PROPOSED AMENDED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Victoza®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 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 the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen

Clear and colourless or almost colourless, isotonic solution;

pH = 8,15.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Glycaemic control:

Victoza® is indicated as an adjunct to diet and exercise to achieve glycaemic control in patients with type 2 diabetes mellitus. Victoza® is indicated for once-daily administration as:

- monotherapy
- combination therapy with one or more oral antidiabetic medicines (metformin, sulphonylureas, sodium-glucose cotransporter 2 inhibitor (SGLT2i) or a thiazolidinedione) when previous therapy does not provide adequate glycaemic control.
- combination therapy with insulin in patients not achieving adequate glycaemic control with Victoza® and metformin.

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 section 5 Pharmacological Properties).

4.2 Posology and method of administration

Monotherapy

To reduce gastro-intestinal adverse effects for all patients, Victoza® should be initiated with a dose of 0,6 mg for at least one week, after which the dose may be increased to 1,2 mg. Based on clinical response and after at least one week the dose can be increased to 1,8

mg to achieve maximum efficacy. Daily doses higher than 1,8 mg are not recommended.

Combination therapy

Victoza® can be used in combination with other glucose lowering agents and no dose adjustments are required for metformin**,** thiazolidinedione and SGLT2i therapy.

When Victoza® is added to a sulphonylurea therapy or insulin, a reduction in the dose of sulphonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see section 4.4 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 or insulin, blood glucose self-monitoring may become necessary to adjust the dose of the sulphonylurea or insulin.

Incompatibilities

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

Special populations

Elderly and Gender

No dosage adjustment is required based on age and gender.

Obesity

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

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see 4.4 Special warnings and precautions for use).

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 4.4 Special warnings and precautions for use).

Paediatric population

Victoza® has not been studied in paediatric patients below 18 years of age (see 4.4 Special warnings and precautions for use).

Method of administration

Victoza® must not be administered intravenously or intramuscularly.

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 Undesirable effects).
The injection site and timing can be changed without dose adjustment.

4.3 Contraindications

- Hypersensitivity to liraglutide or any of its excipients
- A history of previous pancreatitis
- Type 1 diabetes mellitus
- Pregnancy and lactation (see section 4.6 Pregnancy)

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® should not be administered intravenously or intramuscularly.
Victoza® is not a substitute for insulin.
Safety and efficacy of Victoza® in patients below 18 years of age has not been established.

Patients above 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®.

There is no therapeutic experience in patients with end-stage renal disease and Victoza® is therefore not recommended for use in these patients.

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

There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis and Victoza® is therefore not recommended for use in these patients. The use of Victoza® is associated with gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

Hypoglycaemia

Patients receiving Victoza® in combination with a sulphonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by a reduction in the dose of sulphonylurea or insulin.

Immunogenicity

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 patients developed antibodies. Antibody formation has not been associated with reduced efficacy of Victoza®.

Injection site reactions

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

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.

Once acute pancreatitis is confirmed, liraglutide or any other GLP-1 receptor agonist should never again be restarted. Caution should be exercised in patients with a history of pancreatitis.

Thyroid disease

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

Allergic reactions

Allergic reactions including urticaria, rash and pruritus have been reported from marketed use of Victoza®. Cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnoea and oedema have been reported with marketed use of Victoza® (see 4.3 Contraindications).

Dehydration

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 potential risk of dehydration in relation to gastrointestinal side effects and take precaution to avoid fluid depletion.

4.5 Interaction with other medicines and other forms of interaction

In vitro assessment of interaction studies

Victoza® has shown a low potential involvement in pharmacokinetic interactions with other active substances related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of interaction studies

Interaction has been investigated using paracetamol, digoxin, lisinopril, griseofulvin and atorvastatin representing various degrees of solubility

and permeability properties. In addition, the effect of liraglutide on the absorption of ethinyloestradiol and levonorgestrel administered in an oral combination contraceptive medicine has been investigated (see table 1 below).

The minor delay of gastric emptying caused by liraglutide did not affect the absorption of orally administered medicines to any clinically relevant degree and therefore no dose adjustment is required. Few patients treated with Victoza® reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicines.

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 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 Victoza® and insulin detemir when administering a single dose of insulin detemir 0,5 U/kg with Victoza® 1,8 mg at steady state in patients with type 2 diabetes.

228 Table 1

Product	Dose	C_{max}	Median t_{max}	Comments
Paracetamol	Single dose of 1000 mg	Decreased by 31 %	Delayed up to 15 min	No dose adjustment for concomitant use of paracetamol is required
Atorvastatin	Single dose of 40 mg	Decreased by 38 %	Delayed from 1 h to 3 h	No dose adjustment of atorvastatin is required when given with Victoza®
Griseofulvin	Single dose of 500 mg	Increased by 37 %	Did not change	Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required
Lisinopril	Single dose	Decreased by 27 %	Delayed from 6 h to 8 h	No adjustment of lisinopril

	of 20 mg			dose is required
Digoxin	Single dose of 1 mg	Decreased by 31 %	Delayed from 1 h to 1,5 h	No adjustment of digoxin dose is required
Oral Contraception:	Single dose		Delayed up to 1,5 h for both compounds	The contraceptive effect is anticipated to be unaffected when co-administered with Victoza®
Ethinyloestradiol		Decreased by 12 %		
Levonorgestrel		Decreased by 13 %		

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

Pregnancy

Victoza® is contraindicated during pregnancy and lactation.

There is no adequate data for use of Victoza® in pregnant women.

Victoza® crossed the placental barrier in rabbits.

Studies in animals have shown reproductive toxicity and Victoza® should therefore not be used during pregnancy. 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.

In lactating rats, up to 3 % of the maternal dose was present in breast milk. Women on treatment with Victoza® should not breastfeed.

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. Victoza® may affect the ability to drive or use machines. Patients should be advised to ensure that they are aware of the effect of Victoza® on their abilities beforehand and to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza® is used in combination with a sulphonylurea or insulin (see 4.8 Undesirable effects).

4.8 Undesirable effects

The most frequently reported adverse events during clinical trials were gastrointestinal adverse events: nausea and diarrhoea (reported by >

10 % of patients) and vomiting, dyspepsia, upper abdominal pain, constipation, gastritis, flatulence, abdominal distension, gastro-oesophageal reflux disease and eructation (reported by ≥ 1 % and ≤ 10 % of patients).

Headache and upper respiratory tract infections were common.

Furthermore, hypoglycaemia was common and very common especially when Victoza® is used in combination with sulphonylurea.

Severe hypoglycaemia may occur uncommonly and has only been observed when combined with a sulphonylurea.

Table 2: Tabulated summary of side effects occurring during clinical trials and spontaneous (post-marketing) reports

Body system/ adverse reaction terms	**Frequency of occurrence**					
Reactions	**Very Common (≥ 1/10)**	**Common (≥ 1/100, < 1/10)**	**Uncommon (≥ 1/1 000, < 1/100)**	**Rare (≥ 1/10 000, < 1/1 000)**	**Very Rare (≤1/10 000)**	**Not known**

Infections and infestations		Upper respiratory tract infection	Bronchitis Gastroenteritis Osteomyelitis			
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Papillary thyroid cancer Prostate cancer Breast cancer			
Blood and the lymphatic system disorders			Thrombocytopenia			
Metabolism and nutrition disorders		Hypoglycaemia Anorexia Decreased appetite	Dehydration*			
Nervous system disorders		Headache Dizziness	Cerebrovascular accident Syncope Dysgeusia			

Eye disorders			Cataract			
Cardiac disorders		Increased heart rate*	Angina pectoris Acute myocardial infarction Coronary artery disease Atrial fibrillation Congestive cardiac failure Supraventricular tachycardia			
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism			

Gastro-intestinal disorders	Nausea Diarrhoea	Vomiting Dyspepsia Abdominal pain upper Constipation Gastritis Flatulence Abdominal distension Gastro-oesophageal reflux disease Eructation	Appendicitis with perforation Inguinal hernia Pancreatitis Delayed gastric emptying		Pancreatitis* (including necrotising pancreatitis)	
Musculoskeletal, connective tissue and bone disorders			Intervertebral disc protrusion Osteoarthritis			
General disorders and administrati		Fatigue Injection site reactions	Chest pain Malaise*			

on site conditions						
Injury, poisoning and procedural complications			Fall			
Immune system disorders				Anaphylactic reaction*		
Hepatobiliary disorders			Cholelithiasis Cholecystitis			
Skin and subcutaneous tissue disorders		Rash*	Urticaria* Pruritus*			Cutaneous amyloidosis†
Renal and urinary disorders			Renal failure acute* Renal impairment*			
Investigations		Increased lipase				

		Increased amylase				

**spontaneous reports*

†ADR from post marketing sources

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 sulphonylurea (0,02 events/subject year). Very few episodes (0,001 events/subject year) were observed with administration of Victoza® in combination with a non-sulphonylurea.

In the LEADER® trial, severe hypoglycaemic episodes were reported at a lower rate with liraglutide vs placebo (1,0 vs 1,5 events per 100 patient years of exposure; estimated rate ratio 0,69 [0,51 to 0,93]).

For patients treated with premix insulin at baseline and at least for the following 26 weeks, the rate of severe hypoglycaemia for both liraglutide and placebo was 2,2 events per 100 patient years of exposure.

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 the LEADER® trial, the frequency of cholelithiasis and

cholecystitis was 1,5 % and 1,1 % for liraglutide and 1,1 % and 0,7 % for placebo, respectively.

Pancreatitis

Few cases of acute pancreatitis (< 0,2 %) of acute pancreatitis have been reported during long-term, controlled phase 3 during long-term 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 liraglutide and 0,5 % for placebo, respectively.

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 medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications *https://www.sahpra.org.za/Publications/Index/8*.

4.9 Overdose

With overdose, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, glucagon-like peptide-1 (GLP-1) analogues. ATC code: A10BJ02

Mechanism of action

Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analogue with 97 % 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, and 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 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 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.

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.

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.

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 (70 mg/dl)/3,33 mmol/l (60 mg/dl). Following a standard meal, the difference in mean 2-hour postprandial glucose concentration was 6,02 mmol/l (108 mg/dl)/5,63 mmol/l (101 mg/dl). In addition, liraglutide decreased postprandial glucose excursion (incremental postprandial glucose) on average by 1,1 mmol/l (20 mg/dl)/1,08 mmol/l (19 mg/dl).

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 ($AUC_{\tau/24}$) 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

During 24 hour following administration of a single [3H]-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 endogenously metabolised in a similar manner to large proteins without a specific organ as major route of elimination.

Elimination

Following a [3H]-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 s.c. administration of a single dose liraglutide is approximately 1,2 l/h with an elimination half-life of approximately 13 hours.

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.

Paediatric population

Victoza® has not been studied in paediatric patients below 18 years of age (see 4.4 Special warnings and precautions for use).

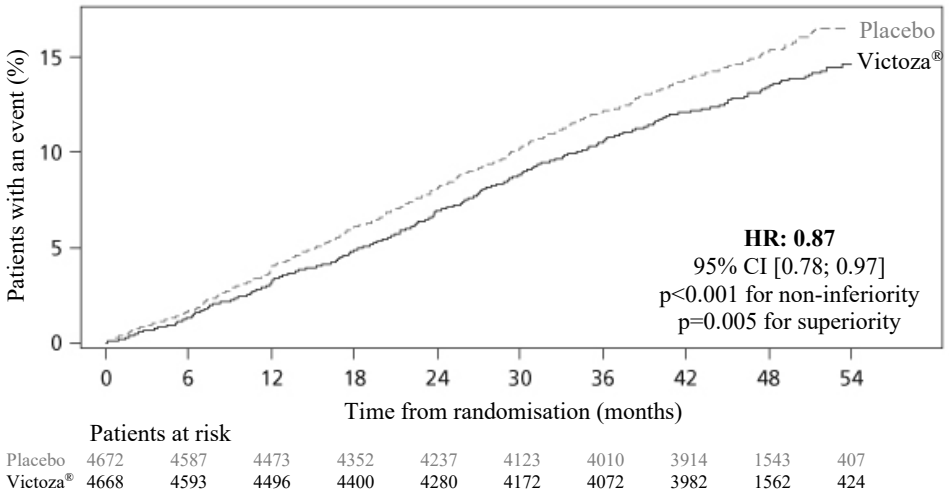
Clinical studies and mechanism of action

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 liraglutide (4,668) or placebo (4,672), both in addition to standards of care for 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 (Figure 1). The estimated hazard ratio was consistently below 1 for all 3 MACE components. 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 (Figure 2).



FAS: full analysis set.

Figure 1 Kaplan Meier plot of time to first MACE - FAS population

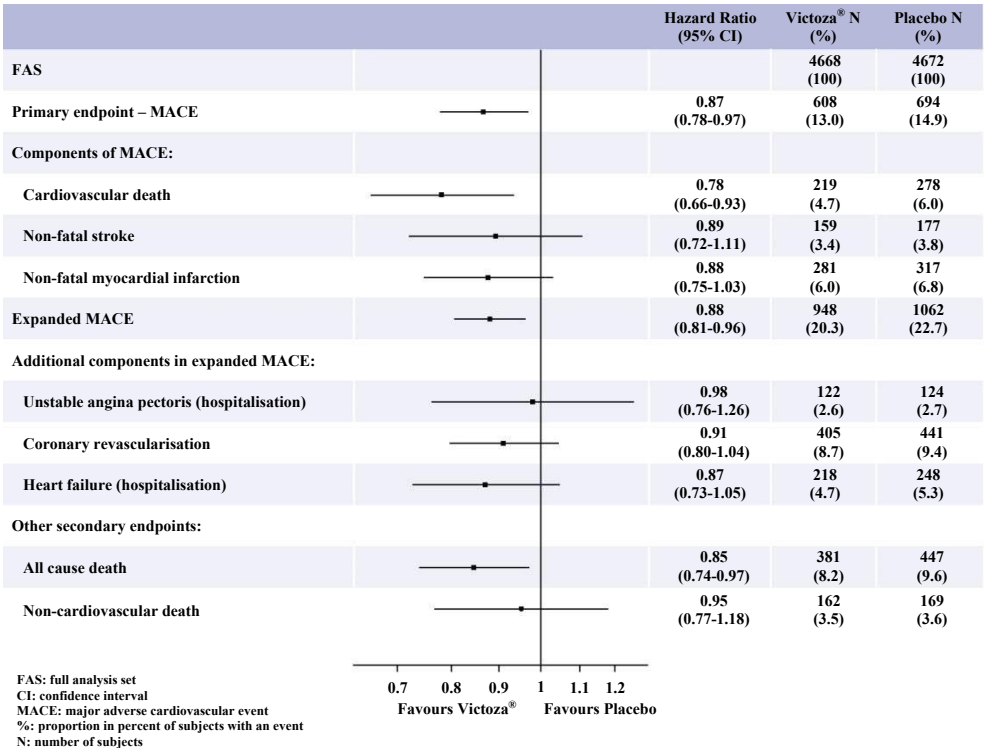


Figure 2 Forest plot of analyses of individual cardiovascular event types - FAS population

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 4.8 Undesirable effects).

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; ETD: -1,29 mmHg [-1,92; -0,48]) whereas diastolic blood pressure decreased less with liraglutide 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 evaluation

In the LEADER® trial, microvascular events comprised nephropathy and retinopathy outcomes. The analysis of time to first microvascular event for liraglutide vs placebo had a HR of 0,84 [0,73, 0,97]. The HR for liraglutide 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].

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]).

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.

535 **Glycaemic control**

536

537 **Table 3 Victoza® clinical phase 3 trials in monotherapy (52 weeks)**

538 **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
Add on to SGLT2i[5] ± metformin (≥ 1500 mg/day)						
Liraglutide 1,8 mg	203	8,00	-1,02	54,8	91,0	-2,92
Placebo	100	7,96	-0,28	13,9	91,4	-2,06

*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

[5]Victoza® add on to SGLT2i was investigated at all doses approved of SGLT2i.

[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:

Table 4: Guideline for titration of insulin glargine:

Self-measured FPG	**Increase in insulin glargine**
≤ 5,5 mmol/l (≤ 100 mg/dl)	No adjustment
> 5,5 and < 6,7 mmol/l (> 100	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.

Victoza® monotherapy for 52 weeks resulted in statistically significant ($p < 0.0014$) and sustained reductions in HbA_{1c} compared with patients receiving glimepiride (Figure 3).

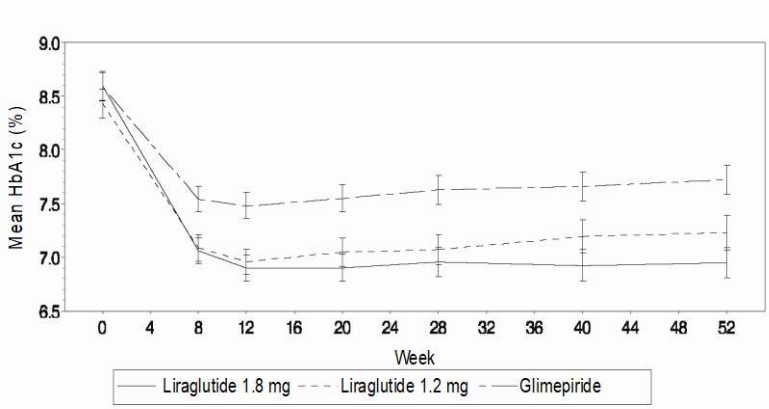


Figure 3 HbA_{1c} level reduced to below 7% and sustained over 12 months when Victoza® is administered to patients previously treated with diet and exercise (Trial 1573).

Postprandial glucose

Victoza® reduced postprandial glucose across all three daily meals by 1, 68 − 2, 71 mmol/l (31 − 49 mg/dl).

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dihydrate

Propylene glycol

Phenol

Water for injections

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

30 months.

After first use: 1 month.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 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 at (2 °C – 8 °C).

Victoza® should be protected from excessive heat and sunlight.

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.

Recap the pen to protect from light.

Keep out of reach and sight of children.

For storage conditions after first opening of the medicine, see section 6.3 Shelf life.

6.5 Nature and contents of container

Pre-filled (multidose, disposable) light blue pen, comprising of a slim pen-shaped injector assembled with a cartridge (3 ml). The cartridge is made of colourless 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.

Each pen contains 3 ml of solution, delivering 30 doses of 0,6 mg, 15 doses of 1,2 mg or 10 doses of 1,8 mg.

Pack sizes of 2 or 3 pens are packed in a cardboard box.

6.6 Special precautions for disposal and other handling

Victoza® should not be used if it does not appear clear and colourless or almost colourless.
Victoza® should 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.
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 pen without an injection needle attached. This prevents contamination, infection and leakage. It also ensures that the dosing is accurate.

For detailed instructions for use, see the Instructions for using the Victoza® pen.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd
150 Rivonia Road
10 Marion Street Office Park,
Building C1 Sandton,
Johannesburg, 2196

8 REGISTRATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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