08-15

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VICTOZA®
NOVO NORDISK A/S

Name of the medicinal product

Victoza® 6 mg/ml solution for injection in pre-filled pen

Qualitative and quantitative composition

One ml of solution contains 6 mg of liraglutide*. One pre-filled pen contains 18 mg liraglutide in 3 ml.

* human glucagon-like peptide-1 (GLP-1) analogue produced by recombinant DNA technology in Saccharomyces cerevisiae.

For a full list of excipients, see pharmaceutical particulars.

Pharmaceutical form

Solution for injection in a pre-filled pen (injection).

Clear, colourless, isotonic solution; pH=8.15.

Clinical particulars

Therapeutic indications

Victoza® is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:

In combination with:

- Metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea.

In combination with:

- Metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

Posology and method of administration

Posology

The starting dose is 0.6 mg liraglutide daily. After at least one week, the dose should be increased to 1.2 mg. Some patients are expected to benefit from an increase in dose from 1.2 mg to 1.8 mg and based on clinical response, after at least one week the dose can be increased to 1.8 mg to further improve glycaemic control. Daily doses higher than 1.8 mg are not recommended.

Victoza® can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione can be continued unchanged.

Victoza® can be added to existing sulphonylurea or to a combination of metformin and sulphonylurea therapy. When Victoza® is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia (see Special warnings and precautions for use).

Self-monitoring of blood glucose is not needed in order to adjust the dose of Victoza®. However, when initiating treatment with Victoza® in combination with a sulphonylurea, blood glucose self-monitoring may become necessary to adjust the dose of the sulphonylurea.

Special populations

Elderly (>65 years old): No dose adjustment is required based on age.

Therapeutic experience in patients ≥75 years of age is limited (See Pharmacokinetic properties).

Renal impairment: No dose adjustment is required for patients with mild renal impairment. There is limited experience in patients with moderate renal impairment. Victoza® can currently not be recommended for use in patients with severe renal impairment including patients with end-stage renal disease (See Pharmacokinetic properties).

Hepatic impairment: The therapeutic experience in patients with hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment (See Pharmacokinetic properties).

Paediatric population: Victoza® is not recommended for use in children below 18 years of age due to lack of data.

Method of administration

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

However, it is preferable that Victoza® is injected around the same time of the day, when the most convenient time of the day has been chosen. For further instructions on administration (See Special precautions for disposal and other handling).

Victoza® must **not** be administered intravenously or intramuscularly.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use

Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV.

There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis and Victoza® is therefore not recommended in these patients.

The use of Victoza® is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

Use of other GLP-1 analogues have been associated with the risk of pancreatitis. There have been few reported events of acute pancreatitis.

Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Victoza® and other potentially suspect medicinal products should be discontinued.

Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in clinical trials in particular in patients with pre-existing thyroid disease (See Undesirable effects).

Patients receiving Victoza® in combination with a sulphonylurea may have an increased risk of hypoglycaemia (See Undesirable effects). The risk of hypoglycaemia can be lowered by a reduction in the dose of sulphonylurea.

Interaction with other medicinal products and other forms of interaction

In vitro, liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 and plasma protein binding.

The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption. Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.

Paracetamol

Liraglutide did not change the overall exposure of paracetamol following a single dose of 1000 mg. Paracetamol C_{max} was decreased by 31% and median t_{max} was delayed up to 15 min. No dose adjustment for concomitant use of paracetamol is required.

Atorvastatin

Liraglutide did not change the overall exposure of atorvastatin to a clinical relevant degree following single dose administration of atorvastatin 40 mg.

Therefore, no dose adjustment of atorvastatin is required when given with liraglutide. Atorvastatin C_{max} was decreased by 38% and median t_{max} was delayed from 1 h to 3 h with liraglutide.

Griseofulvin

Liraglutide did not change the overall exposure of griseofulvin following administration of a single dose of griseofulvin 500 mg. Griseofulvin C_{max} increased by 37% while median t_{max} did not change. Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required.

Lisinopril and digoxin

Single dose administration of lisinopril 20 mg or digoxin 1 mg with liraglutide showed a reduction of lisinopril and digoxin AUC by 15% and 16%, respectively; C_{max} decreased by 27% and 31%, respectively. Lisinopril median t_{max} was delayed from 6 h to 8 h with liraglutide; whereas digox-

in median t_{max} was delayed from 1 h to 1.5 h. No adjustment of lisinopril or digoxin dose is required based on these results.

Oral contraceptives

Liraglutide lowered ethinyloestradiol and levonorgestrel C_{max} by 12 and 13%, respectively, following administration of a single dose of an oral contraceptive product. T_{max} was delayed by 1.5 h with liraglutide for both compounds.

There was no clinically relevant effect on the overall exposure of either ethinyloestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

Warfarin

No interaction study has been performed. Upon initiation of Victoza® treatment in patients on warfarin more frequent monitoring of INR (International Normalised Ratio) is recommended.

Insulin

Combination of Victoza® with insulin has not been evaluated.

Pregnancy and lactation

Pregnancy

There are no adequate data from the use of Victoza® in pregnant women.

Studies in animals have shown reproductive toxicity (See Preclinical safety data).

The potential risk for humans is unknown.

Victoza® must not be used during pregnancy, and the use of insulin is recommended instead. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Victoza® should be discontinued.

Lactation

It is not known whether liraglutide is excreted in human milk. Animal studies have shown that the transfer of liraglutide and metabolites of close structural relationship into milk is low. Because of lack of experience, Victoza® must not be used during breast-feeding.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza® is used in combination with a sulphonylurea.

Undesirable effects

In five large long-term clinical trials over 2500 patients have received treatment with Victoza® alone or in combination with metformin, a sulphonylurea (with or without metformin) or metformin plus rosiglitazone.

Frequencies are defined as: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequently reported adverse reactions during clinical trials were gastrointestinal disorders: nausea and diarrhoea were very common, whereas vomiting, constipation, abdominal pain, and dyspepsia were common. At the beginning of Victoza® therapy, these gastrointestinal adverse reactions may occur more frequently. These reactions usually diminish within a few days or weeks on continued treatment. Headache and Upper respiratory infection were also common. Furthermore, hypoglycaemia was common, and very common when Victoza® is used in combination with a sulphonylurea. Major hypoglycaemia has primarily been observed when combined with a sulphonylurea.

Table 1 lists related adverse reactions identified from Phase 3 studies with Victoza®. The table presents adverse reactions that occurred with a frequency >5% if the frequency was higher among Victoza® -treated patients than patients treated with comparator. The table also includes adverse reactions with a frequency ≥1% if the frequency was >2 times the frequency for comparator-treated subjects.

Table 1 Adverse reactions reported in long term phase 3 controlled studies		
Body system/ adverse reaction terms	**Frequency of occurrence**	
Reactions	**Common**	**Very Common**
Metabolism and nutrition disorders		
Hypoglycaemia	x	
Anorexia	x	
Appetite decreased	x	
Nervous system disorders		
Headache	x	
Gastrointestinal disorders		
Nausea		x
Diarrhoea		x
Vomiting	x	
Dyspepsia	x	
Abdominal pain upper	x	
Constipation	x	
Gastritis	x	
Flatulence	x	
Abdominal distension	x	
Gastroesophageal reflux disease	x	
Eructation	x	
Infections and infestations		
Upper respiratory tract infection	x	
N= 2501 Victoza® treated patients		

In a clinical trial with Victoza® as monotherapy rates of hypoglycaemia reported with Victoza® were lower than rates reported for patients treated with active comparator (glimepiride). The most frequently reported adverse events were gastrointestinal and infections and infestations.

Hypoglycaemia

Most episodes of confirmed hypoglycaemia in clinical studies were minor. No episodes of major hypoglycaemia were observed in the study with Victoza® used as monotherapy. Major hypoglycaemia may occur uncommonly and has primarily been observed when Victoza® is combined with a sulphonylurea (0.02 events/subject year). Very few episodes (0.001 events/subject year) were observed with administration of Victoza® in combination with oral antidiabetics other than sulphonylureas.

Gastrointestinal adverse reactions

When combining Victoza® with metformin, 20.7% of patients reported at least one episode of nausea, and 12.6% of patients reported at least one episode of diarrhoea. When combining Victoza® with a sulphonylurea, 9.1% of patients reported at least one episode of nausea and 7.9% of patients reported at least one episode of diarrhoea. Most episodes were mild to moderate and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea.

Patients >70 years may experience more gastrointestinal effects when treated with Victoza®.

Patients with mild renal impairment (creatinine clearance ≤60-90 ml/min) may experience more gastrointestinal effects when treated with Victoza®.

Withdrawal

The incidence of withdrawal due to adverse reactions was 7.8% for Victoza® - treated patients and 3.4% for comparator-treated patients in the long-term controlled trials (26 weeks or longer). The most frequent adverse reactions leading to withdrawal for Victoza® -treated patients were nausea (2.8% of patients) and vomiting (1.5%).

Immunogenicity

Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop anti-liraglutide antibodies following treatment with Victoza®. On average, 8.6% of patients developed antibodies. Antibody formation has not been associated with reduced efficacy of Victoza®.

Injection site reactions

Injection site reaction has been reported in approximately 2% of subjects receiving Victoza® in long-term (26 weeks or longer) controlled trials. These reactions have usually been mild and did not lead to discontinuation of Victoza®.

Pancreatitis

Few cases (<0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza®. A causal relationship between Victoza® and pancreatitis can neither be established nor excluded.

Thyroid events

The overall rates of thyroid adverse events in all intermediate and long-term trials are 33.5, 30.0 and 21.7 events per 1000 subject years of exposure for

total liraglutide, placebo and total comparators; 5.4, 2.1 and 0.8 events, respectively concern serious thyroid adverse events.

In Victoza® -treated patients, thyroid neoplasms, increased blood calcitonin and goiters are the most frequently thyroid adverse events and were reported in 0.5%, 1% and 0.8% of patients respectively.

Overdose

In a clinical study of Victoza® , one patient with type 2 diabetes experienced a single overdose of 17.4 mg subcutaneous (10 times the maximal recommended maintenance dose of 1.8 mg). Effects of the overdose included severe nausea and vomiting, but not hypoglycaemia. 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.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group:
Other blood glucose lowering drugs, excl. insulins.

ATC code: A10BX07

Mechanism of action

Liraglutide is a GLP-1 analogue with 97% sequence homology to human GLP-1 that binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in humans suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption; binding to albumin; and higher enzymatic stability towards the dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidase (NEP) enzymes, resulting in a long plasma half-life.

Liraglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Liraglutide stimulates insulin secretion in a glucose-dependent manner. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucosedependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying. Liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake.

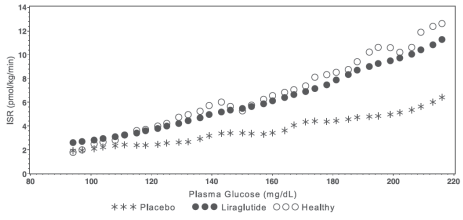
Pharmacodynamic effects

Liraglutide has 24-hour duration of action and improves glycaemic control by lowering fasting and postprandial blood glucose in patients with type 2 diabetes mellitus.

Glucose dependent insulin secretion

Liraglutide increased insulin secretion in relation to increasing glucose concentrations. Using a stepwise graded glucose infusion, the insulin secretion rate was increased following a single dose of liraglutide in patients with type 2 diabetes to a level comparable to that observed in healthy subjects (Fig 1).

Figure 1 Mean Insulin Secretion Rate (ISR) versus glucose concentration following single dose 7.5 µg/kg (~0.66 mg) or placebo in subjects with type 2 diabetes (N=10) and untreated healthy subjects (N=10) during graded glucose infusion



Clinical efficacy

Five double-blind, randomised, controlled clinical trials were conducted to evaluate the effects of Victoza® on glycaemic control. Treatment with Victoza® produced clinically and statistically significant improvements in glycosylated haemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose and post-prandial glucose compared with placebo.

These studies included 3,978 exposed patients

with type 2 diabetes (2,501 subjects treated with Victoza®), 53.7% men and 46.3% women, 797 subjects (508 treated with Victoza®) were ≥65 years of age and 113 subjects (66 treated with Victoza®) were ≥75 years of age.

There was an additional open-label randomised controlled study comparing Victoza® with Byetta.

Glycaemic control

Victoza® in combination therapy, for 26 weeks, with metformin, glimepiride or metformin and rosiglitazone resulted in statistically significant (p<0.0001) and sustained reductions in HbA_{1c} compared with patients receiving placebo (Tables 2 and 3).

Table 2 Results of two 26 week trials. Victoza® in combination with metformin and Victoza® in combination with glimepiride.

Metformin add-on therapy	1.8 mg liraglutide + metformin[3]	1.2 mg liraglutide + metformin[3]	placebo + metformin[3]	glimepiride[2] + metformin[3]
N	242	240	121	242
Mean HbA_{1c} (%)				
Baseline	8.4	8.3	8.4	8.4
Change from baseline	-1.00	-0.97	0.09	-0.98
Patients (%) achieving HbA_{1c} <7%				
All patients	42.4	35.3	10.8	36.3
Previous OAD monotherapy	66.3	52.8	22.5	56.0
Mean body weight (kg)				
Baseline	88.0	88.5	91.0	89.0
Change from baseline	-2.79	-2.58	-1.51	0.95
Glimepiride add-on therapy	**1.8 mg liraglutide + glimepiride[2]**	**1.2 mg liraglutide + glimepiride[2]**	**placebo + glimepiride[2]**	**rosiglitazone[1]+ glimepiride[2]**
N	234	228	114	231
Mean HbA_{1c} (%)				
Baseline	8.5	8.5	8.4	8.4
Change from baseline	-1.13	-1.08	0.23	-0.44
Patients (%) achieving HbA_{1c} <7%				
All patients	41.6	34.5	7.5	21.9
Previous OAD monotherapy	55.9	57.4	11.8	36.1
Mean body weight (kg)				
Baseline	83.0	80.0	81.9	80.6
Change from baseline	-0.23	0.32	-0.10	2.11

[1] Rosiglitazone 4 mg/day;
[2] glimepiride 4 mg/day;
[3] metformin 2000 mg/day

Table 3 Results of two 26 week trials. Victoza® in combination with metformin + rosiglitazone and Victoza® in combination with glimepiride + metformin.

Metformin + rosiglitazone add-on therapy	1.8 mg liraglutide + metformin[2] + rosiglitazone[3]	1.2 mg liraglutide + metformin[2] + rosiglitazone[3]	placebo + metformin[2] + rosiglitazone[3]	N/A
N	178	177	175	
Mean HbA_{1c} (%)				
Baseline	8.56	8.48	8.42	
Change from baseline	-1.48	-1.48	-0.54	
Patients (%) achieving HbA_{1c} <7%				
All patients	53.7	57.5	28.1	
Mean body weight (kg)				
Baseline	94.9	95.3	98.5	
Change from baseline	-2.02	-1.02	0.60	
Metformin + glimepiride add-on therapy	**1.8 mg liraglutide + metformin[2] + glimepiride[4]**	**N/A**	**placebo + metformin[2] + glimepiride[4]**	**insulin glargine[1] + metformin[2] + glimepiride[4]**
N	230	114	232	
Mean HbA_{1c} (%)				
Baseline	8.3	8.3	8.1	
Change from baseline	-1.33	-0.24	-1.09	
Patients (%) achieving HbA_{1c} <7%				
All patients	53.1	15.3	45.8	
Mean body weight (kg)				
Baseline	85.8	85.4	85.2	
Change from baseline	-1.81	-0.42	1.62	

1 The dosing of insulin glargine was open-labelled and was applied according to the following titration guideline. Titration of the insulin glargine dose was managed by the patient after instruction by the investigator.

Guideline for titration of insulin glargine	
Self-measured FPG	Increase in insulin glargine dose (Unit)
≤5.5 mmol/l (≤100 mg/dl) Target	No adjustment
>5.5 and <6.7 mmol/l (>100 and <120 mg/dl)	0 – 2 [a]
≥6.7 mmol/l (≥120 mg/dl)	2

a According to the individualised recommendation by the investigator at the previous visit for example depending on whether subject has experienced hypoglycaemia.
2 Metformin 2000 mg/day; 3 rosiglitazone 4 mg twice daily;
4 glimepiride 4 mg/day.

Proportion of patients achieving reductions in HbA_{1c}
Victoza® in combination with metformin, glimepiride, or metformin and rosiglitazone resulted in a statistically significant (p≤0.0001) greater proportion of patients achieving an HbA_{1c}≤6.5% at 26 weeks compared with patients receiving these agents alone.

Fasting plasma glucose
Treatment with Victoza® alone or in combination with one or two oral antidiabetic drugs resulted in a reduction in fasting plasma glucose of 13-43.5 mg/dl (0.72-2.42 mmol/l). This reduction was observed within the first two weeks of treatment.

Post-prandial glucose
Victoza® reduces post-prandial glucose across all three daily meals by 31-49 mg/dl (1.68-2.71 mmol/l).

Beta-cell function
Clinical studies with Victoza® indicate improved beta-cell function based on measures such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio. Improved first and second phase insulin secretion after 52 weeks treatment with Victoza® was demonstrated in a subset of patients with type 2 diabetes (N=29).

Body weight
Victoza® in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies in a range from 1.0 kg to 2.8 kg.

Larger weight reduction was observed with increasing body mass index (BMI) at baseline.

A reduction in body weight was seen in patients treated with Victoza® irrespective of the occurrence of nausea.

In combination with metformin Victoza® reduced the visceral adipose tissue in a range of 13-17%.

Blood pressure
Over the duration of the studies Victoza® decreased the systolic blood pressure on average of 2.3 to 6.7 mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5 mmHg.

Pharmacokinetic properties

Absorption
The absorption of liraglutide following subcutaneous administration is slow, reaching maximum concentration 8 -12 hours post dosing. Estimated maximum liraglutide concentration was 9.4 nmol/l for a subcutaneous single dose of liraglutide 0.6 mg. At 1.8 mg liraglutide, the average steady state concentration of liraglutide (AUCT/24) reached approximately 34 nmol/l.

Liraglutide exposure increased proportionally with dose. The intra-subject coefficient of variation for liraglutide AUC was 11% following single dose administration.

Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution
The apparent volume of distribution after subcutaneous administration is 11-17 l. The mean volume of distribution after intravenous administration of liraglutide is 0.07 l/kg. Liraglutide is extensively bound to plasma proteins (>98%).

Metabolism
During 24 hours following administration of a single radiolabelled [^{3}H]- liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (≤9% and ≤5% of total plasma radioactivity exposure). Liraglutide is metabolised in a similar manner to large proteins without a specific organ having been identified as major route of elimination.

Elimination
Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or faeces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or faeces (6% and 5%, respectively).

The urine and faeces radioactivity was mainly excreted during the first 6-8 days, and corresponded to three minor metabolites, respectively.

The mean clearance following subcutaneous administration of a single dose liraglutide is approximately 1.2 l/h with an elimination half-life of approximately 13 hours.

Special populations
Elderly: Age had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results

from a pharmacokinetic study in healthy subjects and population pharmacokinetic data analysis of patients (18 to 80 years).

Gender: Gender had no clinically meaningful effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic data analysis of male and female patients and a pharmacokinetic study in healthy subjects.

Ethnic origin: Ethnic origin had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic analysis which included subjects of White, Black, Asian and Hispanic groups.

Obesity: Population pharmacokinetic analysis suggests that body mass index (BMI) has no significant effect on the pharmacokinetics of liraglutide.

Hepatic impairment: The pharmacokinetics of liraglutide was evaluated in subjects with varying degree of hepatic impairment in a single-dose trial. Liraglutide exposure was decreased by 13-23% in subjects with mild to moderate hepatic impairment compared to healthy subjects. Exposure was significantly lower (44%) in subjects with severe hepatic impairment (Child Pugh score >9).

Renal impairment: Liraglutide exposure was reduced in subjects with renal impairment compared to individuals with normal renal function. Liraglutide exposure was lowered by 33%, 14%, 27% and 28%, respectively, in subjects with mild (creatinine clearance, CrCL 50-80 ml/min), moderate (CrCL 30-50 ml/min), and severe (CrCL <30 ml/min) renal impairment and in end-stage renal disease requiring dialysis.

Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, or genotoxicity.

Non-lethal thyroid C-cell tumours were seen in 2-year carcinogenicity studies in rats and mice. In rats, a no observed adverse effect level (NOAEL) was not observed. These tumours were not seen in monkeys treated for 20 months.

These findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot be completely excluded.

No other treatment-related tumours have been found.

Animal studies did not indicate direct harmful effects with respect to fertility but slightly increased early embryonic deaths at the highest dose. Dosing with Victoza® during mid-gestation caused a reduction in maternal weight and foetal growth with equivocal effects on ribs in rats and skeletal variation in the rabbit. Neonatal growth was reduced in rats while exposed to Victoza®, and persisted in the post-weaning period in the high dose group. It is unknown whether the reduced pup growth is caused by reduced pup milk intake due to a direct GLP-1 effect or reduced maternal milk production due to decreased caloric intake.

PHARMACEUTICAL PARTICULARS

List of excipients

Disodium phosphate dihydrate
Propylene glycol
Phenol
Water for injections.

Incompatibilities

Substances added to Victoza® may cause degradation of liraglutide. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

After first use: 1 month.

Special precautions for storage

Store in a refrigerator (2°C - 8°C). Keep away from the cooling element.

Do not freeze.

After first use: Store below 30°C or store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep the cap on the pen in order to protect from light.

Nature and contents of container

Cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained

in a pre-filled multidose disposable pen made of polyolefin and polyacetal.

Each pen contains 3 ml solution, delivering 30 doses of 0.6 mg, 15 doses of 1.2 mg or 10 doses of 1.8 mg.

Pack sizes of 1, 2 or 3 pre-filled pens. Not all pack sizes may be marketed.

Special precautions for disposal and other handling

Victoza® should not be used if it does not appear clear and colourless.

Victoza® must not be used if it has been frozen.

Victoza® can be administered with needles up to a length of 8 mm and as thin as 32G. The pen is designed to be used with NovoFine® or NovoTwist™ disposable needles.

Injection needles are not included.

The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the Victoza® pen without an injection needle attached. This prevents contamination, infection, and leakage. It also ensures that the dosing is accurate.

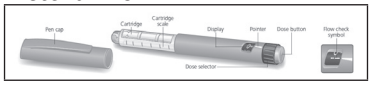
Instructions for using the Victoza® pen Victoza® Pen Needle (example)

Please read these instructions carefully before using your Victoza® pen.

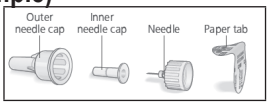
Your Victoza® pen comes with 18 mg of liraglutide. You can select doses of 0.6 mg, 1.2 mg and 1.8 mg.

Victoza® pen is designed to be used with NovoFine® or NovoTwist™ disposable injection needles up to a length of 8 mm and as thin as 32G.

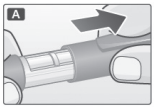
Victoza® Pen



Needle (example)

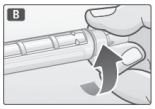


Preparing your Victoza® pen

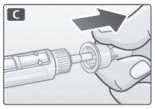


A. Pull off the pen cap.

B. Pull off the paper tab from a new disposable needle. Screw the needle straight and tightly onto your pen.

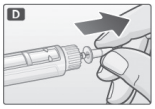


C. Pull off the outer needle cap and keep it for later.



D. Pull off the inner needle cap and throw it away.

⚠ Always use a new needle for each injection to prevent contamination.

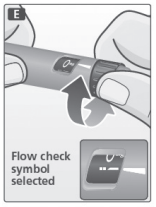


⚠ Be careful not to bend or damage the needle.

⚠ Never put the inner needle cap back on when you have removed it from the needle. This reduces the risk of hurting yourself with the needle.

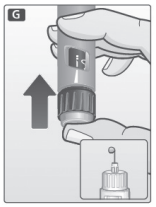
Checking the flow

Always check the flow as follows before you inject with a new pen.



E. Turn the dose selector until the flow check symbol lines up with the pointer.

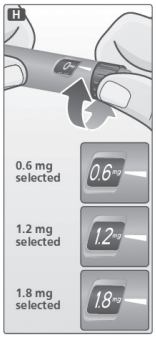
F. Hold the pen with the needle pointing up. Tap the cartridge gently with your finger a few times. This will make any air bubbles collect at the top of the cartridge.



G. Keep the needle pointing up and press the dose button until 0 mg lines up with the pointer. Repeat steps E to G until a drop of liraglutide appears at the needle tip. If no drop appears after six times, change the needle and repeat steps E to G up to six more times. If you still see no drop of liraglutide, the pen is broken and you must use a new one.

Selecting your dose

Always check that the pointer lines up with 0 mg.



H. Turn the dose selector until your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg).

If you selected a wrong dose by mistake, simply change it by turning the dose selector backwards or forwards until the right dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector backwards, as liraglutide may come out.

If the dose selector stops before your needed dose lines up with the pointer, there is not enough liraglutide left for a full dose. Then you can either:

Divide your dose into two injections:
Turn the dose selector in either direction until 0.6 mg or 1.2 mg lines up with the pointer. Inject the dose. Prepare a new pen for injection and inject the remaining number of mg to complete your dose.

Inject the full dose with a new pen:
If the dose selector stops before 0.6 mg lines up with the pointer, prepare a new pen and inject the full dose with the new pen.

⚠ The dose selector clicks when you turn it. You must not use these clicks to select the amount of liraglutide to inject.

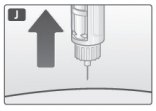
⚠ Do not use the cartridge scale to measure how much liraglutide to inject – it is not accurate enough.

⚠ Do not try to select other doses than 0.6 mg, 1.2 mg or 1.8 mg.

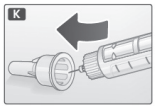
The numbers in the display must line up precisely with the pointer to ensure that you get a correct dose.

Using your injection
Insert the needle into your skin using the injection technique shown by your doctor or nurse. Then follow the instructions below:

I. Press the dose button to inject until 0 mg lines up with the pointer. Be careful not to touch the display with your other fingers or press the dose selector sideways when you inject.

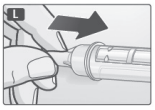


This is because it may block the injection. Keep the dose button pressed down and leave the needle under the skin for at least six seconds. This is to make sure that you get your full dose.



J. Pull out the needle.

After that, you may see a drop liraglutide at the needle tip.
This is normal and has no effect on the dose you have just had.
K. Guide the needle tip into the outer needle cap without touching the outer needle cap.



L. When the needle is covered, carefully push the outer needle cap completely on. Then unscrew the needle. Carefully throw the needle away and put the pen cap back on.
When the pen is empty, carefully throw it away without a needle attached. Please throw the pen and needle away in accordance with local requirements.

⚠ Always remove the needle after each injection and store your Victoza® pen without a needle attached.

⚠ This prevents contamination or infection or leakage of liraglutide. It also ensures that the dosing is accurate.

⚠ Caregivers should be very careful when handling used needles to avoid hurting themselves with the needles.

Please go to www.novonordisk.com for more information.