PRODUCT INFORMATION

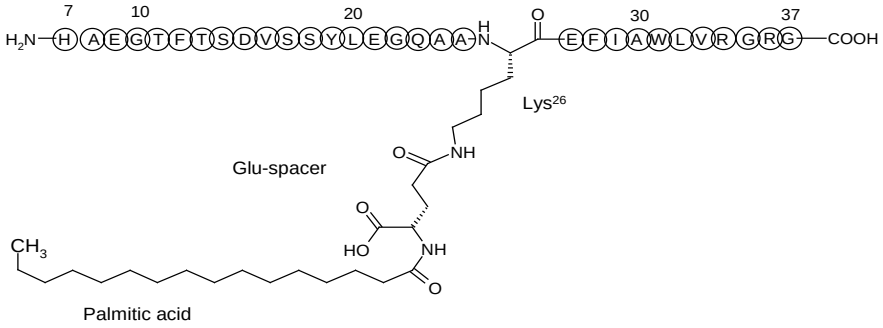
VICTOZA®

liraglutide

NAME OF THE MEDICINE

Victoza (liraglutide (rys)) 6 mg/mL solution for injection in a pre-filled pen.

Liraglutide (rys) has the molecular formula $C_{172}H_{265}N_{43}O_{51}$ and a molecular weight of 3751.20 daltons.



CAS No.: 204656-20-2

DESCRIPTION

Victoza contains liraglutide, a human glucagon-like peptide-1 (GLP-1) analogue that binds to and activates the GLP-1 receptor (GLP-1R). Liraglutide is produced by recombinant DNA technology using *Saccharomyces cerevisiae*. 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.

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.

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.

PHARMACOLOGY

Mechanism of action

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.

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 dipeptidyl peptidase (DPP-IV) and neutral endopeptidase (NEP) enzymes, resulting in a long plasma half-life.

Liraglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Liraglutide stimulates insulin secretion in a glucose-dependent manner 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 may involve a minor delay in gastric emptying (see INTERACTIONS WITH OTHER MEDICINES).

Liraglutide has shown anti-hyperglycaemic efficacy in animal models of pre-diabetes. Liraglutide has been shown *in vitro* to stimulate beta-cell proliferation and prevent 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. The relevance of this to humans is not known. When hyperglycaemia is fully normalised, in animal studies, liraglutide does not increase beta-cell mass.

GLP-1 is a physiological regulator of appetite and food intake and GLP-1R is present in several areas of the brain involved in appetite regulation as well as the intestine. 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-1R, increased key satiety and decreased key hunger signals. Transient inhibition of gastric emptying was also observed. Liraglutide lowers body weight through decreased food intake and loss of predominantly fat mass.

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.

Pharmacodynamics

Liraglutide 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 1). 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.

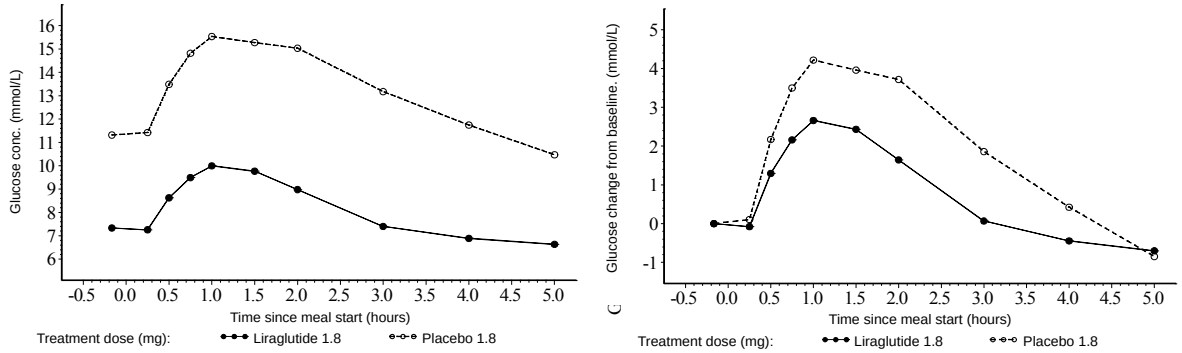


Figure 1 **Mean absolute (left) and incremental (right) postprandial glucose concentrations. Subjects with type 2 diabetes treated with liraglutide 1.8 mg or placebo in a cross-over design (N=18) (Trial 1698)**

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 2).

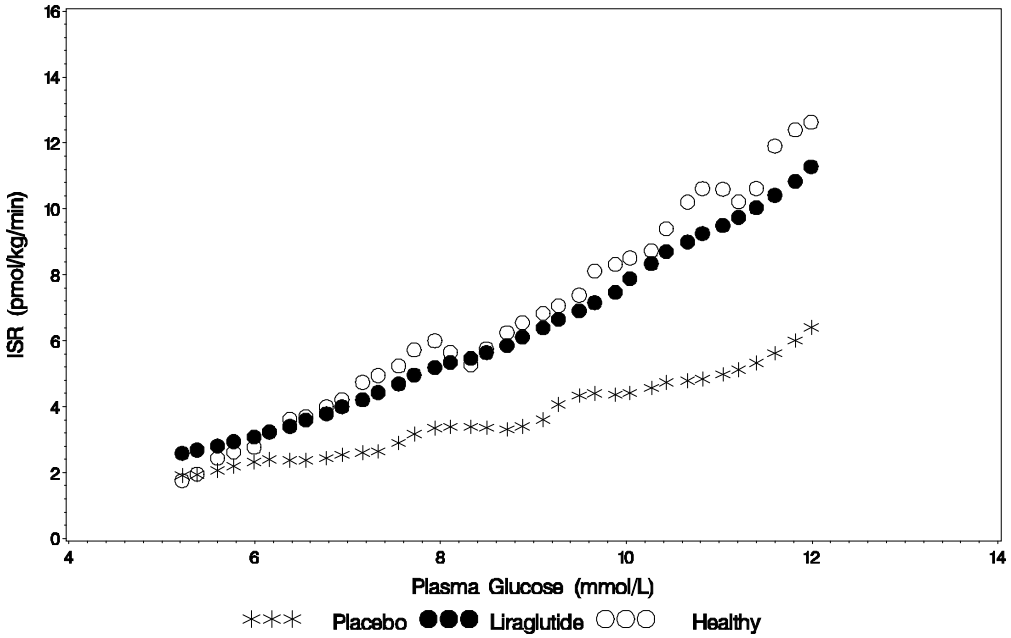


Figure 2 Mean Insulin Secretion Rate (ISR) versus glucose concentration following a single injection of liraglutide 7.5 µg/kg (~0.66 mg) or placebo in subjects with type 2 diabetes (N=10) and untreated healthy subjects (N=10) during graded glucose infusion (Trial 2063)

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 3).

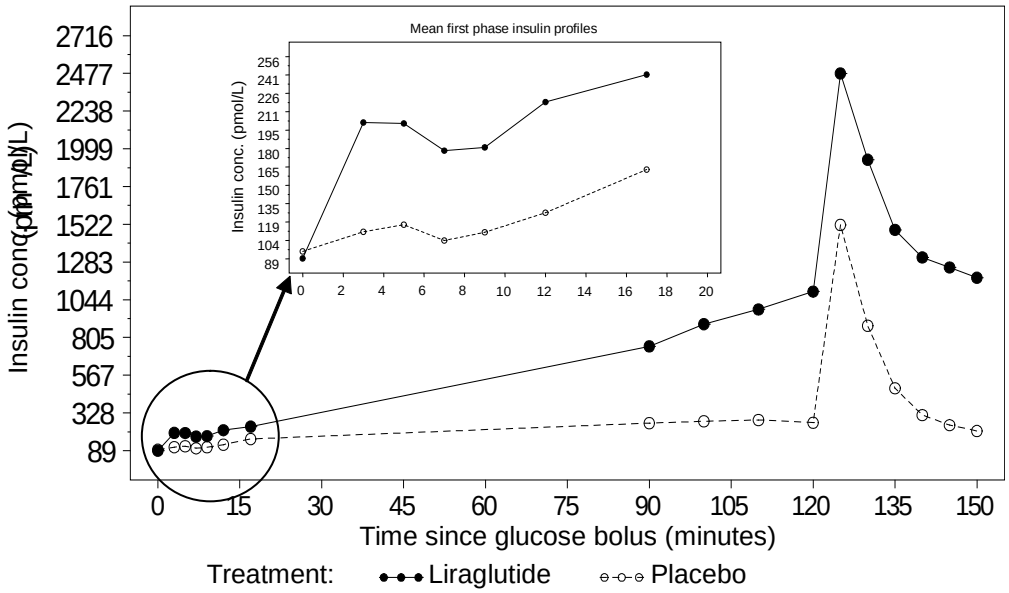


Figure 3 Mean insulin profiles during glucose bolus (inserted), hyperglycaemic clamp and arginine stimulation test (at 120 min) following 6 µg/kg (~0.55 mg) liraglutide or placebo for 10 days in subjects with type 2 diabetes (Trial 1332)

Clinical studies up to 52 weeks have shown a durable secretagogue effect with liraglutide, as well as improvements from baseline in the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio. Liraglutide has not yet been evaluated for use in individuals with impaired glucose tolerance or those who do not yet meet the diagnostic criteria for diabetes mellitus.

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 has been 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

In clinical studies up to 52 weeks involving subjects with elevated body weight liraglutide was observed to significantly lower body weight (see CLINICAL TRIALS, ADVERSE EFFECTS). Specific weight loss studies have not been assessed in type 2 diabetes mellitus.

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.

Pharmacokinetics

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.

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 the 24 hours 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 (≤ 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.

Excretion

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. Liraglutide exposure was decreased by 23% and 13% in subjects with mild or moderate hepatic impairment respectively, compared to healthy subjects.

Exposure was significantly lower (44%) in subjects with severe hepatic impairment (Child Pugh score >9).

Renal impairment

Liraglutide exposure was mildly reduced in subjects with renal impairment compared to individuals with normal renal function in a single-dose trial. Liraglutide exposure was lowered by 33%, 14%, 27% and 26%, respectively, in subjects with mild (creatinine clearance, CrCL 50-80 mL/min), moderate

(CrCL 30-50 mL/min), and severe (CrCL <30 mL/min) renal impairment and in end-stage renal disease requiring dialysis.

Paediatrics
Liraglutide has not been studied in paediatric subjects.

CLINICAL TRIALS

A. Glycaemic control, Phase 2 trial

Study NN2211-1499 was a phase 2, exploratory study. It was a double-blind, double-dummy, randomised, parallel-group, multicentre, dose titration study (with an open labelled oral agent arm i.e. glimepiride + metformin) to assess the effect on glycaemic control of individual maximum effective dose of Victoza as add on therapy to metformin compared to monotherapy (metformin or Victoza alone). Victoza was given in doses of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, as a once daily subcutaneous injection in the abdomen or thigh (in the evening). The study was of five weeks duration. One hundred and forty-four patients were randomised (36 per group). They were on at least 50% of the maximal dose of their oral agent. Fasting serum glucose after five weeks of treatment was the primary endpoint. Victoza alone was superior to metformin alone but inferior to metformin + glimepiride whereas Victoza + metformin was superior to metformin + glimepiride. Results were similar for haemoglobin A_{1c} (HbA_{1c}) but the short duration of the study limits the interpretation of these results.

B. Glycaemic control, Phase 3 individual trials

There were 3,992 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.

These studies included 3,978 exposed subjects (2,501 subjects treated with Victoza), 53.7% men and 46.3% women, 797 subjects (508 treated with Victoza) were ≥65 years of age and 113 subjects (66 treated with Victoza) were ≥75 years of age.

The studies included four studies (LEAD 1, 2, 4 and 5) assessing Victoza in various combinations with metformin, a sulfonylurea and rosiglitazone plus one study where Victoza was used as a single agent (LEAD 3). In the dual therapy studies, patients could be inadequately controlled but were not necessarily failing to respond to monotherapy at baseline.

B.i. Monotherapy

LEAD 3 (Trial 1573) enrolled 746 patients with type 2 diabetes previously treated with diet/exercise and with an HbA_{1c} 7.0-11.0% (inclusive), or with not more than half-maximal oral antidiabetic drug (OAD) monotherapy for at least 2 months and with an HbA_{1c} 7.0-10.0% (inclusive). Patients were randomised to Victoza 1.2 mg, Victoza 1.8 mg, or glimepiride 8 mg, and treated for 52 weeks. Treatment with Victoza 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA_{1c} from baseline compared to glimepiride (Table 1).

Table 1 Results of a 52 week trial of Victoza (LEAD 3) as monotherapy in patients previously treated with diet and exercise.

LEAD 3 – Victoza monotherapy			
	Victoza 1.8 mg	**Victoza 1.2 mg**	**Glimepiride 8 mg/day**
N	246	251	248
HbA_{1c} (%) (Mean)			
Baseline	8.2	8.2	8.2
Change from baseline	-1.14**	-0.84*	-0.51
Subjects (%) achieving HbA_{1c} <7%			
All subjects	50.9	42.8	27.8

* Significantly different (p <0.05) from active comparator

**Significantly different (p <0.0001) from active comparator

B.ii. Combination Therapy

LEAD 1 (Trial 1436) and LEAD 2 (Trial 1572) evaluated 26 weeks' of treatment with Victoza in combination with the OAD glimepiride or metformin respectively. Both trials employed a placebo comparator (LEAD 1 glimepiride alone; LEAD 2 metformin alone) and an active comparator (LEAD 1 glimepiride + rosiglitazone; LEAD 2 metformin + glimepiride).

LEAD 5 (Trial 1697) evaluated 26 weeks' treatment with Victoza in combination with metformin + glimepiride. LEAD 5 assessed the 1.8 mg Victoza dose and compared this with a placebo comparator (metformin + glimepiride) and an active comparator (insulin glargine + metformin + glimepiride).

Primary outcomes for the LEAD 1, 2 and 5 studies are presented in Tables 2 and 3. Treatment with Victoza produced clinically and statistically significant improvements versus the placebo comparators in $HbA_{1c,}$ fasting plasma glucose (FPG) and postprandial glucose (PPG).

B.ii.a) Victoza in combination with one OAD (LEAD 1 and 2 respectively)

LEAD 1 enrolled patients diagnosed with type 2 diabetes, treated with OAD(s) for at least 3 months, with an HbA_{1c}: 7.0-11.0% (inclusive) in subjects on oral monotherapy or 7.0-10.0% (inclusive) in subjects on oral combination therapy. All were switched to glimepiride in the trial. The study enrolled patients on monotherapy who might need a second agent and those already on two agents that might need a third agent. In LEAD 1, the analysis of change in HbA_{1c} from baseline showed that treatment with Victoza at both 1.2 mg and 1.8 mg (+ glimepiride) was superior to treatment with glimepiride alone, and superior to treatment with rosiglitazone + glimepiride (Table 2). For the primary efficacy outcome measure, Victoza 1.2 mg and 1.8 mg in combination with glimepiride were superior to both comparator groups, and Victoza 0.6 mg in combination with glimepiride was superior to glimepiride alone and non inferior to rosiglitazone/glimepiride. Amongst secondary outcomes, Victoza plus glimepiride did not increase weight compared to glimepiride alone whereas glimepiride and rosiglitazone were associated with weight gain.

LEAD 2 enrolled patients diagnosed with type 2 diabetes, treated with OAD(s) for at least 3 months, with an HbA_{1c}: 7.0-11.0% (inclusive) in subjects on oral monotherapy or 7.0-10.0% (inclusive) in subjects on oral combination therapy. All were switched to metformin in the trial. The analysis of change in HbA_{1c} from baseline showed that treatment with Victoza (1.2 mg and 1.8 mg) + metformin was superior to metformin alone and non-inferior to treatment with glimepiride and metformin (Table 2). The primary efficacy outcome measure was the change from baseline in HbA_{1c} after 26 weeks of treatment. Victoza 1.8 mg and 1.2 mg doses in combination with metformin were superior to metformin alone, and non-inferior to glimepiride/metformin. In combination with metformin, Victoza had similar efficacy to the glimepiride/metformin combination. In this study, Victoza 1.2 mg daily was as effective as the higher dose.

Table 2 Results of two 26 week trials of Victoza (LEAD 2 and LEAD 1) in combination with an OAD in subjects previously treated with one or more OADs.

LEAD 2 - Metformin (2,000 mg/day) Add-on Therapy				
	Victoza 1.8 mg + metformin	**Victoza 1.2 mg + metformin**	**Metformin** [1]	**Glimepiride 4 mg/day + metformin** [2]
N	242	240	121	242
HbA_{1c} (%) (Mean)				
Baseline	8.4	8.3	8.4	8.4
Change from baseline	-1.00*	-0.97*	0.09	-0.98
Subjects (%) achieving HbA_{1c} <7%	42.4*			
All subjects	66.3	35.3*	10.8	36.3
Previous OAD monotherapy		52.8	22.5	56.0

LEAD 1 - Glimepiride (4 mg/day) Add-on Therapy				
	Victoza 1.8 mg + glimepiride	**Victoza 1.2 mg + glimepiride**	**Glimepiride** [3]	**Rosiglitazone 4 mg/day + glimepiride** [4]
N	234	228	114	231
HbA_{1c} (%) (Mean)				
Baseline	8.5	8.5	8.4	8.4
Change from baseline	-1.13*#	-1.08*#	0.23	-0.44
Subjects (%) achieving HbA_{1c} <7%				
All subjects	41.6*#	34.5*#	7.5	21.9
Previous OAD monotherapy	55.9	57.4	11.8	36.1

[1] placebo comparator (metformin)
[2] active comparator (metformin + glimepiride)
[3] placebo comparator (glimepiride)
[4] active comparator (glimepiride + rosiglitazone)
*Significantly different from placebo comparator ($p < 0.02$)
Significantly different from active comparator ($p < 0.05$)

B.ii.b) Victoza compared to a basal insulin (LEAD 5)

LEAD 5 enrolled patients diagnosed with type 2 diabetes, previously treated with oral agent(s) for at least 3 months with an HbA_{1c}: 7.5-10.0% (inclusive) in subjects on oral monotherapy or 7.0-10.0% (inclusive) in subjects on oral combination therapy. In LEAD 5, the analysis of change in HbA_{1c} from baseline demonstrated that treatment with Victoza 1.8 mg + glimepiride + metformin was superior to treatment with glimepiride + metformin alone and superior to treatment with insulin glargine + glimepiride + metformin (Table 3).

Table 3 Results of a 26 week trial of Victoza (LEAD 5) in combination with OADs in previous OAD-treated subjects. LEAD 5 also included a comparison with basal insulin.

LEAD 5 - Metformin (2,000 mg/day) + Glimepiride (4 mg/day) Add-on Therapy			
	Victoza 1.8 mg+ metformin + glimepiride	**Metformin + glimepiride** [1]	**Glargine + metformin + glimepiride** [2]
N	230	114	232
HbA_{1c} (%) (Mean)			
Baseline	8.3	8.3	8.1
Change from baseline	-1.33*#	-0.24	-1.09
Subjects (%) achieving HbA_{1c} <7%			
All subjects	53.1*#	15.3	45.8

[1] placebo comparator (metformin + glimepiride)
[2] active comparator (glargine + metformin + glimepiride)
*Significantly different from placebo comparator ($p < 0.01$)
Significantly different from active comparator ($p < 0.02$)

B.ii.c) Victoza in combination with basal insulin (trials 1842, 1842 ext. and 3917)

An open-label randomised study (Trials 1842 and 1842 ext.) in patients with type 2 diabetes not reaching target with OADs was conducted. The trial started with a 12 week run-in period with Victoza + metformin, where 61% reached an HbA_{1c} <7%. The 39% of patients not achieving target were randomised to have insulin detemir once-daily added or continue on Victoza 1.8 mg + metformin for 52 weeks. Addition of insulin detemir provided a further reduction of HbA_{1c} from 7.6% to 7.1% after 52 weeks, no major hypoglycaemic episodes were reported with insulin detemir (see Table 4). Adding insulin detemir did not result in any further clinically significant loss of weight but the initial loss obtained with Victoza + metformin dual therapy during the run-in period was maintained.

Table 4 Results of a 12+26 week trial (trials 1842 and 1842 ext.) where insulin detemir was added to Victoza and metformin in patients not reaching adequate glycaemic control (HbA_{1c} <7.0%) after a 12 weeks run-in period on Victoza.

Insulin detemir add-on therapy					
	Study weeks	**Randomised Victoza 1.8mg + metformin + insulin detemir (N = 160)**	**Randomised Victoza 1.8mg + metformin (N = 149)**	**Treatment difference/ratio [95% CI]**	**P-value**
Mean change in HbA_{1c} from baseline (%)	26	-0.51	+0.02	-0.52 [-0.68 ; -0.36]	<0.0001
	52	-0.50	0.01	-0.51 [-0.70 ; -0.31]	<0.0001
Proportion of patients achieving HbA_{1c} <7% targets (%)	26	43.1	16.8	3.75[a] [2.19 ; 6.45]	<0.0001
	52	51.9	21.5	3.94[a] [2.37 ; 6.55]	<0.0001
Minor hypoglycaemic episodes (per patient year)	26	0.286	0.029	9.91[b] [2.11 ; 46.62]	0.0037
	52	0.228	0.034	6.80[b] [0.78 ; 8.97]	0.0011

[a]*Odds ratio;* [b]*Rate ratio*

Another 26-week double-blind randomised trial (Trial 3917) investigated the efficacy and safety of Victoza 1.8 mg versus placebo in patients with type 2 diabetes inadequately controlled on basal insulin (insulin glargine or insulin detemir) with or without metformin (N=450, mean HbA_{1c} 8.3%). The insulin dose was reduced by 20% for patients with baseline HbA_{1c} ≤8.0% in order to minimise the risk of hypoglycaemia. Patients were allowed to up-titrate their insulin dose to no higher than the pre-randomisation dose. Mean basal insulin dose at baseline for both arms was 40.5 U. Victoza was statistically superior to placebo treatment in reducing HbA_{1c} after 26 weeks (-1.30% for Victoza vs -0.11% for placebo; estimated treatment difference: -1.19%; 95% CI: -1.39 to -0.99). Patients treated with Victoza had a significant decrease in body weight compared to placebo (-3.54 kg vs -0.42 kg, estimated treatment difference -3.11 kg; 95% CI: -3.85 to -2.37). Significantly more patients achieved HbA_{1c} below 7% with Victoza compared with placebo (59.2% vs 14.0%). More patients with Victoza achieved HbA_{1c} <7% with no weight gain and no hypoglycaemic episodes (41.5%) than with placebo (8.6%). Treatment with Victoza reduced the daily need for insulin compared to placebo (35.82 U vs 40.05 U). The proportion of patients with minor hypoglycaemic episodes was significantly higher when adding Victoza compared to placebo (18.2% vs 12.4%; 1.26 vs 0.83 events per patient year of exposure). No severe hypoglycaemic episodes were reported in the trial. The safety profile of Victoza was generally similar to that observed in other studies with Victoza.

C. Glycaemic control across trials

C.i. HbA_{1c}

Victoza monotherapy for 52 weeks resulted in statistically significant (p≤0.0014) and sustained reductions in HbA_{1c} compared with patients receiving glimepiride (Figure 4). Victoza in combination therapy for 26 weeks with metformin or a sulfonylurea resulted in statistically significant (p <0.001) and sustained reductions in HbA_{1c} compared with subjects in the placebo comparator groups (Figure 4).

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 less effective than the other Victoza doses of 1.2 mg and 1.8 mg.

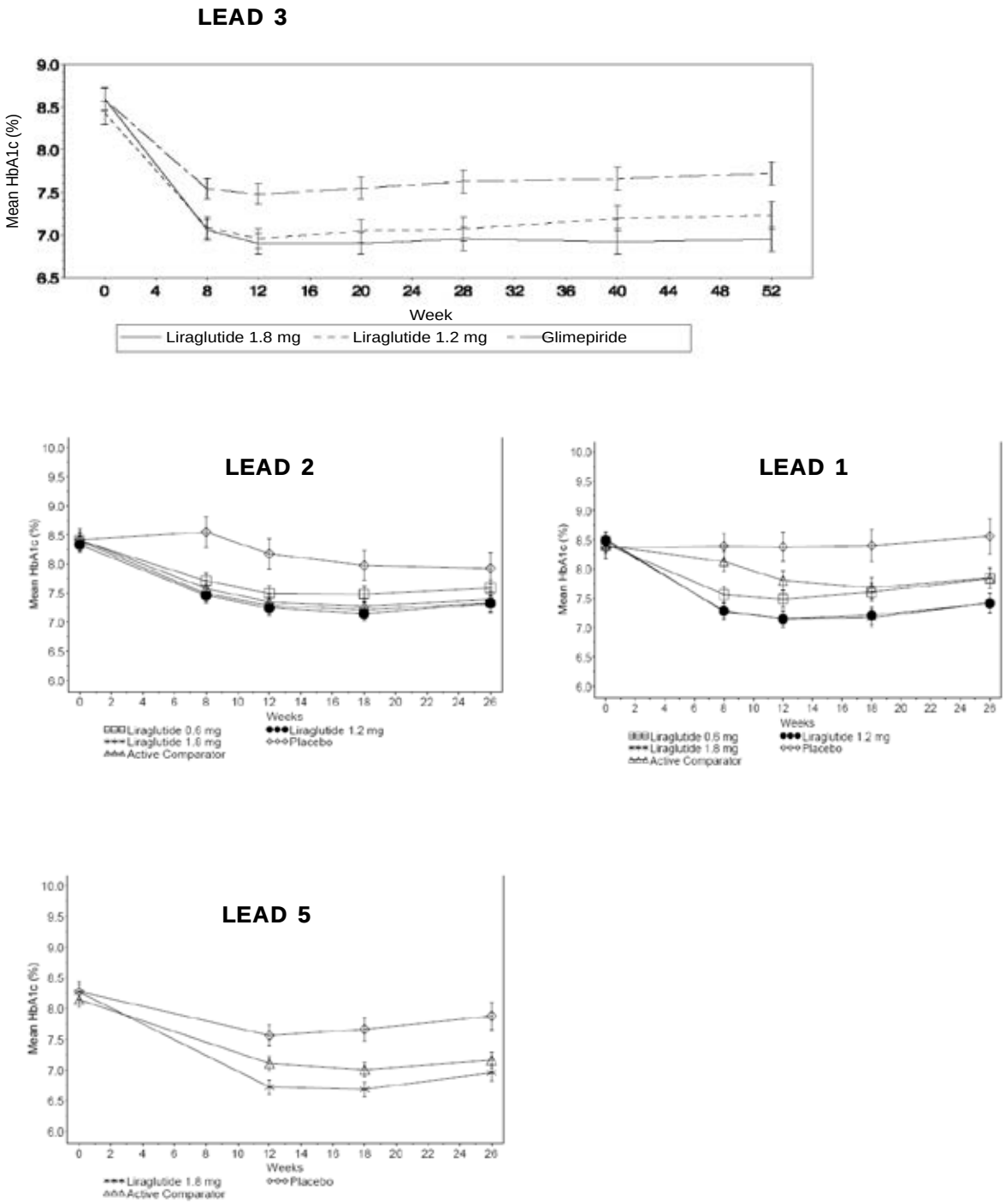


Figure 4 **Mean HbA_{1c} (%) over Time ± SEM, ITT Analysis Set Note: The Primary endpoint was change from baseline to the end of the study.**

C.ii. Fasting plasma glucose

Treatment with Victoza 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.

C.iii. Postprandial glucose

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

D. Glycaemic control in patients with renal impairment

In a double-blind study (Trial 3916) comparing the efficacy and safety of Victoza 1.8 mg versus placebo as add-on to basal or premixed insulin and/or OAD 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.

E. Body weight across trials

Body weight was assessed amongst predefined secondary endpoints. Specific weight loss studies have not been assessed in type 2 diabetes. In the clinical programme, statistically significant reductions in mean body weight from baseline were consistently observed. Treatment with Victoza was associated with an initial reduction in mean body weight within the first 8 weeks, that was sustained over the duration of studies (Figure 5). Larger weight reduction was observed with increasing body mass index at baseline. Reductions in body weight were seen, irrespective of the occurence of nausea.

No morbidity data or mortality data are presently available to support long-term benefit from Victoza induced weight loss in patients with type 2 diabetes.

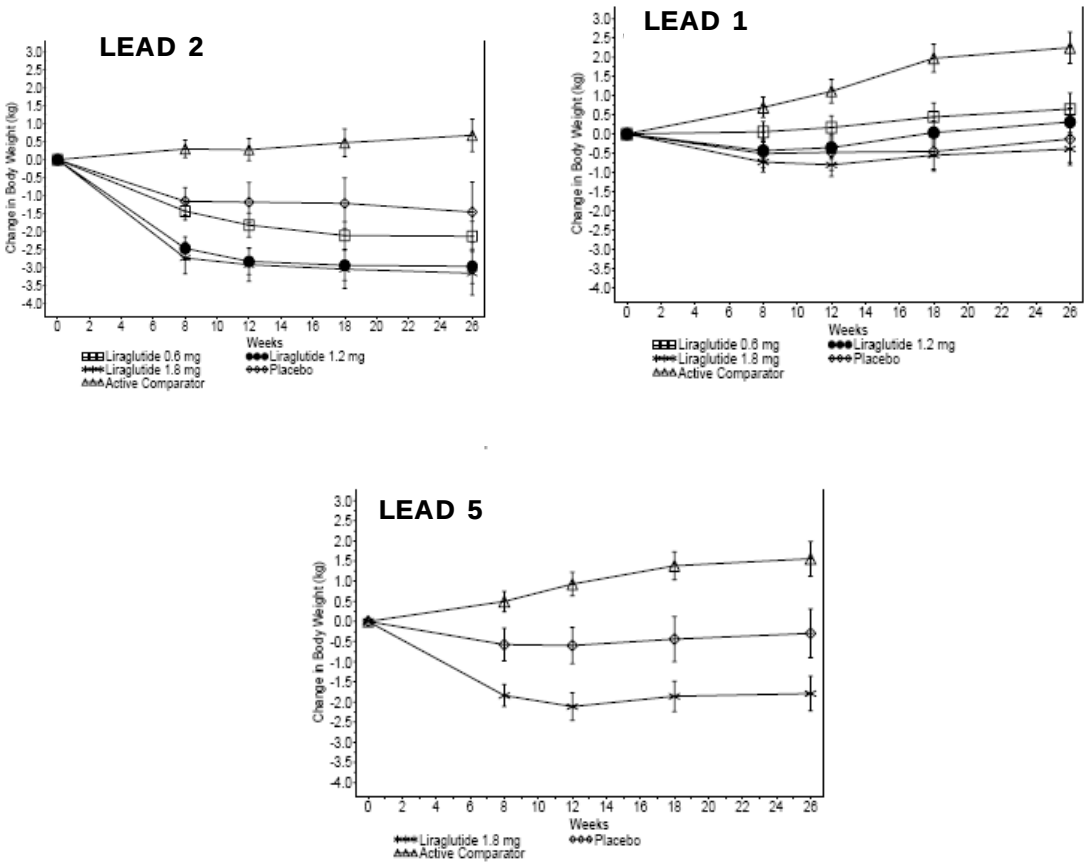


Figure 5 Change in Body Weight over Time, Mean ±2 SEM

F. Cardiovascular evaluation

F.i. Phase 2 and 3a trials

F.i.a) Major adverse cardiovascular events

Post-hoc analysis of serious major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke) from all intermediate and long-term phase 2 and 3a 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.

F.i.b) Blood pressure

Victoza reduced systolic blood pressure with a mean range of 2-6 mm Hg within the first two weeks of treatment in long-term clinical trials. The reduction in systolic blood pressure occurred before weight loss.

F.i.c) Lipids

Victoza showed no adverse effects on lipid parameters.

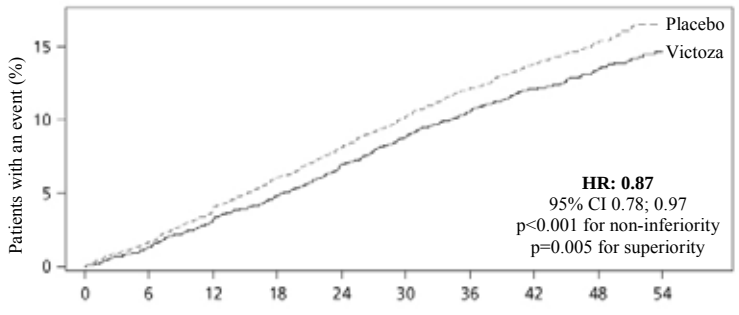
F.ii. Cardiovascular outcomes, phase 3b LEADER trial

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. Patients had type 2 diabetes and were anti-diabetic medication naïve or treated with one or more OADs or insulin (human NPH insulin, long-acting insulin or premixed insulin – either alone or in combination with OAD(s)) - at baseline (SOC). Patients were also at high risk of cardiovascular events, defined as either 50 years of age and with concomitant cardiovascular, cerebrovascular, peripheral vascular disease, chronic renal failure or chronic heart failure, or 60 years of age and other specified risk factors of vascular disease.

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.

F.ii.a) Cardiovascular events

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 number of subjects that needed to be treated with Victoza for 3 years to prevent the first MACE was 66. The estimated hazard ratio (HR) was consistently below 1 for all 3 MACE components.



Patients at risk

Victoza	4672	4587	4473	4352	4237	4123	4010	3914	1543	407
Placebo	4668	4593	4496	4400	4280	4172	4072	3982	1562	424

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 (Figure 7).

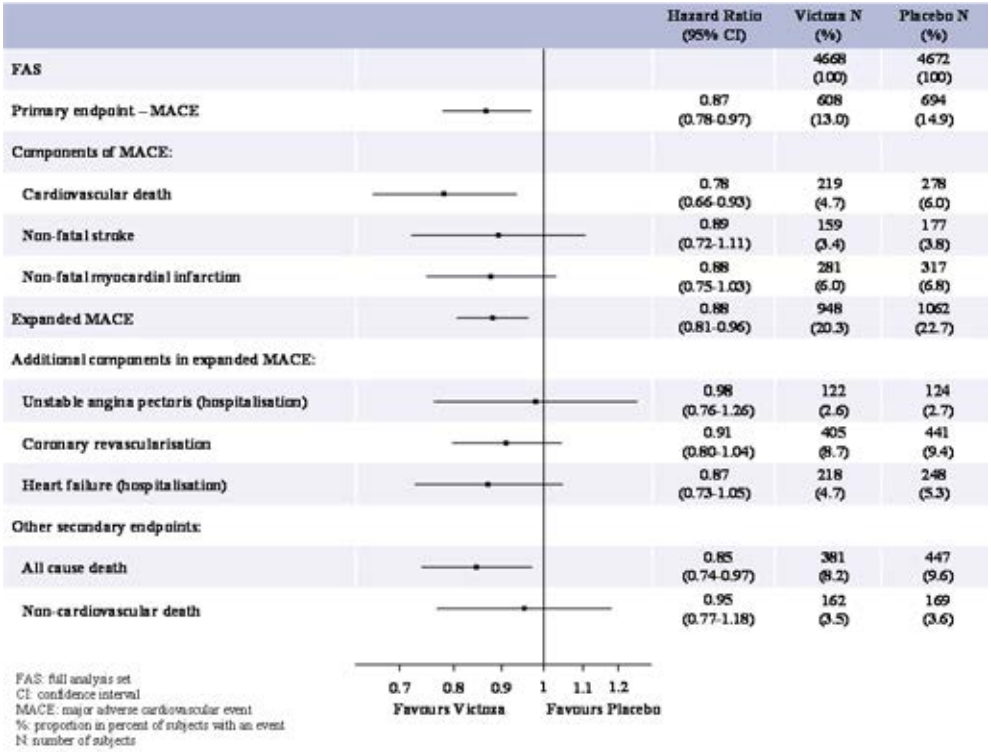


Figure 7 Forest plot of analyses of individual cardiovascular event types – FAS population

F.ii.b) Blood pressure and heart rate

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, although the study was not designed to specifically investigate clinical effects of increased heart rate, no long-term clinical impact of increased heart rate on the risk of cardiovascular events was observed.

F.ii.c) Microvascular events

In the LEADER trial, microvascular events comprised nephropathy (new onset of persistent macroalbuminuria, persistent doubling of serum creatinine and eGFR ≤ 45 mL/min/1.73 m^2 per Modification of Diet in Renal Disease (MDRD), need for continuous renal replacement therapy and death due to renal disease) and retinopathy (need for retinal photocoagulation or treatment with intravitreal agents, vitreous haemorrhage and diabetes-related blindness) 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].

F.ii.d) Glycaemic control in patients at high cardiovascular risk

A significant and sustained reduction in HbA_{1c} from baseline (mean baseline HbA_{1c} was 8.7%) to month 36 was observed with Victoza vs placebo, in addition to standard of care (-1.16% vs -0.77%; ETD -0.40% [-0.45; -0.34], p<0.001). 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]).

F.ii.e) Body weight
In the LEADER trial, 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]).

G. 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.

H. Other effects
Victoza improved insulin sensitivity compared to a sulfonylurea for 52 weeks as assessed by HOMA-IR. The clinical significance of this has not been established.

I. Other clinical data
In an open label study (Trial 1860) comparing 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 (mean HbA_{1c} 8.5%), Victoza at both doses was statistically superior to sitagliptin treatment in reducing HbA_{1c} after 26 weeks (-1.24%, -1.50%, -0.90%, for Victoza 1.2 mg, 1.8 mg and sitagliptin respectively; $p<0.0001$). Patients treated with Victoza had a significant decrease in body weight compared to that of patients treated with sitagliptin (-2.9 kg, -3.4 kg, -1.0 kg in Victoza 1.2 mg, 1.8 mg and sitagliptin treatment groups, respectively, $p<0.0001$). Greater proportions of patients treated with Victoza experienced transient nausea compared to patients treated with sitagliptin (20.8%, 27.1%, 4.6% in Victoza 1.2 mg, 1.8 mg and sitagliptin treatment groups respectively). 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%, -1.51%, -0.88% in Victoza 1.2 mg, 1.8 mg and sitagliptin treatment groups respectively, $p<0.0001$).

In an open label study (Trial 1797) comparing efficacy and safety of Victoza 1.8 mg once daily and exenatide 10 µg twice daily in patients inadequately controlled on metformin and/or sulphonylurea therapy (mean HbA_{1c} 8.3%), Victoza was statistically superior to exenatide treatment in reducing HbA_{1c} after 26 weeks (-1.12% vs - 0.79% respectively, with the estimated treatment difference being -0.33% (95% CI: -0.47% to -0.18%), $p<0.0001$). More patients achieved HbA_{1c} below 7% with Victoza compared with exenatide (54.2% vs 43.4% respectively, $p=0.0015$). Both treatments resulted in mean body weight loss of approximately 3 kg.

In an open label study (Trial 3867) 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%, with the estimated treatment difference being -0.62% (95% CI: -0.80% to -0.44%), $p<0.0001$). 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. However, gastrointestinal adverse events were more frequently reported with liraglutide treatment (43.6% vs 37.1%). No new safety information was identified with Victoza.

INDICATIONS

Glycaemic control
Victoza is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:

- as monotherapy when metformin is contraindicated or is not tolerated

- in combination with other glucose lowering medicines.

Prevention of cardiovascular events
In patients where Victoza is indicated to improve glycaemic control, Victoza is indicated to reduce the risk of cardiovascular events in those at high cardiovascular risk, as an adjunct to standard of care therapy (see CLINICAL TRIALS).

CONTRAINDICATIONS

Victoza is not to be used in patients with hypersensitivity to liraglutide or any of its excipients.

PRECAUTIONS

Victoza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Insulin is the correct treatment for these conditions.

Victoza is not a substitute for insulin. Insulin should not be discontinued in patients dependent on insulin.

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

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. Use of Victoza is not recommended in these patients since it is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

Dehydration and renal impairment
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 medications 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.

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

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.

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, Victoza should be discontinued; if acute pancreatitis is confirmed, Victoza 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.

In glycaemic control clinical trials of Victoza in patients with type 2 diabetes, there have been 13 cases of pancreatitis among Victoza-treated patients and 1 case in a comparator (glimepiride) treated patient (2.1 vs 0.7 cases per 1000 patient-years). Nine of the 13 cases with Victoza were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a Victoza-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be

established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. In most cases, treatment of pancreatitis has led to recovery.

In the LEADER trial, acute pancreatitis was confirmed by adjudication in 18 Victoza-treated patients (1.1 cases per 1000 patient years of observation) and 23 placebo-treated patients (1.7 cases per 1000 patient years of observation), both on a background of standard of care. In addition, there were no cases of chronic pancreatitis confirmed by adjudication in Victoza-treated patients and 2 cases in placebo-treated patients. The LEADER trial enrolled 267 patients with a medical history of acute or chronic pancreatitis; of these, 2 out of 147 (1.4%) in the Victoza group and 6 out of 120 (5.0%) in the placebo group had a new event of acute pancreatitis confirmed by adjudication.

Hypoglycaemia

Due to the glucose-dependent insulinotropic mechanism of action of Victoza, when used in combination with metformin alone, no increase in the frequency of hypoglycaemia was observed over that of placebo in combination with metformin.

Patients receiving Victoza in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia (see Table 6 in ADVERSE EFFECTS). The risk of hypoglycaemia can be lowered by a reduction in the dose of sulfonylurea or insulin.

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.

Genotoxicity

Liraglutide was not mutagenic in the bacterial Ames assay, and not clastogenic in human lymphocytes *in vitro*, or in rat lymphocytes and bone marrow *in vivo*.

Carcinogenicity

Liraglutide caused thyroid C-cell adenomas and carcinomas in two-year studies in mice and rats. C-cell neoplasia was observed in mice at subcutaneous doses ≥1 mg/kg/day (relative exposure based on plasma AUC, ≥7.7) and in rats at all doses tested (≥0.075 mg/kg/day subcutaneously; relative exposure, ≥0.5). No tumours or other C-cell proliferative changes were seen in monkeys treated with liraglutide for 20 months (≤5 mg/kg/day subcutaneously; relative exposure, ≤64). The findings in mice and rats are mediated by a specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot presently be completely excluded.

Effects on fertility

No adverse effects on fertility were observed in male and female rats given subcutaneous doses of liraglutide at ≤1 mg/kg/day, yielding exposure to liraglutide (plasma AUC) 11-13 times higher than that of patients at the maximum recommended human dose.

Use in pregnancy

Pregnancy Category: B3

Increased embryofetal death and minor fetal skeletal abnormalities (kinked ribs) were observed in rats given liraglutide at 1 mg/kg/day by subcutaneous injection (yielding 11-times the plasma AUC in humans at the maximum recommended clinical dose). In rabbits treated at doses ≥0.01 mg/kg/day (relative exposure, ≥0.2), there was retardation of fetal growth and an increased incidence of several minor skeletal and visceral abnormalities. Postnatal body weight gain was reduced in the offspring of rats treated with liraglutide during gestation and lactation. These findings may have occurred secondary to reduced maternal food consumption. Placental transfer of liraglutide and/or its metabolites was demonstrated in the animal species.

There are limited data from the use of liraglutide in pregnant women. Victoza should 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.

Use in lactation

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

Incompatibilities

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

INTERACTIONS WITH OTHER MEDICINES

***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**

Drug-drug interaction has been investigated using medicines that were carefully selected to represent compounds of various degrees of solubility and permeability properties, including paracetamol (acetaminophen), digoxin, lisinopril, griseofulvin and atorvastatin. In addition, the effect of liraglutide on the absorption of ethinylestradiol and levonorgestrel administered in an oral combination contraceptive drug has been investigated.

The delay of gastric emptying caused by liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption of the compounds that were studied, however clinically relevant interactions with other compounds where the effect is dependent on C_{max} and t_{max}, drugs with narrow therapeutic index, or medications associated with local gastrointestinal irritation (e.g. bisphosphonates, potassium chloride) cannot be excluded.

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 to a clinically relevant degree following single dose administration of atorvastatin 40 mg. Therefore, no dose adjustment of atorvastatin is required when given with liraglutide. Atorvastatin C_{max} was decreased by 38% and median t_{max} was delayed from 1 h to 3 h with liraglutide.

Griseofulvin

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

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

Lisinopril
A single dose administration of lisinopril 20 mg with liraglutide resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median t_{max} was delayed from 6 h to 8 h with liraglutide. No dose adjustment of lisinopril is required based on these results.

Oral contraceptives
Liraglutide lowered 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 Victoza 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.

ADVERSE 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 reactions 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 or insulin. Severe hypoglycaemia has primarily been observed when combined with a sulfonylurea.

Very few of the reported adverse reactions were serious in nature.

Tabulated summary of adverse reactions
Table 5 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 (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000).

Table 5 Adverse reactions reported in long-term phase 3a controlled trials, the long-term cardiovascular outcome trial (LEADER) and spontaneous (post-marketing) reports

MedDRA system organ class	Very common	Common	Uncommon	Rare	Very rare
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			
Cardiac disorders		Increased heart rate			
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Dyspepsia Abdominal pain upper Constipation Gastritis Flatulence Abdominal distension Gastroesophageal reflux disease Eructation			Pancreatitis (including necrotising pancreatitis)
Hepatobiliary disorders			Cholelithiasis Cholecystitis		
Skin and subcutaneous tissue disorder		Rash	Urticaria Pruritus		
Renal and urinary disorders			Renal impairment# Renal failure acute#		
General disorders and administration site conditions		Fatigue Injection site reactions	Malaise		
Investigations		Increased lipase** Increased amylase**			

N=2501 Victoza-treated subjects in phase 3a trials, except for **

* Frequency is very common when used in combination with insulin.

** From controlled phase 3b and 4 clinical trials only where these were measured.

See 'PRECAUTIONS'

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 year; estimated rate ratio 0.69 [0.51 to 0.93]) (see CLINICAL TRIALS).

Table 6 presents the incidence of confirmed hypoglycaemic episodes (number of episodes divided by subject years of exposure).

Table 6 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 + Rosiglitazone**
(26 week study)	0.43	0.14
Combination with Metformin + Rosiglitazone (LEAD 4)	**Liraglutide + Metformin + Rosiglitazone**	**Placebo + Metformin + Rosiglitazone**
(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

*Phase 3a trials only i.e. not including LEADER phase 3b cardiovascular outcomes trial

Gastrointestinal adverse events

Most episodes of nausea were mild to moderate, transient and rarely led to discontinuation of therapy (Figure 6). In long-term clinical trials, some patients (0.6%) reported decreased weight as an adverse event.

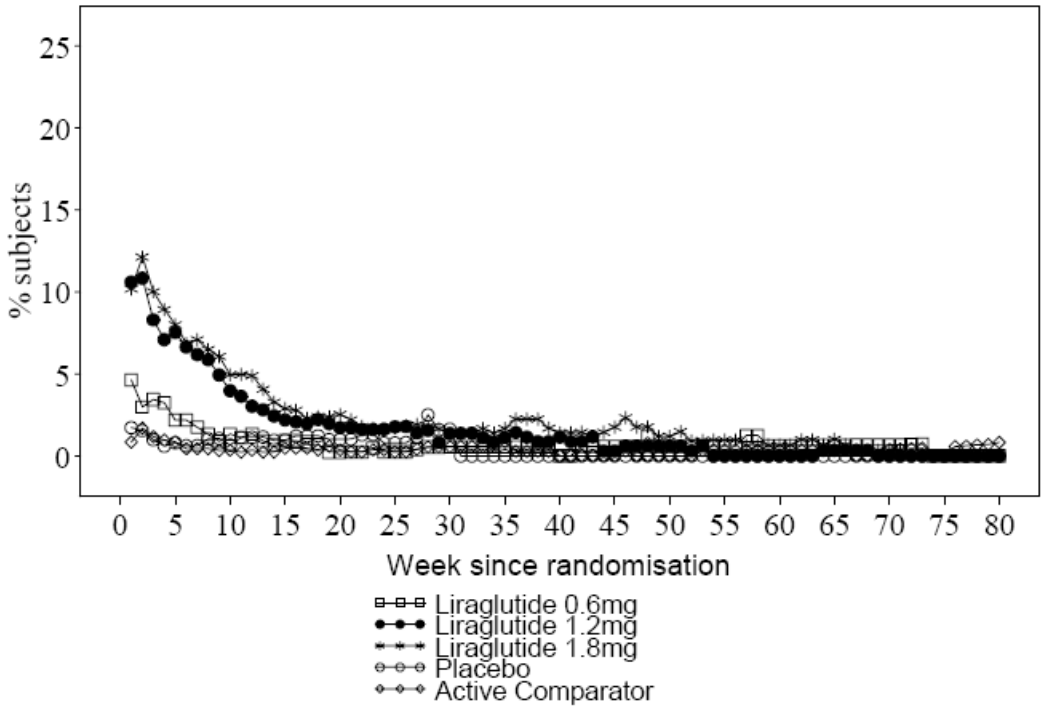


Figure 6 Percentage of subjects with nausea adverse events by week and treatment - all long-term trials - safety analysis set

In subjects treated with Victoza combined with metformin, 20.7% reported at least one episode of nausea, and 12.6% reported at least one episode of diarrhoea, respectively. When combining Victoza with a sulfonylurea 9.1% of subjects reported at least one episode of nausea and 7.9% of subjects reported at least one episode of diarrhoea.

The incidence of withdrawal due to adverse events was 7.8% for Victoza-treated subjects 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 subjects were nausea (2.8% of subjects) 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.

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 Victoza and 1.1% and 0.7% for placebo, respectively (see CLINICAL TRIALS).

Injection site reactions
Injection site reactions have been reported in approximately 2% of subjects who received Victoza in long-term controlled trials (26 weeks or longer). 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 (see PRECAUTIONS). 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).

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

DOSAGE AND ADMINISTRATION

Administration
Victoza is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that Victoza is injected around the same time each day, when the most convenient time of the day has been chosen.

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.

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. Based on clinical response and tolerability, 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.

Victoza may be used when previous therapies provide insufficient glycaemic control: in dual combination with metformin or a sulfonylurea; or in triple combination with metformin and sulfonylurea; or in combination with insulin with or without metformin.

When Victoza is added to existing metformin therapy, the current dose of metformin can be continued unchanged.

When Victoza is added to sulfonylurea therapy or to a combination of metformin and sulfonylurea therapy or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see PRECAUTIONS). During clinical trials physicians were advised, at their discretion, to lower the dose of the sulfonylurea by approximately half to minimise the risk of unacceptable hypoglycaemia.

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

Victoza should not be used in combination with another GLP-1 receptor agonist.

Specific patient groups
Elderly (>65 years old)
No dose adjustment is required based on age (see Pharmacokinetics).

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

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 Pharmacokinetics and PRECAUTIONS).

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

Special precautions for disposal and other 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 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® 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 to store the Victoza pen without the injection needle attached. This prevents contamination, infection and leakage. It also ensures that dosing is accurate.

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

From clinical trials and post-market use, deliberate or accidental administration of doses up to 40 times the recommended maintenance dose (72 mg) have been reported, including one case of a 10-fold overdose (18 mg daily) given for 7 months. These included instances where patients needed hospitalisation either due to severe events of vomiting, nausea and diarrhoea or as a precaution. In some reports glucose infusion was administered but none were associated with severe hypoglycaemia. All patients were reported to have recovered from the events without complications.

In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

PRESENTATION AND STORAGE CONDITIONS

Presentations

Cartridge (type 1 glass) with a plunger (bromobutyl) and a laminate rubber sheet (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polyolefin and polyacetal.

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

Pack sizes of 1, 2, 3, 5 or 10 pre-filled pens. Not all pack sizes may be marketed.

Storage conditions

Store in a refrigerator (2°C to 8°C). Keep away from the 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°C to 8°C).

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

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.

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

NAME AND ADDRESS OF THE SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited
Level 3
21 Solent Circuit
Baulkham Hills NSW 2153

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

26 August 2010

DATE OF MOST RECENT AMENDMENT

05 January 2018