 and the unpress limit of the range up to 0.0 and the unpress limit of the range up to 0.0 and the unpress limit of the unpress limit of the top of the range up to 0.0 and the unpress limit of the top of the range up to 0.0 and the unpress limit of the top of the up to 0.0 and the unpress limit of the top of the top of the top of the up to 0.0 and the up

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

placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum actiotonin 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, 19% of patients treated with Victoza 1.8 mg/day dealpaced paw and parsister treated.

1.9% of patients treated with Victoza 1.8 mg/day developed new and persistent calcitoning

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-

nt serum calcitonin measurements out to 12 months. 1.3% of patients treated with

Victoza 1.8 mg/day had new and persistent levations 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

Patients with MTC usually have calcitonin values >50 ng/L. In Victoza clinical trials, among

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 = 2014. Calcitonin playedings to 2014 of 201

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

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 nordules noted on howical examination or next imaning ontained for rither

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

In clinical trials of Victoza, there were 7 cases of pancreatitis among Victoza-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years).

Five cases with Victoza were reported as acute pancreatitis and two cases with Victoza were

reported as chronic pancreatitis. In one case in a Victoza-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established.

Revised: 1/2010

Victoza 1.2 mg, Victoza 1.8 mg or placebo (see Clinical Studies (14)). Withdrawals WILLIARMAN
The incidence of withdrawal due to adverse events was 7.8% for Victoza-treated patients and 3.4% for comparator-treated patients in the five controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza-treated patients and 0.5% of comparator-

ated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mai during the first 2-3 months of the trials. Tables 1 and 2 summarize the adverse events reported in >5% of Victoza-treated patients in

Table 1 Adverse events reported in >5% of Victoza-treated patients or >5% of

glimeniride-treated natients: 52-week mo

| | All Victoza N=497 | Glimepiride N=248 |
|-----------------------------------|----------------------|----------------------|
| Adverse Event Term | (%) | (%) |
| Nausea | 28.4 | 8.5 |
| Diarrhea | 17.1 | 8.9 |
| Vomiting | 10.9 | 3.6 |
| Constipation | 9.9 | 4.8 |
| Upper Respiratory Tract Infection | 9.5 | 5.6 |
| Headache | 9.1 | 9.3 |
| Influenza | 7.4 | 3.6 |
| Urinary Tract Infection | 6.0 | 4.0 |
| Dizziness | 5.8 | 5.2 |
| Sinusitis | 5.6 | 6.0 |
| Nasopharyngitis | 5.2 | 5.2 |
| Back Pain | 5.0 | 4.4 |
| Hypertension | 3.0 | 6.0 |

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

| | Add-on to Metformin Trial | | | | |
|--------------------|-------------------------------------|---------------------------------|-------------------------------------|--|--|
| | All Victoza + Metformin N=724 | Placebo + Metformin N=121 | Glimepiride + Metformin N=242 | | |
| Adverse Event Term | (%) | (%) | (%) | | |
| Nausea | 15.2 | 4.1 | 3.3 | | |
| Diarrhea | 10.9 | 4.1 | 3.7 | | |
| Headache | 9.0 | 6.6 | 9.5 | | |
| Vomiting | 6.5 | 0.8 | 0.4 | | |

| | Add-on to Glimepiride Trial | | | | |
|--------------------|---------------------------------------|-----------------------------------|---|--|--|
| | All Victoza + Glimepiride N=695 | Placebo + Glimepiride N=114 | Rosiglitazone + Glimepiride N=231 | | |
| Adverse Event Term | (%) | (%) | (%) | | |
| Nausea | 7.5 | 1.8 | 2.6 | | |
| Diarrhea | 7.2 | 1.8 | 2.2 | | |
| Constipation | 5.3 | 0.9 | 1.7 | | |
| Dyspepsia | 5.2 | 0.9 | 2.6 | | |

| Add-on to Metformin + Glimepiride | | | | | |
|-----------------------------------|---|-----|-----|--|--|
| | Victoza 1.8 + Placebo + Glargine Metformin + Metformin + Metformin Glimepiride Glimepiride Glimepiride N=230 N=114 N=232 | | | | |
| Adverse Event Term | (%) | (%) | (%) | | |
| Nausea | 13.9 | 3.5 | 1.3 | | |
| Diarrhea | 10.0 | 5.3 | 1.3 | | |
| Headache | 9.6 | 7.9 | 5.6 | | |
| Dyspepsia | 6.5 | 0.9 | 1.7 | | |
| Vomiting | 6.5 | 3.5 | 0.4 | | |

| | Add-on to Metformin + Rosiglitazone | | | |
|--------------------|---|-----|--|--|
| | All Victoza + Placebo + Metformin + Metformin + Rosiglitazone N=355 N=175 | | | |
| Adverse Event Term | (%) | (%) | | |
| Nausea | 34.6 | 8.6 | | |
| Diarrhea | 14.1 | 6.3 | | |
| Vomiting | 12.4 | 2.9 | | |
| Decreased Appetite | 9.3 | 1.1 | | |
| Anorexia | 9.0 | 0.0 | | |
| Headache | 8.2 | 4.6 | | |
| Constipation | 5.1 | 1.1 | | |
| Fatique | 5.1 | 1.7 | | |

Gastrointestinal adverse events

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

Immunogenicity Consistent with the potentially immunogenic properties of protein and peptide Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza-treated patients in the five clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end 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 endowed were the set of the service of anti-line of the service of the 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. Crossunderestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liragluidie antibodies to native glucagon-like peptide-1 (GIP-1) occurred in 6.9% of the Victoza-treated patients in the 52-week monotherapy trial and in 4.8% of the Victoza-treated patients in the 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GIP-1, and thus the potential for clinically significant neutralization of native GIP-1 was not assessed. Antibodies that had a neutralizing effect on liragluited in an *in vitro* assay occurred in 2.3% of the Victoza-treated patients in the 52-week monotherapy trial and in 1.0% of the Victoza-treated nations in the 52-week add-on combination theraper 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

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 emparing events the second bit and all antibody-negative active and all antibody-negative active and antibody-negative to the second bit.

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 HbA₁.

In clinical trials of Victoza, events from a composite of adverse events potentially related to in clinical trials of victoza, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza-treated patients. Patients

who developed anti-liraglutide antibodies were not more likely to develop events from the

munogenicity events composite than were patients who did not develop anti-liraglutide

ection site reactions (e.g., injection site rash, erythema) were reported in approximately

2% of Victoza-treated patients in the five clinical trials of at least 26 weeks duration. Less

In clinical trials of Victoza, there were 6 reported cases of papillary thyroid carcinoma in

diameter and were diagnosed in surgical nathology specimens after thyroidectomy r

by findings on protocol-specified screening with serum calcitonin or thyroid ultras

patients treated with Victoza and 1 case in a comparator-treated patient (1.9 vs. 0.6 cases

In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of

another person for treatment occurred in 7 Victoza-treated patients (2.6 cases per 1000

another person for treatment occurred in / viccas-treated patients (2.6 cases per 1000 patient-years) and in no comparator-treated patients. Six of these 7 patients treated with Victoza were also taking a sulfonylurea. One other patient was taking Victoza in combinat with metformin but had another likely explanation for the hypoglycemia (this event occurr during hospitalization and after insulin infusion) (Table 3). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently

been reported in patients who were not taking a concomitant sulfonylurea. Both patients were receiving Victoza, one as monotherapy and the other in combination with metformin

Both patients had another likely explanation for the hypoglycemia (one received insulin

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

Victoza Treatment Active Comparator Placebo Comparato

25.0 (1.66)

2 4 (0.04)

0

22.3 (0.87)

Rosiglitazone

4.3 (0.12)

0.9 (0.02

None

nsulin glargine Metformin

28.9 (1.29)

1.7 (0.04)

iride (N=7

ride (N=2

None

o + Met

(N=121)

0

2.5 (0.06)

Placebo +

2.6 (0.17)

ho + Metfo

osiglitazo (N=175)

0

46(015)

bo + Metfo

(N=114)

0

16.7 (0.95)

ride (N=11

Glimepiride (N=24

during a frequently-sampled intravenous glucose tolerance test, and the other had

Victoza (N=497)

9.7 (0.24)

(N=724)

0.1 (0.001)

3.6 (0.05)

toza + Glimer

(N=695)

0.1 (0.003)

7.5 (0.38)

72 + Motf

79(049)

0.6 (0.0

toza + Meti + Glimepiri (N=230)

2.2 (0.06)

27.4 (1.16)

comparator (colon). Causality has not been established

In a pooled analysis of clinical trials, the incidence rate (ner 1,000 patient-years) for

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

In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubir

concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

7.1 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 medication are concomitantly administered with Victoza.

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

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 fo 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

osiglitazon (N=355)

0.9 (0

+ Ros

tracranial hemorrhage and uncertain food intake).

per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest

than 0.2% of Victoza-treated natients discontinued due to injection site reactions

treated patients in the 26-week add-on combination therapy trials.

h Victoza treatment

antibodies

Hypoglycemia

Injection site reactions

Papillary thyroid carcinoma

erapy

Patient not able t

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Patient able t elf-treat

Add-on to Metformir

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Not classified

Laboratory Tests

8.1 Pregnancy

Pregnancy Category

DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

ent not able t

Motforr

management should be initiated. If pancreatitis is confirmed. Victoza should not be restarted. Use with caution in natients with a history of nancreatitis 5.3 Use with Medications Known to Cause Hypoglycemia

One additional case of pancreatitis has subsequently been reported in a Victoza-treated

fully for signs and symptoms of pancreatitis (including persistent severe abdomi netimes radiating to the back and which may or may not be accompanied by vo

pancreatitis is suspected, Victoza and other potentially suspect medications should be

discontinued promptly, confirmatory tests should be performed and appropriate

One advantuate active particleatus inas subsequenting veen reporter un a victuazinteated patient. Some patients had other risk factors for pancreatifics, such as a history of cholelthiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatific with Victoza retartment. After initiation of Victoza, and after dose increases, observe patients

Patients receiving Victoza in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, have an increased risk of hypoglycernia. In the clinical trials of a teast 20 weeks duration hypoglycernia requiring the assistance of another person for treatment occurred in 7 Victo treated patients and in no comparator-treated patients. Six of these 7 patients treated wit Victoza were also taking a sulforylurea. The risk of hypoglycernia may be lowered by a reduct in the dose of sulfonylurea or other insulin secretagogues [see Adverse Reactions (6.1)]. ant occurred in 7 Victoz

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

ADVERSE REACTIONS

6.1 Clinical Trials Experience 6.1 Clinical trials experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Victoza was evaluated in a 52-week monotherapy trial and in four 26-week, add-on combination therapy trials. In the monotherapy trial natients were treated with add-on combination therapy trials. In the monotherapy trial, patients were treated with Victoza 1.2 mg daily, Victoza 1.8 mg daily, or glimepiride 8 mg daily. In the add-on to metformin trial, patients were treated with Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or glimepiride 4 mg. In the add-on to glimepiride trial, patients were treated with Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or rosiglitazone 4 mg. In the add-on to metformin + glimepiride trial, patients were treated with Victoza 1.8 mg, placebo, or insulin glargine. In the add-on to metformin + rosiglitazone trial, patients were treated with Victoza 1.9 Mg. Victoza 1.8 mg, placebo, or insulin glargine. In the add-on to metformin + rosiglitazone trial, patients were treated with Victoza 1.9 Mg. Victoza 1.9

treated patients. The most common adverse reactions leading to withdrawal for Victoza

the five controlled trials of 26 weeks duration or longe



toza® 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 LIS tent Nos. 6.004.297, 6.235.004. 6,582,404 and other patents pending.

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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

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 biotrical concils were mischanen complanyer. 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

and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical nernia 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 control of the other and and the set of the presence of the set of the incidence of total major fetal abnormalities at all doses. and historical controls at 0.01 mg/kg/day (kidneys, scapula), \geq 0.01 mg/kg/day (eves,

and nistorical controls at 0.01 mg/kg/day (kine/kg, scapiua), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and scaral 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. control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide In pregnant temale rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day linaglutide 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 from 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 excrete 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 liraglutide was excreted unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use

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

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

8.6 Renal Impairment

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

8-9693-31-001-4



8.7 Hepatic Impairment

nited experience in patients with mild, moderate or severe hepatic impairment. Therefore. Victoza should be used with caution in this natient nonulation No dose adjustment of Victoza is recommended for 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

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

11 DESCRIPTION

Victoza contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 recentor agonist The peptide precursor of liraglutide, an aniard of mining the random stars as a GLP-1 neterior agoins 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 anginine 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:

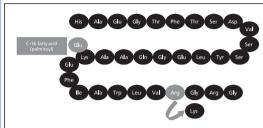


Figure 1 Structural Formula of liraglutide

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. 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 c20% of total circulating endogenous GLP-1. Like GLP-1(7-37), Iraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenyly cyclase by the the human section. ulatory 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 Euglide and the second second second second second in a glucose-dependent in 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 peptidase and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokineti 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 influsion. In these patients, on average, the ISR response was increased in a glucose-dependent manner (Figure 2).

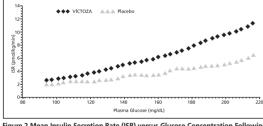


Figure 2 Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose Victoza 7.5 mcg/kg (~ 0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion

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 OTc study. Victoza at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongat

12.3 Pharmacokinetics

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 paraministrational L20 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, liraduitide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous

ministration 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 UKg. Liraglutide is extensively bound to plasma protein (>98%). *Metabolism* - During the initial 24 hours following administration of a single [¹H]-liraglutide does to healthy subjects, the major component in plasma was intact liraglutide. Ligalutide is

endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

Elimination - Following a [⁴H]-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 dearance following the mean apparent dearance following the first 6-8 days. 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 R3 ward) and population pharmacekinetic y in healthy elderly subjects (65 to 83 years) and population phar nts 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. liradutide 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 sever (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 airment was on average 11%, 14% and 42% lower, respectively (see Use in Specific Populations (8.7)

Drug Interactions vitro assessment of drug-drug interactions

Victoza has low potential for pharmacekinetic 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 $C_{\rm max}$ of Victoza (8-12 h) would coincide with the absorption peak of the Refore admi co-administered drug

A single does 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 b 16%; C_{max} decreased by 31%. Digoxin median time to maximal concentration (T_{max}) was delayed from 1 h to 1.5 h. Lisinopril

Lamophi 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 Victoz Atorvastatin

Alcovacation 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. Acetaminonhen

/ictora did not change the overall exposure (ALIC) of acetaminophen following a single dose of acetaminophen 1000 mg, administered 8 hours after the dose of Victoza at steady state. Acetaminophen Conar, available and a state of the dose of Victoza at steady state. Griseofulvin

Victoza did not change the overall exposure (ALIC) of griseofulvin following co-administration To a single does of griseofulvin 500 mg with Victoza at steady state. Griseofulvin C_{max} increased y 37% while median T_{max} did not change. Oral Contracentives

A single dose of an oral contracentive combination product containing 0.03 mg ethinylestradiol

A single tops to an oral contraceptive Continuation product Containing OOS in geninglesization and 0.15 mg devonoregester laws administered under fed conditions and 7 hours after the dose of Victoza at steady state. Victoza lowered ethinylestradiol and levonorgester levosure (AUC) or 12% and 13%, respectively. There was no effect of Victoza on the overall exposure (AUC) or thinylestradiol. Victoza increased the levonorgestrel AUC₀ by 18%. Victoza delayed T_{max} for both ethinylestradiol and levonorgestrel by 1.5 h. NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2, -2, -10 and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in the MRHD of 1.8 mg/day based on plasma AUC comparison. benian 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 incidences of 13% and 19% in males and 6% and 20% in temales, 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 donsal 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 the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 ma/ml.).

prenicity study was conducted in male and female Sprague Dawley rats at A 104-week carcinogenicity study was conducted in male and temale sprague bawley rats doess 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 with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/da groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas wa 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 Percentinos (6 11).

Precautions (5,1)].

Lizadutide was negative with and without metabolic activation in the Ames test for 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 untig 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 39/78 patients with type 2 diabetes participated in 5 double-blind (one of these trials had an open-label active control insulin glargine arm), randomized, controlled clinical trials, one of 52 weeks duration and four of 26 weeks duration. These 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. The 4 add-on

monotherapy and in combination with one of two oral anti-diabetic medications. The 4 add-on combination therapy trials enrolled patients who were previously treated with anti-diabetic therapy, and approximately two-thirds of patients in the monotherapy trial also were previously treated with anti-diabetic therapy. In total, 272 (7%) of the 3978 patients in these 5 trials were new to anti-diabetic therapy. In these 5 clinical trials, patients ranged in age from 19-80 years old and 54% were men. Approximately 77% of patients were Caucasian, and 6% were Black. In the 2 trials where ethnicity was captured, 27% of patients were Hispanic/Latino and 73% were

Non-Hispanic/Latino. In each of these trials, treatment with Victoza produced clinically and statistically significant improvements in hemoglobin A₁, and fasting plasma glucose (EPG ompared to placebo. Victoza did not have adverse effects on blood pressu

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 intestinal intolerance [see Dosage and Administration (2)]

14.1 Monotherany

this 52-week trial 746 patients were randomized to Victoza 1.2 mg. Victoza 1.8 mg. or ride 8 mg. Patients who were randomized to glimepiride were initially treated aily for two weeks, increasing to 4 mg daily for another two weeks, and finally

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 HbA₁ compared to glimepiride (Table 4). The percentage of patients who discontinued due to ineffective therapy was 3.6% in the Victoza 1.8 mg treatment group, 6.0% in the Victoza 1.2 mg treatment group. Table 4 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 Change from baseline | 8.2 | 8.2 | 8.2 |
| (adjusted mean) ^b Difference from glimepiride arm | -1.1 | -0.8 | -0.5 |
| (adjusted mean) ⁶ 95% Confidence Interval | -0.6** (-0.8, -0.4) | -0.3* (-0.5, -0.1) | |
| Patients (%) achieving A _{1c} <7% | 51 | 43 | 28 |
| Fasting Plasma Glucose (mg/dL) (Mean) | | | |
| Baseline Change from baseline (adjusted mean) ^b | -26 | -15 | -5 |
| Difference from glimepiride arm (adjusted mean) ^b 95% Confidence Interval | -20** (-29, -12) | -10* (-19, -1) | |
| Body Weight (kg) (Mean) Baseline | 92.6 | 92.1 | 93.3 |
| Change from baseline (adjusted mean) ^b Difference from glimepiride arm | -2.5 | -2.1 | +1.1 |
| (adjusted mean) ^b 95% Confidence Interval | -3.6** (-4.3, -2.9) | -3.2** (-3.9, -2.5) | |

aIntent-to-treat population using last observation on study ean adjusted for baseline valu

p-value <0.05 *p-value <0.0001

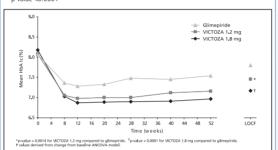


Figure 3 Mean HbA_{1c} for patients who completed the 52-week trial and for the Last Observation Carried Forward (LOCF. intent-to-treat) data at Week 52 (Monotherapy)

14.2 Combination Therapy 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

maintenance period of moutes weeks, burning the tradition period, does of metodmini 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 HbA12 reduction relative to placebo add-on to metformin and resulted in a similar mean HbA_{1c} reduction relative to glimepiride 4 mg add-on to metformin (Table 5). The percentage of patients who discontinued due to ineffective therapy was 5.4% in the Victoza 1.8 mg + metformin treatment group, 3.3% in the Victoza 1.2 mg + metformin treatment group, 23.8% in the placebo + metformin treatment group, and 3.7% in the glimepiride +

Table 5 Results of a 26-week trial of Victoza as add-on to metformin

| | 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 Change from baseline | 8.4 | 8.3 | 8.4 | 8.4 |
| (adjusted mean) ^b Difference from placebo + | -1.0 | -1.0 | +0.1 | -1.0 |
| metformin arm (adjusted mean) ^b 95% Confidence Interval Difference from glimepiride + | -1.1** (-1.3, -0.9) | -1.1** (-1.3, -0.9) | | |
| metformin arm (adjusted mean) ^b 95% Confidence Interval | 0.0 (-0.2, 0.2) | 0.0 (-0.2, 0.2) | | |
| 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 Difference from placebo + | -30 | -30 | +7 | -24 |
| metformin arm (adjusted mean) ^b 95% Confidence Interval Difference from glimepiride + | -38** (-48, -27) | -37** (-47, -26) | | |
| metformin arm (adjusted mean) ^b 95% Confidence Interval | -7 (-16, 2) | -6 (-15, 3) | | |
| Body Weight (kg) (Mean) Baseline Change from baseline | 88.0 | 88.5 | 91.0 | 89.0 |
| (adjusted mean) ^b Difference from placebo + | -2.8 | -2.6 | -1.5 | +1.0 |
| metformin arm (adjusted mean) ^b 95% Confidence Interval Difference from glimepiride + | -1.3* (-2.2, -0.4) | -1.1* (-2.0, -0.2) | | |
| metformin arm (adjusted mean) b 95% Confidence Interval | -3.8** (-4.5, -3.0) | -3.5** (-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.

-value <0.05 *p-value <0.0001

Add-on to Sulfonylurea In this 26-week trial, 1041 patients were randomized to Victoza 0.6 mg, Victoza 1.2 mg, Victoza 1.8 mg, placebo, or rosigilitazone 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 6). The percentage of patients who discontinued due to ineffective therapy was 3.0% in the Victoza 1.8 mg + glimepiride treatment group, 3.5% in the Victoza 1.2 mg + glimepirid treatment group, 17.5% in the placebo + glimepiride treatment group, and 6.9% in the nepiride treatment group

Table 6 Results of a 26-week trial of Victoza as add-on to sulfonylurea Victoza 1.2 mg + Victoza 1.8 mg + Placebo + 4 mg⁺ + Intent-to-Treat Population (N) 11/ 234 228 HbA₁, (%) (Mean) 8.5 8.5 8.4 8.4 Baseline Change from baseline (adjusted mean) ^b Difference from placebo + glimepiride arm (adjusted r 95% Confidence Interval -1.1 -1.1 +0.2 -0.4 -1.4** -1.3** Patients (%) achieving A_{1c} <7% 42 35 22 Fasting Plasma Glucose (mg/dL) (Mean) 174 177 171 179 "hanne from haseline -29 -28 +18 -16 (adjusted mean) " Difference from placebo +

| 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 95% Confidence Interval | -0.1 (-0.9, 0.6) | 0.4 (-0.4, 1.2) | | |

alntent-to-treat population using last observation on study bLeast squares mean adjusted for baseline value

one, one-half of the maximal approved United States dose. *p-value <0.0001

Add-on to Metformin and Sulfonvlurea

Add-on to Mettormin 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 undervent a 2 week period of titration utils Victora. During the triat the to third the Victora 1.8 mg undervent a 2 week 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 s100 mg/dL. Therefore, optimal titration of the insulin plarmine drose was on a chieved in most patients. titration of the insulin glargine dose was not achieved in most patients.

tratation of the insulin glargine dose was not achieved in most patients. Treatment with Victoza as add-on to glimepiride and metformin resulted in a statistically significant mean reduction in HbA_{1c} compared to placebo add-on to glimepiride and metformin (Table 7). The percentage of patients who discontinued due to ineffective therapy was 0.9% in the Victoza 1.8 mg + metformin + glimepiride treatment group, 0.4% in the insulin glargine + metformin + glimepiride treatment group, and 11.3% in the placebo + metformin + glimepiride treatment group.

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

| sultonylurea | | | | |
|---|--|---|---|--|
| | 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 Change from baseline (adjusted mean) ^b Difference from placebo + metformin + glimepinde arm (adjusted mean) ^b 95% Confidence Interval | 8.3 -1.3 -1.1** (-1.3, -0.9) | 8.3 -0.2 | 8.1 -1.1 | |
| Patients (%) achieving A _{1c} <7% | 53 | 15 | 46 | |
| Fasting Plasma Glucose (mg/dL) (Mean) Baseline | 165 | 170 | 164 | |

| Change from baseline (adjusted mean) ^b Difference from placebo + metformin + glimepiride arm (adjusted mean) ^b 95% Confidence Interval | -28 -38** (-46, -30) | +10 | -32 |
|--|---------------------------------------|--------------|-------------|
| Body Weight (kg) (Mean) Baseline Change from baseline (adjusted mean) ^b Difference from placebo + metformin + glimepinde arm (adjusted mean) ^b 95% Confidence Interval | 85.8 -1.8 -1.4* (-2.1, -0.7) | 85.4 -0.4 | 85.2 1.6 |

Intent-to-treat population using last observation on study ILeast squares mean adjusted for baseline value I For insulin glargine, optimal titration regimen was not achieved for 80% of patients.

*p-value <0.05 **p-value <0.0001

Add-on to Metformin and Thiazolidinedione

Adu-on to interformin and integrationtenione 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 rosigilitazone (8 mg) plus metformin (2000 mg). Patients underwer 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 (8 mg/day) and met/formin (2000 mg/day) and completed the final dose of rosiglitazone (8 mg/day) and met/formin (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 HbA12 compared to placebo add-on to metformin and siglitazone (Table 8). The percentage of patients who discontinued due to ineffective Intergy was 1.7% in the Victoza 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the Victoza 1.2 mg + metformin + rosiglitazone treatment group, and 16.4% in the placebo + metformin + rosiglitazone treatment group.

Table 8 Results of a 26-week trial of Victoza as add-on to metformin and

| thiazolidinedione ^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 Change from baseline | 8.6 -1.5 | 8.5 -1.5 | 8.4 -0.5 | |
| (adjusted mean) ^b Difference from placebo + metformin + rosiglitazone arm (adjusted mean) ^b 95% Confidence Interval | -1.5 -0.9** (-1.1, -0.8) | -0.9** (-1.1, -0.8) | -0.5 | |
| Patients (%) achieving A _{1c} <7% | 54 | 57 | 28 | |
| Fasting Plasma Glucose (mg/dL) (Mean) Baseline Change from baseline (adjusted mean) ^b Difference from placebo + metformin + rosiglitazone arm (adjusted mean) ^b 95% Confidence Interval | 185 -44 -36** (-44, -27) | 181 -40 -32** (-41, -23) | 179 -8 | |
| Body Weight (kg) (Mean) Baseline Change from baseline (adjusted mean) ^b Difference from placebo + metformin + rosigiltazone arm (adjusted mean) ^b 95% Confidence Interval | 94.9 -2.0 -2.6** (-3.4, -1.8) | 95.3 -1.0 -1.6** (-2.4, -1.0) | 98.5 +0.6 | |

alntent-to-treat population using last observation on study bLeast squares mean adjusted for baseline value

*p-value < 0.0001

16 HOW SUPPLIED/STORAGE HANDLING

16.1 How Supplied

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

2 × Victoza pen NDC 0169-4060-12 3 × Victoza pen NDC 0169-4060-13

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

16.2 Recommended Storage Prior to first use, Victoza should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C) (Table 9). Do not store in 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 inlight. Always remove and safely discard the needle after each injection and store the Victoza per without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy.

Table 9 Recommended Storage Conditions for the Victoza Pen

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

17 PATIENT COUNSELING INFORMATION

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

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

17.3 Never Share a Victoza Pen Between Patients

usel 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

17.4 Instructions

bould be informed of the notential risks and benefits of Victoza and of alternative Patients Should be informed of the polential risks and betrents or victoze and or alemative 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 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 reneved. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom, or if multiplesue mentione participation of the prescription of the patients the starting victor and the patients the starting victor and the patients the starting victor and the starting victor and the starting victor victor and victor any known symptom persists or worsens.

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

17.6 FDA-Approved Medication Guide

See separate leaflet

Rx only

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