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. 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.

Combination therapy with basal insulin in patients not achieving adequate glycaemic control with Victoza® and metformin.

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.
Victoza® is not a substitute for insulin.
The addition of liraglutide in patients already treated with insulin has not been evaluated.
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 has 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).
Signs and symptoms of dehydration, including renal impairment and acute renal failure have been reported in patients treated with Victoza®.
Patients treated with Victoza® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.
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 1,000 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.

Digoxin

A single dose administration of digoxin 1 mg with liraglutide resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median time to maximum concentration (t_{max}) was delayed from 1 h to 1.5 h. No dose adjustment of digoxin is required based on these results.

Lisinopril

A single dose administration of lisinopril 20 mg with liraglutide 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 liraglutide. No dose adjustment of lisinopril 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 and other coumarin derivatives

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

Insulin

No pharmacokinetic or pharmacodynamic interactions were observed between liraglutide and insulin detemir when administering a single dose of insulin detemir 0.5 U/kg with liraglutide 1.8 mg at steady state in patients with type 2 diabetes.

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 2,500 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.
Table 1 lists Victoza® adverse reactions reported in long term phase 3 controlled studies and spontaneous (postmarketing) reports. The adverse reactions identified in long term phase 3 studies are presented if they occurred with a frequency >5% and if the frequency was higher among Victoza®-treated patients than patients treated with comparator. Adverse reactions with a frequency ≥1% if the frequency was >2 times the frequency for comparator-treated subjects are also included.
Frequencies for related spontaneous reports (postmarketing) have been calculated based on their incidence in phase 3 clinical studies.

Table 1 Adverse reactions reported in long term controlled phase 3 studies and spontaneous (postmarketing) reports.

Body system/adverse reaction	Frequency of occurrence	
	Phase 3 studies	Spontaneous reports
Metabolism and nutrition disorders		
Hypoglycaemia	Common	
Anorexia	Common	
Appetite decreased	Common	
Nervous system disorders		
Headache	Common	
Gastrointestinal disorders		
Nausea	Very common	
Diarrhoea	Very common	
Vomiting	Common	
Dyspepsia	Common	
Abdominal pain upper	Common	
Constipation	Common	
Gastritis	Common	
Flatulence	Common	
Abdominal distension	Common	
Gastroesophageal reflux disease	Common	
Eructation	Common	
Pancreatitis (including necrotising pancreatitis)		Very rare
Immune system disorders		
Anaphylactic reaction		Rare
Infections and infestations		
Upper respiratory tract infection	Common	
General disorders and administration site conditions		
Malaise		Uncommon
Injection site reactions	Common	
Renal and urinary disorders		
Renal failure acute #		Uncommon
Renal impairment #		Uncommon
Metabolism and nutrition disorders		
Dehydration #		Uncommon
Skin and subcutaneous tissue disorders		
Urticaria		Uncommon
Rash		Common
Pruritus		Uncommon
Cardiac disorders		
Increased heart rate		Common

N= 2,501 Victoza® treated patients
# See Special warnings and precautions for use

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.
When insulin detemir was added to liraglutide 1.8 mg and metformin no major hypoglycaemic events were observed. The rate of minor hypoglycaemic episodes was 0.286 events per subject year. In the comparator groups treated with liraglutide 1.8 mg and metformin the rates of minor hypoglycaemic events were 0.029 and 0.129 events per subject years, respectively.

Gastrointestinal adverse reactions

Most episodes of nausea were mild to moderate, transient and rarely lead to discontinuation of therapy.
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®.

Pancreatitis

Few cases (<0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza®. Pancreatitis was also reported from marketed use. 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 were 33.5, 30.0 and 21.7 events per 1,000 subject years of exposure for total liraglutide, placebo and total comparators; 5.4, 2.1 and 1.2 events, respectively concern serious thyroid adverse events.
Thyroid neoplasm, increased blood calcitonin and goiters were the most frequently reported thyroid adverse events. The rates per 1,000 subject years of exposure were 6.8, 10.9 and 5.4 of liraglutide treated patients in comparison with 6.4, 10.7 and 2.1 of placebo treated and 2.4, 6.0 and 1.8 of total comparator treated patients respectively.

Allergic reactions

Allergic reactions including urticaria, rash and pruritus have been reported from marketed use of Victoza®.
Few cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnoea, oedema have been reported with marketed use of Victoza®.

Overdose

From clinical trials and marketed use overdoses have been reported up to 40 times the recommended maintenance dose (72 mg). Events reported included severe nausea and severe vomiting. None of the reports included severe hypoglycaemia. All patients 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 glucose-dependent 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.

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 postprandial 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 exenatide.
In a 52 week clinical trial, the addition of insulin detemir to Victoza® 1.8 mg and metformin in patients not achieving glycaemic targets on Victoza® and metformin alone, resulted in a HbA_{1c} decrease from baseline of 0.54%, compared to 0.20% in the Victoza® 1.8 mg and metformin control group. Weight loss was sustained.

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 2,000 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 2,000 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.

Postprandial glucose

Victoza® reduces postprandial 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.

Other clinical trials

In a study comparing the efficacy and safety of Victoza® (1.2 mg and 1.8 mg) and sitagliptin (a DPP-4 inhibitor, 100 mg) in patients inadequately controlled on metformin therapy, Victoza® at both doses was superior to sitagliptin treatment in reducing HbA_{1c} after 26 weeks (-1.24%, -1.50% vs -0.90%, p<0.0001).
Significantly more patients achieved HbA_{1c} below 7% with Victoza® compared with sitagliptin (43.7% and 56.0% vs 22.0%, p<0.0001). Patients treated with Victoza® had a significant decrease in body weight compared to that of patients treated with sitagliptin (-2.9 kg and -3.4 kg vs -1.0 kg, p<0.0001). Greater proportions of patients treated with Victoza® experienced nausea vs subjects treated with sitagliptin. However, nausea was demonstrated to be transient. The rate of minor hypoglycaemia was not significantly different between Victoza® and sitagliptin treatment (0.178 and 0.161 vs 0.106 episodes per subject year). The reductions in HbA_{1c} and superiority vs sitagliptin observed after 26 weeks of Victoza® treatment (1.2 mg and 1.8 mg) were sustained after 52 weeks of treatment (-1.29% and -1.51% vs -0.88%, p<0.0001). Switching patients from sitagliptin to Victoza® after 52 weeks of treatment resulted in additional and statistically significant reduction in HbA_{1c} (0.24% and 0.45%, 95% CI: 0.41 to 0.07 and -0.67 to 0.23) at week 78, but a formal control group was not available.
In a study comparing the efficacy and safety of Victoza® 1.8 mg and exenatide 10 µg twice daily in patients inadequately controlled on metformin and/or sulphonylurea therapy, Victoza® was superior to exenatide treatment in reducing HbA_{1c} after 26 weeks (-1.12% vs -0.79%, p<0.0001). Significantly more patients achieved HbA_{1c} below 7% with Victoza® compared with exenatide (54.2% vs 43.4%, p=0.0015). Both treatments resulted in mean body weight loss of approximately 3 kg. The proportion of patients reporting nausea was lower with Victoza® than with exenatide. The rate of minor hypoglycaemia in the Victoza® group was significantly lower compared to that in the exenatide group (1.932 versus 2.600 events per subject year, p=0.01). Switching patients from exenatide to Victoza® after 26 weeks of treatment resulted in an additional reduction in HbA_{1c} (-0.32%, p<0.0001) at week 40 while bringing another 13% of patients below HbA_{1c} 7%.

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 (AUC_{tau}) 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.

Marketing Authorisation Holder

Novo Nordisk A/S, Novo Allé, DK-2880 Bagsvær d, Denmark

novo nordisk®

8-9695-00-018-1

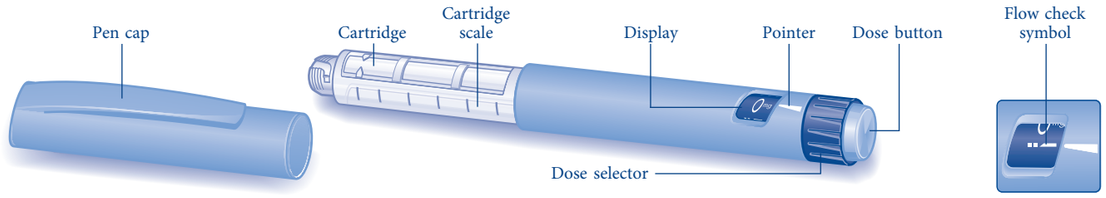
INSTRUCTIONS FOR USING THE VICTOZA® PEN

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

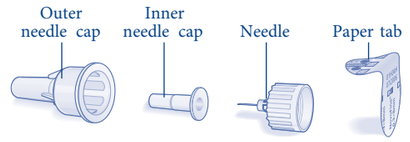
Your Victoza® pen comes with 18 mg of liraglutide. You can select doses of 0.6 mg, 1.2 mg and 1.8 mg.

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

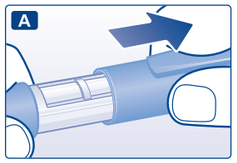


Needle (example)

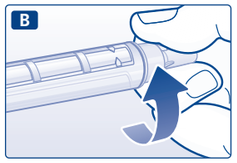


Preparing your Victoza® pen

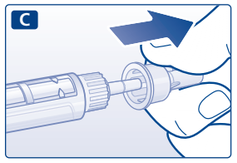
A Pull off the pen cap.



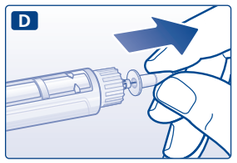
B Pull off the paper tab from a new disposable needle. Screw the needle straight and tightly onto your pen.



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.

Caring for your Victoza® pen

Your Victoza® pen is accurate and safe to use.
But you must take care of it:

- Do not try to repair your pen or pull it apart.
- Keep your pen away from dust, dirt and all kinds of liquids.
- Clean the pen with a cloth moistened with a mild detergent. Do not try to wash it, soak it or lubricate it – this can harm the pen.

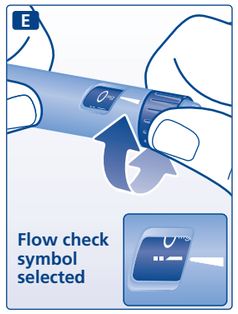
⚠ Important information

- Do not share your Victoza® pen with anyone else.
- Keep your Victoza® pen out of reach of others, especially children.

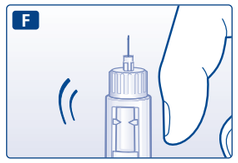
Checking the flow

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

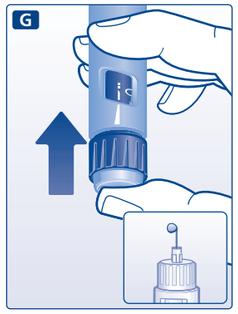
E Turn the dose selector until the flow check symbol lines up with the pointer.



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.



⚠ If you have dropped your pen against a hard surface or suspect that something is wrong with it, always put on a new disposable needle and check the flow before you inject.

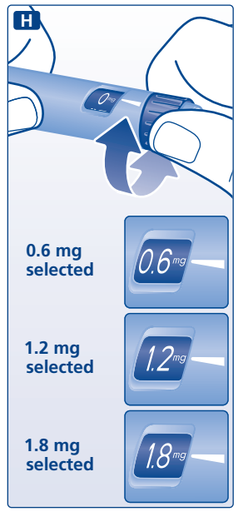
Selecting your dose

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.

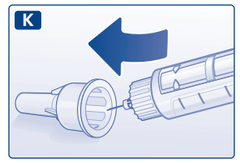
Using your injection

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

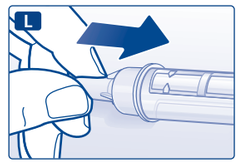
I Press the dose button to inject until 0 mg lines up with the pointer. Be careful not to touch the display with your other fingers or press the dose selector sideways when you inject. This is because it may block the injection. Keep the dose button pressed down and leave the needle under the skin for 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 of 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.