New Zealand Datasheet

1 PRODUCT NAME
VICTOZA® solution for injection 6 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Victoza contains liraglutide, a human glucagon-like peptide-1 (GLP-1) analogue that binds to and activates the GLP-1 receptor (GLP-1R). One ml contains 6 mg salt-free anhydrous liraglutide. Liraglutide is produced by recombinant DNA technology using *Saccharomyces cerevisiae*.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Victoza is a sterile, clear, colourless or almost colourless, isotonic solution of liraglutide 6 mg/ml (pH=8.15). Victoza is a solution for injection in a pre-filled pen. One mL of solution contains 6 mg salt-free anhydrous liraglutide. One pre-filled pen contains 18 mg liraglutide in 3 mL.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Glycaemic control
Victoza is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus

Prevention of cardiovascular events
Victoza is indicated to prevent Major Adverse Cardiovascular Events (MACE: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus at high cardiovascular risk, as an adjunct to standard of care therapy (see Clinical Trials).

4.2 Dose and method of administration
Dosage
To improve gastrointestinal tolerability, the starting dose is 0.6 mg Victoza 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 sulfonylurea or combined metformin and sulfonylurea therapy or insulin. When Victoza is added to sulfonylurea therapy or insulin, a reduction in the dose of sulfonylurea should be considered to reduce the risk of hypoglycaemia (see section 4.4)

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 sulfonylurea or an insulin, blood glucose self-monitoring may become necessary to adjust the dose of the sulfonylurea or the insulin.

Specific patient groups:
Elderly (> 65 years old)
No dosage adjustment is required based on age (see section 5.2).

Patients with hepatic impairment
No dose adjustment is required for patients with hepatic impairment (see section 5.2).

Patients with renal impairment
No dose adjustment is required for patients with mild, moderate or severe renal impairment. There is no therapeutic experience in patients with end-stage renal disease and Victoza is therefore not recommended for use in these patients (see section 5.2).

Children and adolescents
The safety and efficacy of Victoza in children and adolescents below age 18 have not been established. No data are available.

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. Injection sites should always be rotated within the same region in order to reduce the risk of cutaneous amyloidosis (see section 4.8). 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 Instructions for use and handling.

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

In case of a missed dose, Victoza should be administered as soon as possible within 12 hours from the time of the planned dose. If the dose is missed for more than 12 hours, Victoza should be taken as planned on the next day. An extra dose or an increased dose of Victoza must not be administered on the following day to make up for the missed dose.

Instructions for use and handling
The Victoza pen is for use by one person only.

Victoza should not be used if it does not appear clear and colourless, or almost colourless.

Victoza which has been frozen must not be used.

After the first use of the Victoza pen, the product can be stored for 1 month at room temperature (not above 30°C) or in a refrigerator (2 - 8°C).

The patient should be advised to discard the needle after each injection.

Any unused product or waste material should be disposed of in accordance with local requirements.

4.3 Contraindications
Hypersensitivity to liraglutide or any of its excipients.

4.4 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.

There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV and Victoza is therefore not recommended in these patients.

There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis. Use of Victoza is not recommended in these patients since it is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

Aspiration in association with general anaesthesia or deep sedation
Cases of pulmonary aspiration have been reported in patients receiving GLP-1 RAs undergoing general anaesthesia (GA) or deep sedation despite reported adherence to preoperative fasting recommendations. Therefore, the increased risk of residual gastric content because of delayed gastric emptying should be considered prior to performing procedures with GA or deep sedation.

Acute pancreatitis
Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued; if acute pancreatitis is confirmed, liraglutide should not be restarted. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Dehydration
Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients treated with GLP-1 receptor agonists. Some of the events occurred in patients with pre-existing renal impairment and/or on medicines that affect renal function. Although renal function improved with symptomatic treatment in most patients, some patients have required haemodialysis. 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.

Thyroid disease
Thyroid adverse events, such as goitre, have been reported in clinical trials, in particular in patients with pre-existing thyroid disease and Victoza should therefore be used with caution in these patients.

Hypoglycaemia
Patients receiving Victoza in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia (see Table 2 in section 4.8). The risk of hypoglycaemia can be lowered by a reduction in the dose of sulfonylurea or insulin.

4.5 Interaction with other medicines and other forms of interaction

***In vitro* assessment of drug-drug interaction**
Liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 (CYP) and plasma protein binding.

***In vivo* assessment of drug-drug interaction**

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 and therefore no dose adjustment is required.

Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.

Paracetamol (Acetaminophen)
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 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 ethinylestradiol and levonorgestrel C_{max} by 12% and 13%, respectively, following administration of a single dose of an oral contraceptive product. T_{max} was 1.5 h later with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinylestradiol 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. A clinically relevant interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin cannot be excluded. Upon initiation of liraglutide treatment in patients on warfarin or other coumarin derivatives, more frequent monitoring of International Normalised Ratio (INR) 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.

4.6 Fertility, 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 5.3 Preclinical safety data). The potential risk for humans is unknown. Victoza must not be used during pregnancy and the use of insulin is recommended. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Victoza should be discontinued.

Breastfeeding

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

Fertility

Apart from a slight decrease in the number of live implants, animal studies did not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. It is unlikely that the ability to drive or use machines should be impaired by Victoza. 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 sulfonylurea or insulin.

4.8 Undesirable effects

Summary of safety profile

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 events may occur more frequently; these reactions usually diminish within a few days or weeks on continued treatment.

Headache and upper respiratory tract infections were also common. Furthermore, hypoglycaemia was common, and very common when Victoza was used in combination with sulfonylurea. Severe hypoglycaemia has primarily been observed when combined with a sulfonylurea.

Tabulated summary of adverse reactions

Table 1 lists adverse reactions reported in long-term phase 3a controlled trials, the LEADER trial and spontaneous (post-marketing) reports. Frequencies for all events have been calculated based on their incidence in phase 3a clinical trials.

The reactions are listed below as MedDRA preferred term by system organ class and absolute frequency. 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) and not known (cannot be estimated from the available data).

Table 1: Adverse reactions from long-term controlled phase 3a studies, the long-term cardiovascular outcome trial (LEADER®) and spontaneous (post-marketing) reports

MedDRA system organ class	Very common	Common	Uncommon	Rare	Very rare	Not known

Infections and infestations		Upper respiratory tract infection				
Immune system disorders				Anaphylactic reactions		
Metabolism and nutrition disorders		Hypoglycaemia* Anorexia Appetite decreased	Dehydration#			
Nervous system disorders		Headache Dizziness	Dysgeusia			
Cardiac disorders		Increased heart rate				
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Dyspepsia Abdominal pain upper Constipation Gastritis Flatulence Abdominal distension Gastro-esophageal reflux disease Eructation	Delayed gastric emptying		Pancreatitis (including necrotising pancreatitis)	
Hepatobiliary disorders			Cholelithiasis Cholecystitis			
Skin and subcutaneous tissue disorder		Rash	Urticaria Pruritus			Cutaneous amyloidosis†
Renal and urinary disorders			Renal impairment# Renal failure acute#			
General disorders and administration site conditions		Injection site reactions Fatigue	Malaise			
Investigations		Increased lipase** Increased amylase**				

N= 2,501 Victoza treated patients in phase 3a trials except for **
*Frequency is very common when used in combination with insulin
See Warnings and Precautions
** From controlled phase 3b and 4 clinical trials only where these were measured.
† Adverse reaction from post marketing sources

Description of selected adverse events

Hypoglycaemia

Most episodes of confirmed hypoglycaemia in clinical studies were minor.

No episodes of severe hypoglycaemia were observed in the study with Victoza used as monotherapy. Severe hypoglycaemia may occur uncommonly and has primarily been observed when Victoza is combined with a sulfonylurea (0.02 events/subject year). Very few episodes (0.001 events/subject year) were observed with administration of Victoza in combination with a non-sulfonylurea. In the LEADER trial, severe hypoglycaemic episodes were reported at a lower rate with Victoza vs placebo (0.01 vs 0.015 events per patient years; estimated rate ratio 0.69 [0.51 to 0.93]) (see Clinical Trials).

When insulin detemir was added to Victoza 1.8 mg and metformin, no major hypoglycaemic events were observed. The rate of minor hypoglycaemic episodes was 0.228 events per

subject year. In the comparator groups treated with Victoza 1.8 mg and metformin, the rates of minor hypoglycaemic events were 0.034 and 0.115 events per subject year, respectively.

The table below presents incidence as the proportion of patients experiencing at least one confirmed hypoglycaemic episode.

Table 2: Hypoglycaemia in long-term controlled clinical studies of Victoza monotherapy or combinations with oral antidiabetic drugs (OAD)

	Number of episodes divided by subject years of exposure	
Monotherapy (LEAD 3)	**Liraglutide**	**Placebo + Sulfonylurea**
(52 week study)	0.27	1.70
Combination with Metformin (LEAD 2)	**Liraglutide + Metformin**	**Metformin + Sulfonylurea**
(26 week study)	0.05	0.87
Combination with Sulfonylurea (LEAD 1)	**Liraglutide + Sulfonylurea**	**Sulfonylurea + Thiazolidinedione**
(26 week study)	0.43	0.14
Combination with Metformin + Thiazolidinedione (LEAD 4)	**Liraglutide + Metformin + Thiazolidinedione**	**Placebo + Metformin + Thiazolidinedione**
(26 week study)	0.50	0.18
Combination with Metformin + Sulfonylurea (LEAD 5)	**Liraglutide + Metformin + Sulfonylurea**	**Insulin glargine + Metformin + Sulfonylurea**
(26 week study)	1.21	1.33

Gastrointestinal adverse events
Most episodes of nausea were mild to moderate, transient and rarely led to discontinuation of therapy (Figure 1).

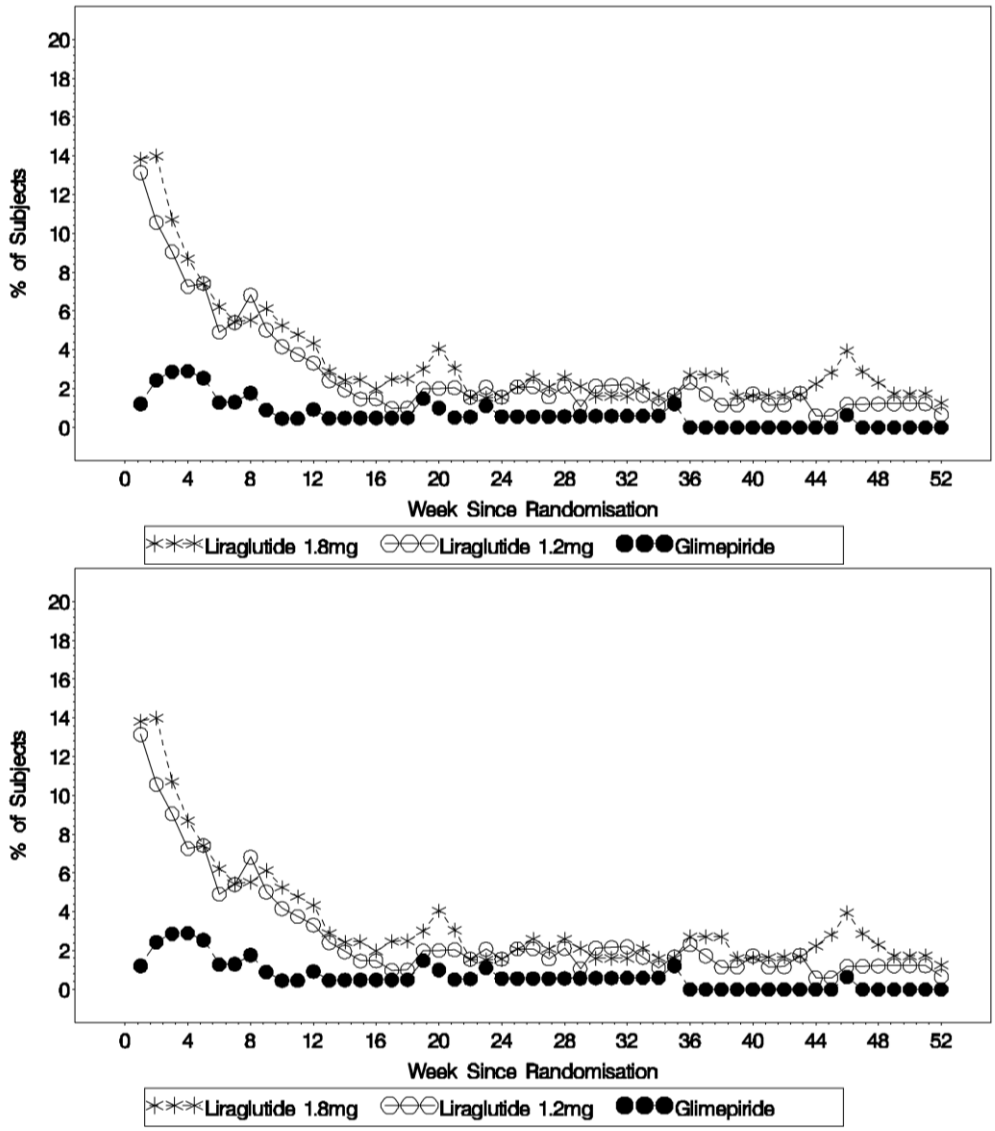


Figure 1: Percentage of patients with nausea adverse events by week - long-term trial (LEAD 3; Trial 1573)

At least one episode of nausea was reported in 20.7% of patients treated with Victoza combined with metformin and in 9.1% when combined with sulfonylurea. At least one episode of diarrhoea was reported in 12.6% of patients treated with Victoza® combined with metformin and in 7.9% when combined with sulfonylurea.

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

Patients >70 years may experience more gastrointestinal effects when treated with Victoza. Patients with mild and moderate renal impairment (creatinine clearance 60-90 ml/min and 30–59 ml/min, respectively) may experience more gastrointestinal effects when treated with Victoza.

Injection site reactions

Injection site reactions have been reported in approximately 2% of patients who received Victoza in long-term (26 weeks or longer) controlled trials. The majority of these reactions were mild.

Pancreatitis
Few cases of acute pancreatitis (<0.2%) have been reported during long-term controlled phase 3 clinical trials with Victoza. Pancreatitis was also reported from marketed use. In the LEADER trial, the frequency of acute pancreatitis confirmed by adjudication was 0.4% for Victoza and 0.5% for placebo, respectively (see Clinical Trials).

Cholelithiasis and cholecystitis
Few cases of cholelithiasis (0.4%) and cholecystitis (0.1%) have been reported during long-term, controlled phase 3a clinical trials with Victoza. In a long-term cardiovascular outcome trial (LEADER), the frequency of cholelithiasis and cholecystitis was 1.5% and 1.1% for Victoza and 1.1% and 0.7% for placebo, respectively.

Skin and subcutaneous tissue disorders
Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing cutaneous amyloidosis. There may be a potential risk of change in Victoza absorption or effect following Victoza injections at sites with cutaneous amyloidosis.

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.

Post-marketing adverse effects
The following adverse reactions have been reported during post approval use of liraglutide, the active ingredient of VICTOZA. Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations
- Urinary Tract Infection

Gastrointestinal disorders
- Intestinal obstruction*
  *Grouped term covering PTs Intestinal obstruction, Ileus, small intestinal obstruction

Nervous system disorders
- Dysaesthesia

Skin and subcutaneous tissue disorders
- Alopecia

Eye Disorders
- Non-arteritic anterior ischaemic optic neuropathy (NAION)*
  *Cases of NAION have been reported with GLP-1 RAs, including liraglutide. A sudden loss of vision should lead to ophthalmological examination

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

From clinical trials and marketed use, overdoses have been reported up to 40 times the recommended maintenance dose (72 mg). One case of a 10-fold overdose (18 mg daily) given for 7 months has been reported. Generally, the patients reported severe nausea, vomiting and diarrhoea, but recovered without complications. Severe hypoglycaemia has been observed.

In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. The patient should be observed for clinical signs of dehydration and blood glucose should be monitored. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Glucagon-like peptide-1 (GLP-1) analogues: ATC code A10BJ02.

Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analogue 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. Liraglutide exhibits 97% homology to human GLP-1. In liraglutide, the lysine at position 34 has been replaced with arginine, and a palmitic acid has been attached via a glutamoyl spacer to lysine at position 26.

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 enzymatic stability towards the DPP-IV and 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 and improves beta-cell function. 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.

GLP-1 is a physiological regulator of appetite and calorie intake and GLP-1 receptor (GLP-R) is present in several areas of the brain involved in appetite regulation.

In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions including the hypothalamus, where liraglutide, via specific activation of the GLP-1 receptor, increased satiety and decreased hunger signals, thereby leading to lower body weight.

GLP-1 receptors are also expressed in specific locations in the heart, vasculature, immune system, and kidneys. Human and animal studies have shown that activation of these receptors with liraglutide may mediate cardiovascular and microvascular effects, including reduced inflammation. Animal studies show that liraglutide attenuates the development of atherosclerosis.

Liraglutide has been shown to delay the progression of diabetes in animal models of pre-diabetes. Liraglutide has been shown *in vitro* to be a potent agent for specific stimulation of beta-cell proliferation and prevention of both cytokine and free fatty acid induced beta-cell death (apoptosis). *In vivo*, liraglutide increases insulin biosynthesis, and beta-cell mass in diabetic animal models. When glucose is fully normalised, liraglutide does not increase beta-cell mass.

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

The difference between liraglutide 1.8 mg / 1.2 mg and placebo in reduction of mean fasting glucose was found to be 3.90 mmol/l / 3.33 mmol/l (Figure 2). Following a standard meal, the difference in mean 2-hour postprandial glucose concentration was 6.02 mmol/l / 5.63 mmol/l. In addition, liraglutide decreased postprandial glucose excursion (incremental postprandial glucose) on average by 1.1 mmol/l / 1.08 mmol/l.

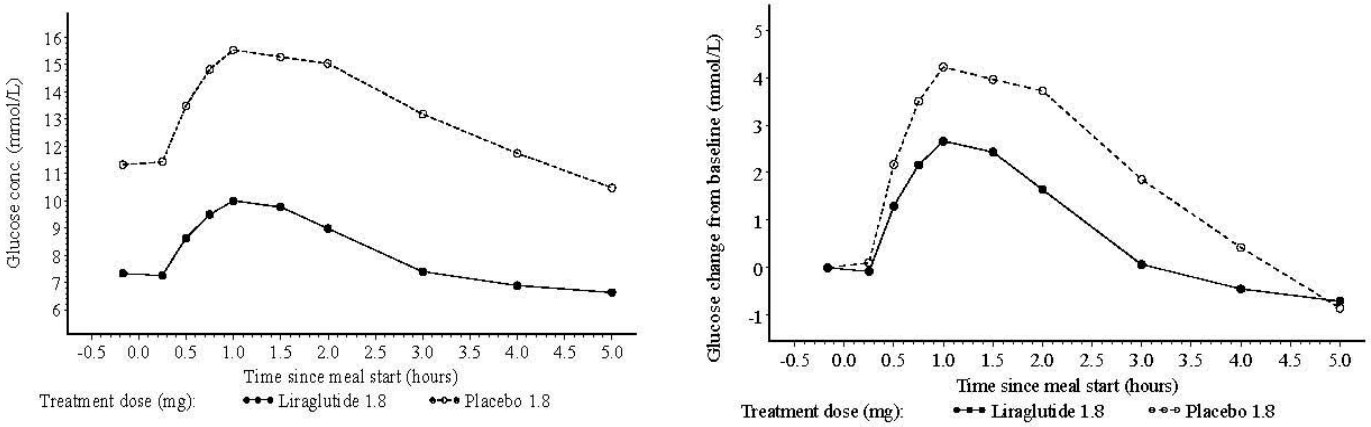


Figure 2: Mean absolute (left) and incremental (right) postprandial glucose concentrations. Subjects with type 2 diabetes treated with liraglutide 1.8 mg or placebo in a cross-over design (N=18) (Trial 1698)

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 injection of liraglutide in subjects with type 2 diabetes to a level indistinguishable to that observed in healthy subjects (Figure 3).

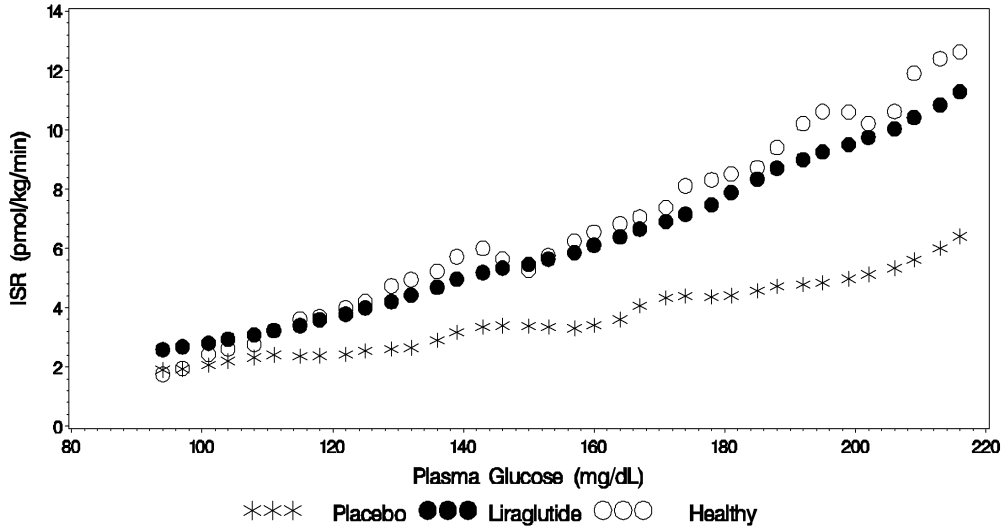


Figure 3: Mean Insulin Secretion Rate (ISR) versus glucose concentration following a single injection of liraglutide 7.5 µg/kg (~0.66 mg) or placebo in subjects with type 2 diabetes (N=10) and untreated healthy subjects (N=10) during graded glucose infusion (Trial 2063)

Beta-cell function

Liraglutide improved beta-cell function as measured by first- and second phase insulin response and maximal beta-cell secretory capacity. A pharmacodynamic study in subjects with type 2 diabetes demonstrated restoration of first phase insulin secretion (intravenous bolus of glucose), improved second phase insulin secretion (hyperglycaemic clamp) and maximal insulin secretory capacity (arginine stimulation test) (Figure 4).

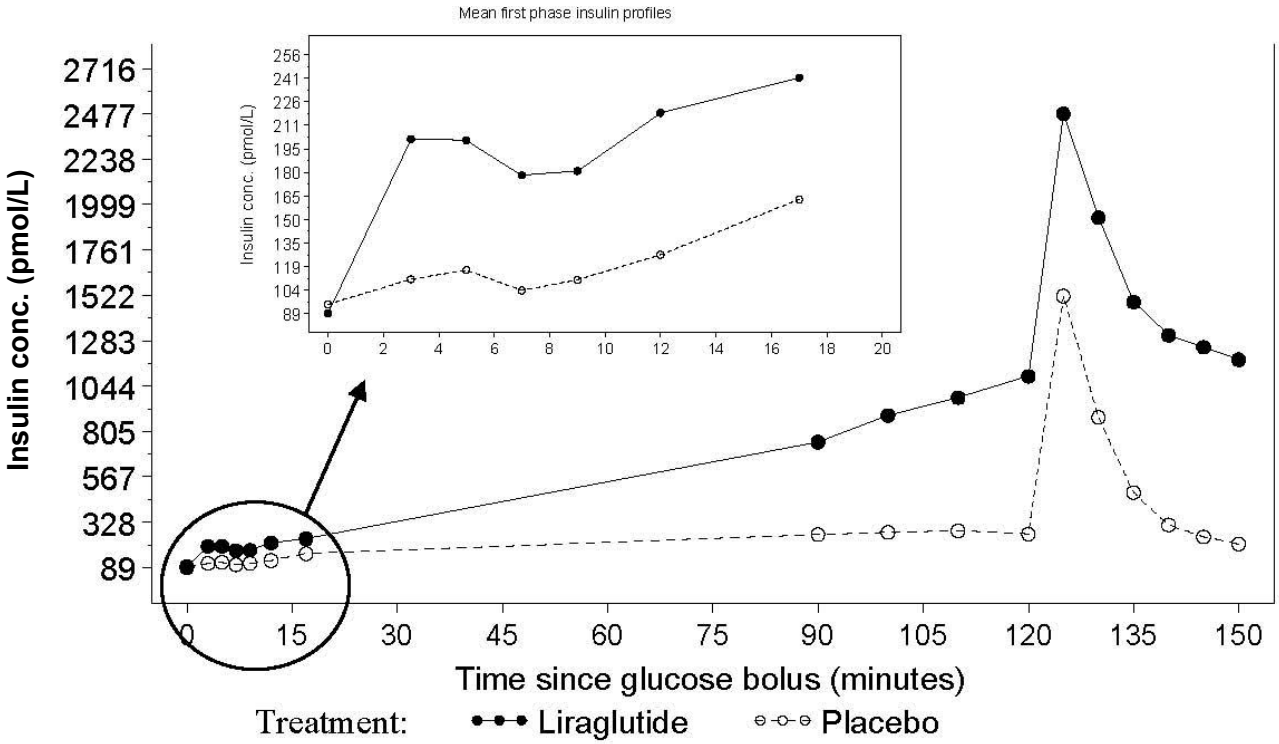


Figure 4: Mean insulin profiles during glucose bolus (inserted), hyperglycaemic clamp and arginine stimulation test (at 120 min) following 6 µg/kg (~0.55 mg) liraglutide or placebo for 10 days in subjects with type 2 diabetes (Trial 1332)

Clinical studies up to 52 weeks with liraglutide have shown improved and sustained beta-cell function, using measures such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio.

Glucagon secretion
Liraglutide lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. Liraglutide did not impair glucagon response to low glucose concentration. Furthermore, a lower endogenous glucose release was observed with liraglutide.

Gastric emptying
Liraglutide caused a minor delay in gastric emptying, thereby reducing the rate at which postprandial glucose appeared in the circulation.

Body weight, body composition and energy intake
In clinical studies up to 52 weeks involving patients with elevated body weight liraglutide significantly lowered body weight. Computerized tomography (CT) and Dual X-ray absorptiometry (DEXA) scans showed that this weight loss was primarily from fat tissue. These findings are considered to be explained by reduced sensation of hunger and reduced energy intake, seen during liraglutide treatment.

Cardiac Electrophysiology (QTc)
In a cardiac repolarisation study liraglutide at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

Clinical Trials
There were 3992 subjects with type 2 diabetes randomised in five double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of Victoza on glycaemic control. Treatment with Victoza produced clinically and statistically significant improvements in haemoglobin A_{1c}, fasting plasma glucose (FPG) and post-prandial glucose (PPG) compared with placebo.

These studies included 3978 exposed patients (2501 patients treated with Victoza), 53.7% men and 46.3% women, 797 patients (508 treated with Victoza) were ≥ 65 years of age and 113 patients (66 treated with Victoza) were ≥ 75 years of age.

Glycaemic control
Table 3 Victoza clinical phase 3a trials in monotherapy (52 weeks) and in combination with oral antidiabetics (26 weeks)

	N	Mean baseline HbA_{1c} (%)	Mean HbA_{1c} change from baseline (%)	Patients (%) achieving HbA_{1c} <7%	Mean baseline weight (kg)	Mean weight change from baseline (kg)
Monotherapy						
Liraglutide 1.2 mg	251	8.18	-0.84*	42.8[1], 58.3[3]	92.1	-2.05**
Liraglutide 1.8 mg	246	8.19	-1.14**	50.9[1], 62.0[3]	92.6	-2.45**
Glimepiride 8 mg/day	248	8.23	-0.51	27.8[1], 30.8[3]	93.3	1.12
Add-on to metformin (2,000 mg/day)						

Liraglutide 1.2 mg	240	8.3	-0.97†	35.3[1], 52.8[2]	88.5	-2.58**
Liraglutide 1.8 mg	242	8.4	-1.00†	42.4[1], 66.3[2]	88.0	-2.79**
Placebo	121	8.4	0.09	10.8[1], 22.5[2]	91.0	-1.51
Glimepiride 4 mg/day	242	8.4	-0.98	36.3[1], 56.0[2]	89.0	0.95
Add-on to glimepiride (4 mg/day)						
Liraglutide 1.2 mg	228	8.5	-1.08**	34.5[1], 57.4[2]	80.0	0.32**
Liraglutide 1.8 mg	234	8.5	-1.13**	41.6[1], 55.9[2]	83.0	-0.23**
Placebo	114	8.4	0.23	7.5[1], 11.8[2]	81.9	-0.10
Rosiglitazone 4 mg/day	231	8.4	-0.44	21.9[1], 36.1[2]	80.6	2.11
Add-on to metformin[2] (2,000 mg/day) + rosiglitazone (4 mg twice daily)						
Liraglutide 1.2 mg	177	8.48	-1.48	57.5[1]	95.3	-1.02
Liraglutide 1.8 mg	178	8.56	-1.48	53.7[1]	94.9	-2.02
Placebo	175	8.42	-0.54	28.1[1]	98.5	0.60

Add-on to metformin[2] (2,000 mg/day) + glimepiride (4 mg/day)						
Liraglutide 1.8 mg	230	8.3	-1.33*	53.1[1]	85.8	-1.81**
Placebo	114	8.3	-0.24	15.3[1]	85.4	-0.42
Insulin glargine[4]	232	8.1	-1.09	45.8[1]	85.2	1.62

*Superiority (p<0.01) vs active comparator; **Superiority (p<0.0001) vs active comparator; †Non-inferiority (p<0.0001) vs active comparator

[1]all patients; [2]previous OAD monotherapy; [3]previous diet treated patients

[4]the dosing of insulin glargine was open-labelled and was applied according to Guideline for titration of insulin glargine. 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 patient has experienced hypoglycaemia.

Victoza monotherapy for 52 weeks resulted in statistically significant (p<0.0014) and sustained reductions in HbA_{1c} compared with patients receiving glimepiride (Figure 5).

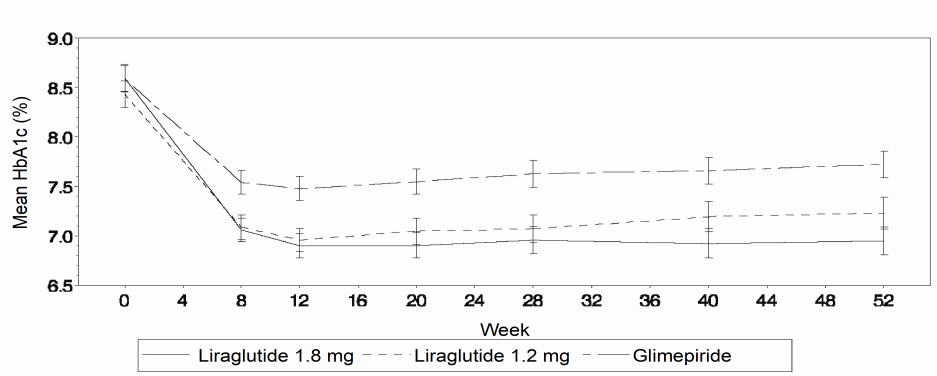


Figure 5 HbA_{1c} level reduced to below 7% and sustained over 12 months when Victoza® is administered to patients previously treated with diet and exercise (Trial 1573).

Patients with an HbA_{1c} above 9.5% at baseline experienced a mean reduction in HbA_{1c} of 2.1% after treatment with Victoza as monotherapy, while patients treated with Victoza in combination studies experienced mean reductions in HbA_{1c} of 1.1−2.5%.

Table 4 Results of a 12+26 week trial where insulin detemir was added to liraglutide and metformin in patients not reaching adequate glycaemic control (HbA_{1c} <7.0%) after a 12 weeks run-in period on liraglutide.

Insulin detemir add-on therapy			
	Patients reaching HbA_{1c} target following 12 weeks of liraglutide + metformin therapy	**Patients not reaching HbA_{1c} target following 12 weeks of liraglutide + metformin therapy**	
	Continued therapy	**Insulin detemir added following week 12**	**Continued therapy**
N (exposed)	498	162	161
Insulin dose (average at week 38)		39U	
HbA_{1c} (%) (Mean)			
Baseline	7.72		
Change from baseline			
12 week	-1.3	-0.6	-0.7
38 week	-1.1	-1.1	-0.8
Patients (%) achieving HbA_{1c} <7%			
12 week	100%	0.0%	0.6%
38 week	76%	43%	17%
Body weight (kg) (Mean)			
Baseline	99.0kg	99.5kg	98.8kg
Change from baseline			
12 week	-4.35kg	-3.53kg	-3.46kg
38 week	-4.8kg	-4.0kg	-4.7kg

Note: The trial initially included 988 patients in run-in. The patients who had previously been on metformin + sulfonylurea were asked to stop sulfonylureabut all patients continued their

pre-trial metformin regimen. After run-in, 498 patients (61% of run-in completers) achieved target HbA_{1c} <7% with liraglutide + metformin, hence continued treatment in a 'non-randomised' arm, while the remaining 323 patients (39%) with an HbA_{1c} ≥7% were randomised to either continue unchanged treatment with Victoza 1.8 mg + metformin as control (N=161) or receive additional intensification with insulin detemir as add-on therapy (N=162).

In patients not achieving glycaemic control on Victoza and metformin, the addition of insulin detemir provided superior efficacy compared to Victoza and metformin alone after 26 weeks of treatment (estimated treatment difference of -0.52% in HbA_{1c}).

Victoza in combination therapy, for 26 weeks, with metformin, a sulfonylurea or a metformin and a thiazolidinedione resulted in statistically significant ($p < 0.0001$) and sustained reductions in HbA_{1c} compared to patients receiving placebo.

The efficacy of Victoza 0.6 mg was also tested in combination with a sulfonylurea or with metformin and was found to be superior to placebo but lower than the other Victoza doses of 1.2 mg and 1.8 mg.

Proportion of patients achieving reductions in HbA_{1c}
Victoza monotherapy resulted in a statistically significant ($p \leq 0.0007$) greater proportion of patients achieving an HbA_{1c} <7% at 52 weeks compared with patients receiving glimepiride. Victoza in combination with metformin, a sulfonylurea, or a metformin and thiazolidinedione resulted in a statistically significant ($p \leq 0.0001$) greater proportion of patients achieving an HbA1c ≤ 6.5% at 26 weeks compared with patients receiving these agents alone.

In patients not achieving glycaemic control on Victoza and metformin, the proportion of patients reaching HbA1c targets of <7% and ≤6.5% was statistically significantly higher with insulin detemir + Victoza 1.8 mg + metformin treatment compared to Victoza1.8 mg + metformin treatment ($p \leq 0.0001$/ $p=0.0016$).

In all 26 week combination studies, more patients reached an HbA1c<7% when Victoza was used as add-on rather than as replacement therapy.

Use in patients with renal impairment
In a double-blind study comparing the efficacy and safety of Victoza 1.8 mg versus placebo as add-on to insulin and/or oral antidiabetic drugs in patients with type 2 diabetes and moderate renal impairment, Victoza was superior to placebo treatment in reducing HbA_{1c} after 26 weeks (-1.05% vs -0.38%, $p<0.0001$). Significantly more patients achieved HbA_{1c} below 7% with Victoza compared with placebo (52.8% vs 19.5% $p<0.0001$). Patients treated with Victoza had a statistically significant decrease in body weight compared to that of patients treated with placebo (-2.41 kg vs -1.09 kg, $p=0.0052$). There was a comparable risk of hypoglycaemic episodes between the two treatment groups. The safety profile of Victoza was generally similar to that observed in other studies with Victoza.

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 0.72-2.42 mmol/l. This reduction was observed within the first two weeks of treatment.

Postprandial glucose
Victoza reduced postprandial glucose across all three daily meals by 1.68-2.71mmol/l.

Body Weight

Victoza monotherapy for 52 weeks was associated with sustained weight reduction.

Victoza in combination with metformin, metformin and sulfonylurea or metformin and thiazolidinedione was associated with sustained weight reduction over the duration of studies.

The weight loss observed in patients treated with Victoza in combination with metformin was sustained after addition of insulin detemir.

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

Treatment with Victoza monotherapy for 52 weeks reduced mean waist circumference by 3.0-3.6 cm.

A reduction in body weight was seen in subjects 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%.

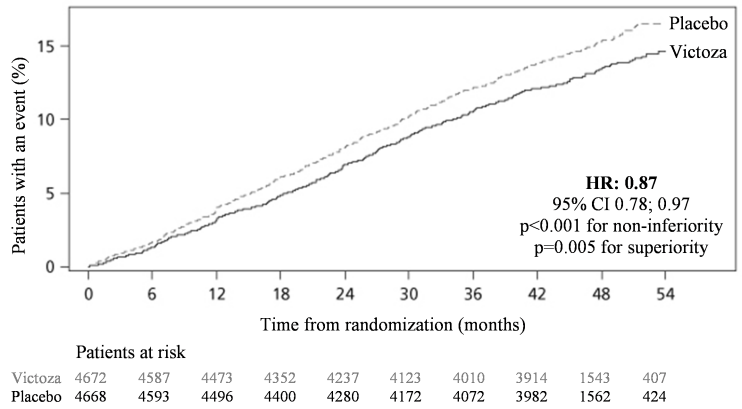
Non-alcoholic fatty liver disease
Victoza reduced hepatic steatosis in patients with type 2 diabetes.

Cardiovascular evaluation
Post-hoc analysis of serious major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke) from all intermediate and long-term phase 2 and 3 trials (ranging from 26 and up to 100 weeks duration) including 5,607 patients (3,651 exposed to Victoza), showed no increase in cardiovascular risk (incidence ratio of 0.75 (95% CI 0.35; 1.63) for Victoza versus all comparators.

The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial was a multicentre, placebo-controlled, double-blind clinical trial. 9,340 patients were randomly allocated to either Victoza (4,668) or placebo (4,672), both in addition to standards of care for managing HbA_{1c} and cardiovascular (CV) risk factors.

Primary outcome or vital status at end of trial was available for 99.7% and 99.6% of participants randomised to Victoza and placebo, respectively. The duration of observation was minimum 3.5 years and up to a maximum of 5 years. The study population included patients ≥65 years (n=4,329) and ≥75 years (n=836), and patients with mild (n=3,907), moderate (n=1,934) or severe (n=224) renal impairment. The mean age was 64 years and the mean BMI was 32.5 kg/m². The mean duration of diabetes was 12.8 years.

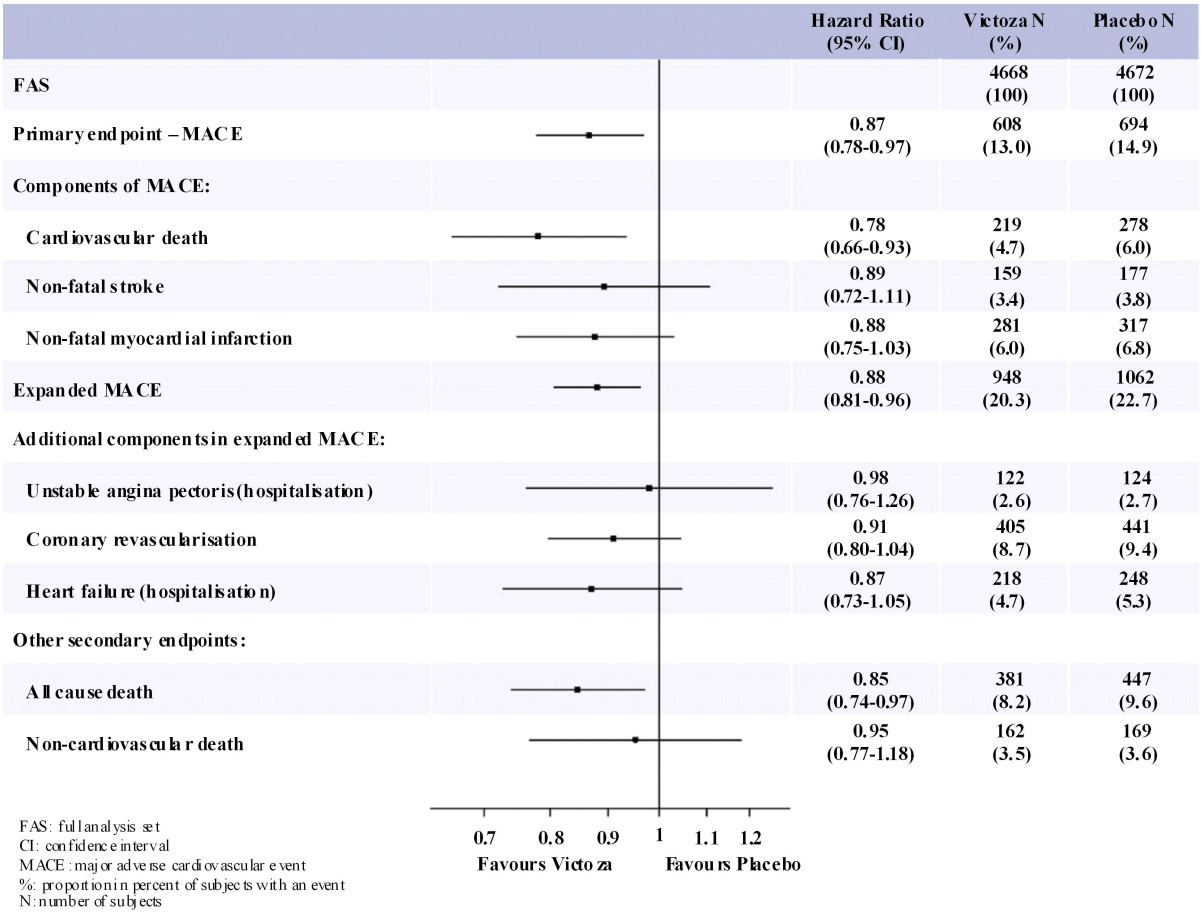
The primary endpoint was the time from randomisation to first occurrence of any major adverse cardiovascular events (MACE): CV death, non-fatal myocardial infarction, or non-fatal stroke. Victoza significantly reduced the risk of MACE vs placebo with an estimated hazard ratio [95% CI] of 0.87 [0.78, 0.97] (p=0.005), corresponding to a relative risk reduction of 13% (Figure 6). The estimated hazard ratio (HR) was consistently below 1 for all 3 MACE components.



FAS: full analysis set.

Figure 6 Kaplan Meier plot of time to first MACE – Full analysis set (FAS) population

Victoza also significantly reduced the time to first expanded MACE (primary MACE, unstable angina pectoris leading to hospitalisation, coronary revascularisation, or hospitalisation due to heart failure) and other secondary endpoints (all cause death or non-cardiovascular death) (Figure 7).



FAS: full analysis set
CI: confidence interval
MACE: major adverse cardiovascular event
%: proportion in percent of subjects with an event
N: number of subjects

Figure 7 Forest plot of analyses of individual cardiovascular event types – FAS population

A significant and sustained reduction in HbA_{1c} from baseline to month 36 was observed with Victoza vs placebo, in addition to standard of care (-1.16% vs -0.77%; estimated treatment difference [ETD] -0.40% [-0.45; -0.34]). The need for treatment intensification with insulin was reduced by 48% with Victoza vs placebo in insulin-naive patients at baseline (HR 0.52 [0.48; 0.57]). A significant and sustained reduction in body weight from baseline to month 36 was also seen with Victoza vs placebo (-2.74 kg vs -0.47 kg, respectively; ETD -2.26 [-2.54; -1.99]). The adverse event profile reported was overall comparable to that observed in completed Victoza clinical trials in type 2 diabetes mellitus (see section 4.2).

Blood pressure and heart rate

Victoza reduced systolic blood pressure with a mean range of 2.3−6.7 mmHg within the first two weeks of treatment in long-term clinical trials. Victoza reduced the occurrence of metabolic syndrome according to the Adult Treatment Panel III (ATPIII) definition. The reduction in systolic blood pressure occurred before weight loss.

In the LEADER trial, systolic blood pressure was reduced with Victoza vs placebo (-1.4 mmHg vs -0.2 mmHg; estimated treatment difference [ETD]: -1.20 mmHg [-1.92; -0.48]) whereas diastolic blood pressure decreased less with Victoza vs placebo (-0.8 mmHg vs -1.4 mmHg, respectively, ETD: 0.59 [0.19; 0.99]) after 36 months. A mean increase in heart rate from baseline of 2 to 3 beats per minute has been observed with Victoza in long-term clinical trials including LEADER. In the LEADER trial, no long-term clinical impact of increased heart rate on the risk of cardiovascular events was observed.

Microvascular events

In the LEADER trial, microvascular events comprised nephropathy and retinopathy outcomes. The analysis of time to first microvascular event for Victoza vs placebo had an HR of 0.84 [0.73, 0.97]. The HR for Victoza vs placebo was 0.78 [0.67, 0.92] for time to first nephropathy event and 1.15 [0.87, 1.52] for time to first retinopathy event.

The estimated treatment ratio for change in urinary albumin/creatinine excretion from baseline to month 36 was 0.81 [0.76, 0.86].

Immunogenicity across trials

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-liraglutide antibodies following treatment with Victoza. On average, 8.6% of subjects developed antibodies. Antibody formation has not been associated with reduced efficacy of Victoza.

Other clinical data

In an open label study comparing the efficacy and safety of Victoza 1.8 mg with lixisenatide 20 µg in 404 patients inadequately controlled on metformin therapy (mean HbA_{1c} 8.4%), Victoza was superior to lixisenatide in reducing HbA_{1c} after 26 weeks of treatment (-1.83% vs -1.21%, $p<0.0001$). Significantly more patients achieved HbA_{1c} below 7% with Victoza compared to lixisenatide (74.2% vs 45.5%, $p<0.0001$), as well as the HbA_{1c} target below or equal to 6.5% (54.6% vs 26.2%, $p<0.0001$). Significantly greater reduction in fasting plasma glucose was achieved with Victoza than lixisenatide (-2.85 vs -1.70 mmol/L, $p<0.0001$). Body weight loss was observed in both treatment arms (-4.3 kg with Victoza and -3.7 kg with lixisenatide). The safety profiles of Victoza and lixisenatide were overall comparable. No new safety information was identified with Victoza.

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 patients 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 sulfonylureatherapy, 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%.

Victoza improved insulin sensitivity compared to a sulfonylurea for 52 weeks as assessed by HOMA-IR.

Patient reported outcomes

In a clinical study comparing Victoza with glimepiride in patients with type 2 diabetes the Victoza 1.8 mg daily monotherapy over 52 weeks significantly improved overall health-related quality of life ($p \leq 0.02$) as defined by combined mental and emotional health and general perceived health. Mental and emotional health ($p = 0.01$) and the component subscales psychological distress ($p = 0.03$) and psychological well being ($p = 0.01$) improved significantly with Victoza 1.8 mg daily monotherapy compared with glimepiride, as did general perceived health ($p = 0.03$). Treatment with either Victoza 1.2 mg daily or 1.8 mg daily significantly improved weight concern compared with glimepiride ($p < 0.01$), while Victoza 1.8 mg daily also significantly improved weight image ($p < 0.01$).

Results from another clinical study comparing Victoza 1.8 mg and 1.2 mg to glimepiride both in combination with metformin showed that subjects treated with the Victoza 1.8 mg combination had a significantly lower and dose-dependent frequency of perceived hyperglycaemia. Victoza 1.2 mg and 1.8 mg, both in combination with metformin, had a significantly lower frequency of hyperglycaemia than metformin alone.

Patients treated with 0.6 mg, 1.2 mg and 1.8 mg of liraglutide in combination with metformin had a significantly lower frequency of perceived hypoglycaemia compared to glimepiride in combination with metformin.

In the LEADER trial, Victoza significantly reduced deterioration in patient reported quality of life compared to placebo (as measured by EQ5D index, ETD 0.018 [0.001; 0.035] and VAS score, ETD 1.302 [0.101; 2.504]) (see section 3.1.9).

5.2 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 ($AUC_{T/24}$) 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. Liraglutide can be administered subcutaneously in the abdomen, thigh, or upper arm.

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 protein (>98%).

Metabolism/biotransformation

During a 24 hours period following administration of a single [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected ($\leq$ 9 % and $\leq$ 5% of total plasma radioactivity exposure). Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ 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.

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

Special populations

Elderly

No dosage adjustment is required based on age. 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 subjects (18 to 80 years).

Gender

No dosage adjustment is required based on 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 subjects and a pharmacokinetic study in healthy subjects.

Ethnicity

No dosage adjustment is required based on ethnicity. Ethnicity had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic analysis.

Obesity

No dosage adjustment is required based on 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 were evaluated in subjects with varying degrees of hepatic impairment in a single-dose trial. Subjects with mild (Child Pugh score 5-6) to severe (Child Pugh score > 9) hepatic impairment were included in the trial. Exposure was not higher in subjects with impaired hepatic function compared to healthy subjects and thus hepatic impairment did not have any clinically relevant effect on the pharmacokinetics of liraglutide.

Renal impairment
The pharmacokinetics of liraglutide was evaluated in subjects with varying degrees of renal impairment in a single-dose trial. 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. Renal impairment did not have any clinically relevant effect on the pharmacokinetics of liraglutide.

Paediatrics
Victoza has not been studied in paediatric subjects.

5.3 Preclinical safety data
Preclinical 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 liraglutide during midgestation 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 liraglutide, and persisted in the post-weaning period in the high dose group. Whether these effects are related to decreased caloric intake as a direct GLP-1 effect is unknown.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Each ml of Victoza also contains the following inactive ingredients: 1.42 mg dibasic sodium phosphate dihydrate, 14.0 mg propylene glycol, 5.5 mg phenol, hydrochloric acid q.s., sodium hydroxide q.s. and water for injections to 1 ml.

6.2 Incompatibilities
Substances added to Victoza may cause degradation of liraglutide. Victoza must not be mixed with other medicinal products, e.g. infusion fluids.

6.3 Shelf life
The shelf-life for Victoza is 30 months. The in-use time is 1 month.

6.4 Special precautions for storage
Store in a refrigerator (2°C to 8°C). 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 first use of the Victoza pen, the product can be stored for 1 month at room temperature (not above 30°C) or in a refrigerator (2 to 8°C).

Victoza should be protected from excessive heat and sunlight.

Victoza pen is for use by one person only.

Victoza should not be used if it does not appear clear and colourless, or almost colourless.

Any unused product or waste material should be disposed of in accordance with local requirements.

Keep the pen cap on when the Victoza pen is not in use in order to protect from light.

Always remove the injection needle 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. The patient should be advised to discard the needle after each injection.

6.5 Nature and contents of container
Pre-filled (multidose, disposable) pen, comprising of a pen injector assembled with a cartridge (3 ml). The cartridge is made of glass (type 1), containing a bromobutyl rubber closure shaped as a plunger and closed with a bromobutyl/polyisoprene rubber closure. The pen injector is made of polyolefin and polyacetal. When incinerated these materials only result in non-toxic waste products (carbon dioxide and water).

The Victoza pen contains 30 doses of 0.6 mg, 15 doses of 1.2 mg or 10 doses of 1.8 mg.

Pack sizes: 1 pen, 2 pens, 3 pens.

Not all pack sizes may be marketed.

Injection needles are not included. 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®
disposable needles.

6.6 Special precautions for disposal
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.

7 MEDICINE SCHEDULE
Prescription Medicine.

8 SPONSOR

Novo Nordisk Pharmaceuticals Ltd
PO Box 51-268
Pakuranga
Auckland

Telephone: (09) 916 5590
Fax: (09) 916 5595

9 DATE OF FIRST APPROVAL

24 June 2010.

10 DATE OF REVISION OF THE TEXT

27 August 2026.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of NAION, alopecia and dysaesthesia as post-marketing adverse events