

## PRODUCT INFORMATION

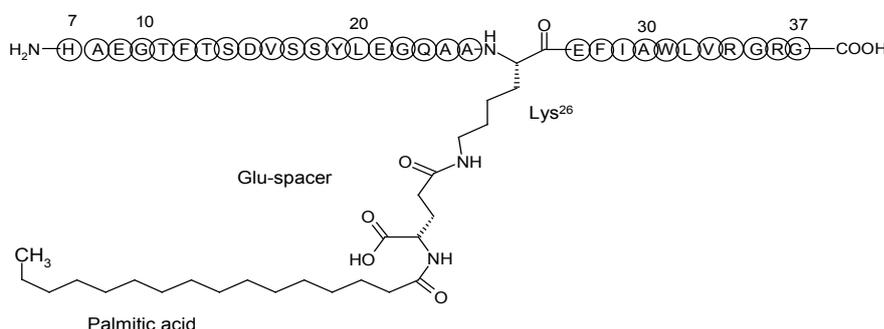
**VICTOZA<sup>®</sup>**

liraglutide

### NAME OF THE MEDICINE

Victoza (liraglutide (rys)) solution for injection.

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

Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analogue that binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Liraglutide exhibits 97% homology to human GLP-1. In liraglutide, the lysine at position 34 has been replaced with arginine, and a palmitic acid has been attached via a glutamoyl spacer to lysine at position 26.

Liraglutide is produced by recombinant DNA technology using *Saccharomyces cerevisiae*. 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*

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.

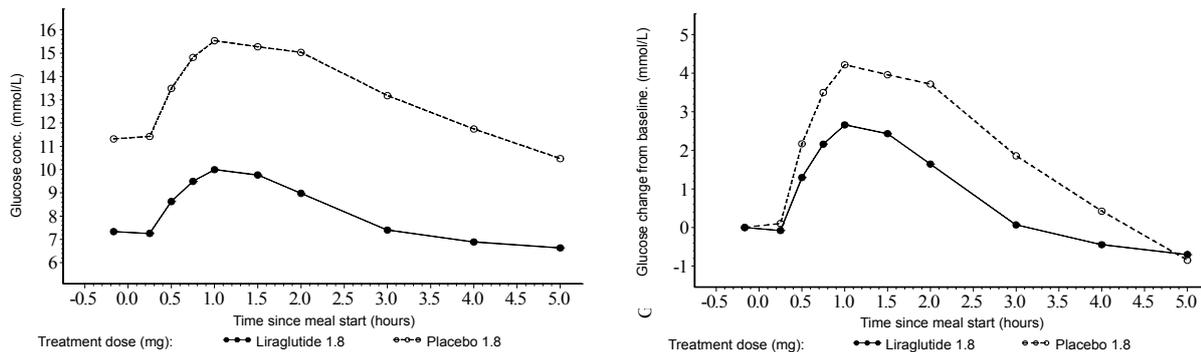
The mechanism of blood glucose lowering also may involve a minor delay in gastric emptying (see Interactions).

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.

### 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.

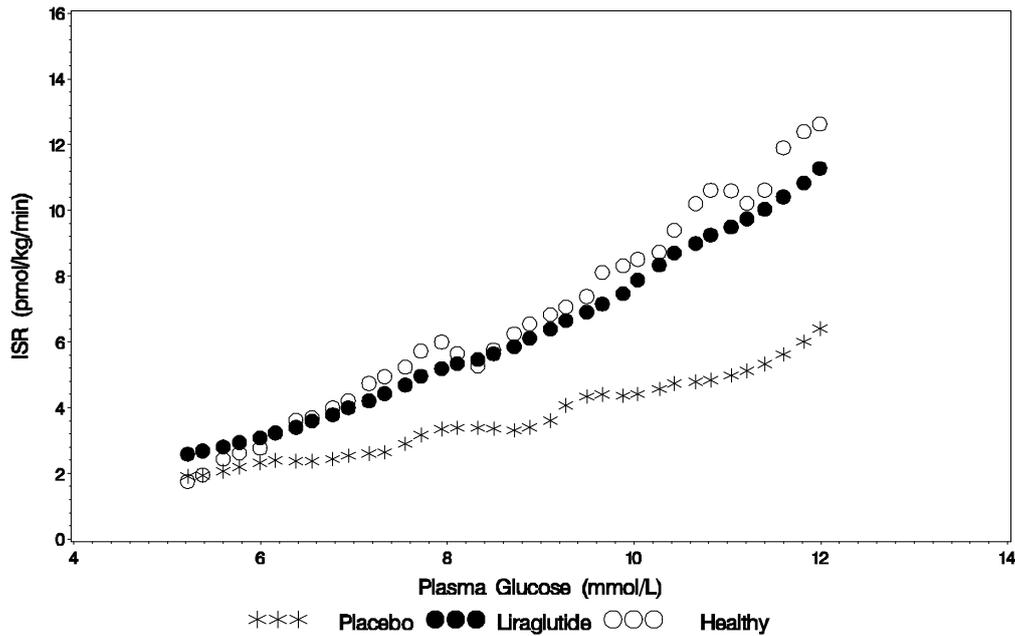
The difference between liraglutide 1.8 mg / 1.2 mg and placebo in reduction of mean fasting glucose was found to be 3.90 mmol/L / 3.33 mmol/L (Figure 1). Following a standard meal, the difference in mean 2-hour postprandial glucose concentration was 6.02 mmol/L / 5.63 mmol/L. In addition, liraglutide 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

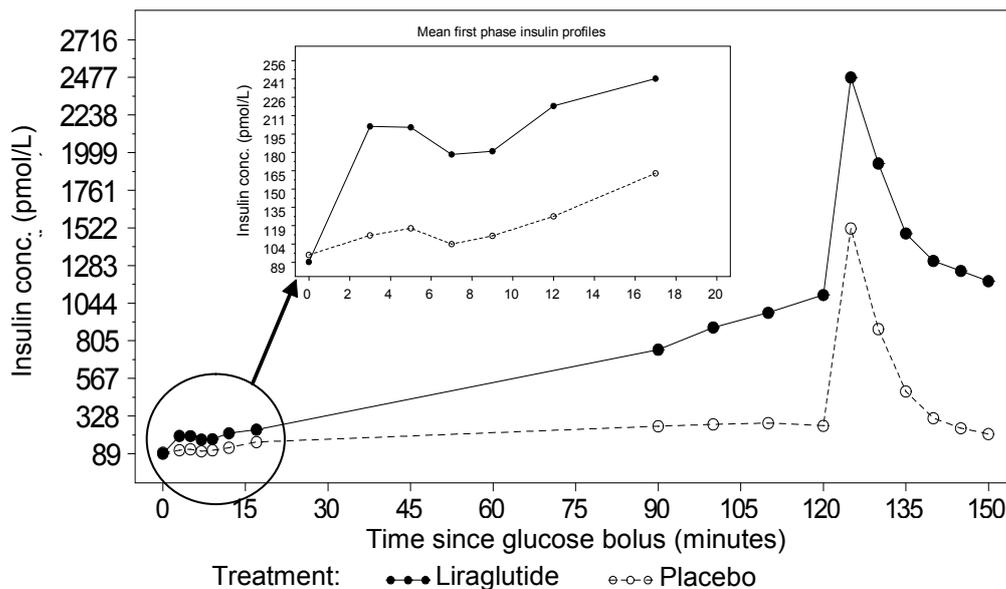
Liraglutide increased insulin secretion in relation to increasing glucose concentrations. Using a stepwise graded glucose infusion, the insulin secretion rate was increased following a single injection of liraglutide in subjects with type 2 diabetes to a level indistinguishable to that observed in healthy 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 [<sup>3</sup>H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected ( $\leq 9\%$  and  $\leq 5\%$  of total plasma radioactivity exposure). Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of elimination.

#### *Excretion*

Following a [<sup>3</sup>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 s.c. 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 was evaluated in subjects with varying degree 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. 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**

### ***Phase 2***

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 HbA<sub>1c</sub> but the short duration of the study limits the interpretation of these results.

### **Phase 3**

There were 3992 subjects with type 2 diabetes randomised in five double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of Victoza on glycaemic control.

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

LEAD 1 (Trial 1436) and LEAD 2 (Trial 1572) evaluated 26 weeks of treatment with Victoza in combination with the oral antidiabetic drug (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 studies are presented in Table 1 and 2. Treatment with Victoza produced clinically and statistically significant improvements versus the placebo comparators in haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), fasting plasma glucose (FPG) and postprandial glucose (PPG).

#### *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<sub>1c</sub>: 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<sub>1c</sub> 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 1). 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<sub>1c</sub>: 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<sub>1c</sub> 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 1). The primary efficacy outcome measure was the change from baseline in HbA<sub>1c</sub> 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 1 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.**

<b>LEAD 2 - Metformin Add-on Therapy</b>				
	<b>Victoza 1.8 mg + metformin</b>	<b>Victoza 1.2 mg + metformin</b>	<b>Metformin [1]</b>	<b>Glimepiride + metformin [2]</b>
<b>N</b>	242	240	121	242
<b>HbA<sub>1c</sub> (%) (Mean)</b>				
Baseline	8.4	8.3	8.4	8.4
Change from baseline	-1.00*	-0.97*	0.09	-0.98
<b>Subjects (%) achieving HbA<sub>1c</sub> &lt;7%</b>				
All subjects	42.4*	35.3*	10.8	36.3
Previous OAD monotherapy	66.3	52.8	22.5	56.0
<b>LEAD 1 - Glimepiride Add-on Therapy</b>				
	<b>Victoza 1.8 mg + glimepiride</b>	<b>Victoza 1.2 mg + glimepiride</b>	<b>Glimepiride [3]</b>	<b>Rosiglitazone + glimepiride [4]</b>
<b>N</b>	234	228	114	231
<b>HbA<sub>1c</sub> (%) (Mean)</b>				
Baseline	8.5	8.5	8.4	8.4
Change from baseline	-1.13*#	-1.08*#	0.23	-0.44
<b>Subjects (%) achieving HbA<sub>1c</sub> &lt;7%</b>				
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)

*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<sub>1c</sub>: 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<sub>1c</sub> 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 2).

**Table 2 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.**

<b>LEAD 5 - Metformin + Glimepiride Add-on Therapy</b>			
	<b>Victoza 1.8 mg+ metformin + glimepiride</b>	<b>Metformin + glimepiride [1]</b>	<b>Glargine + metformin + glimepiride [2]</b>
<b>N</b>	230	114	232
<b>HbA<sub>1c</sub> (%) (Mean)</b>			
Baseline	8.3	8.3	8.1
Change from baseline	-1.33*#	-0.24	-1.09
<b>Subjects (%) achieving HbA<sub>1c</sub> &lt;7%</b>			
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)

*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<sub>1c</sub> <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<sub>1c</sub> from 7.6% to 7.1% after 52 weeks, no major hypoglycaemic episodes were reported with insulin detemir (see Table 3). 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 3 Results of a 12+26 week trial (trials 1842 and 1842 ext.) where insulin detemir was added to liraglutide and metformin in patients not reaching adequate glycaemic control (HbA<sub>1c</sub> <7.0%) after a 12 weeks run-in period on liraglutide.**

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

<sup>a</sup>Odds ratio; <sup>b</sup>Rate ratio

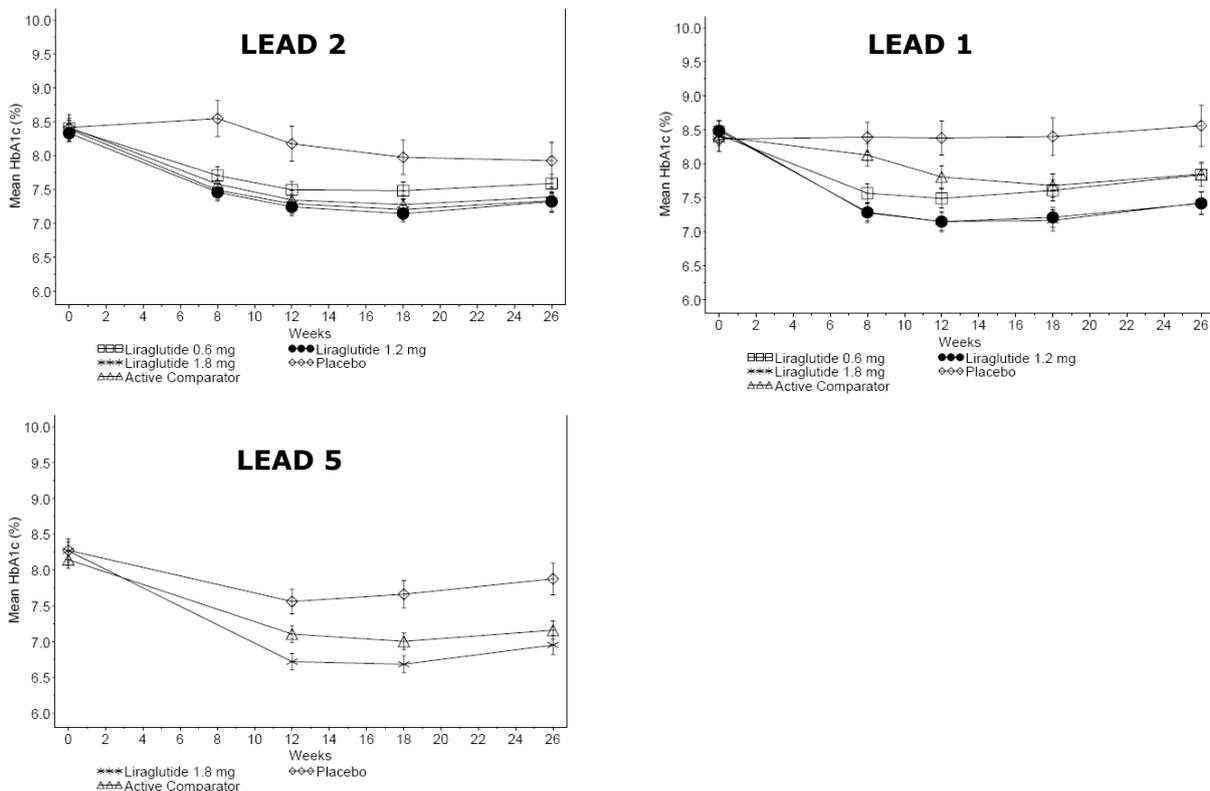
Another 26-week double-blind randomised trial (Trial 3917) investigated the efficacy and safety of Victoza 1.8 mg versus placebo in patients with type 2 diabetes inadequately controlled on basal insulin (insulin glargine or insulin detemir) with or without metformin (N=450, mean HbA<sub>1c</sub> 8.3%). The insulin dose was reduced by 20% for patients with baseline HbA<sub>1c</sub> ≤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<sub>1c</sub> 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<sub>1c</sub> below 7% with Victoza compared with placebo (59.2% vs 14.0%). More patients with Victoza achieved HbA<sub>1c</sub> <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 liraglutide.

**Glycaemic control**

*HbA<sub>1c</sub>*

Victoza in combination therapy for 26 weeks with metformin or a sulfonylurea resulted in statistically significant (p <0.001) and sustained reductions in HbA<sub>1c</sub> 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<sub>1c</sub> (%) over Time ± SEM, ITT Analysis Set Note: The Primary endpoint was change from baseline to the end of the study.

**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.

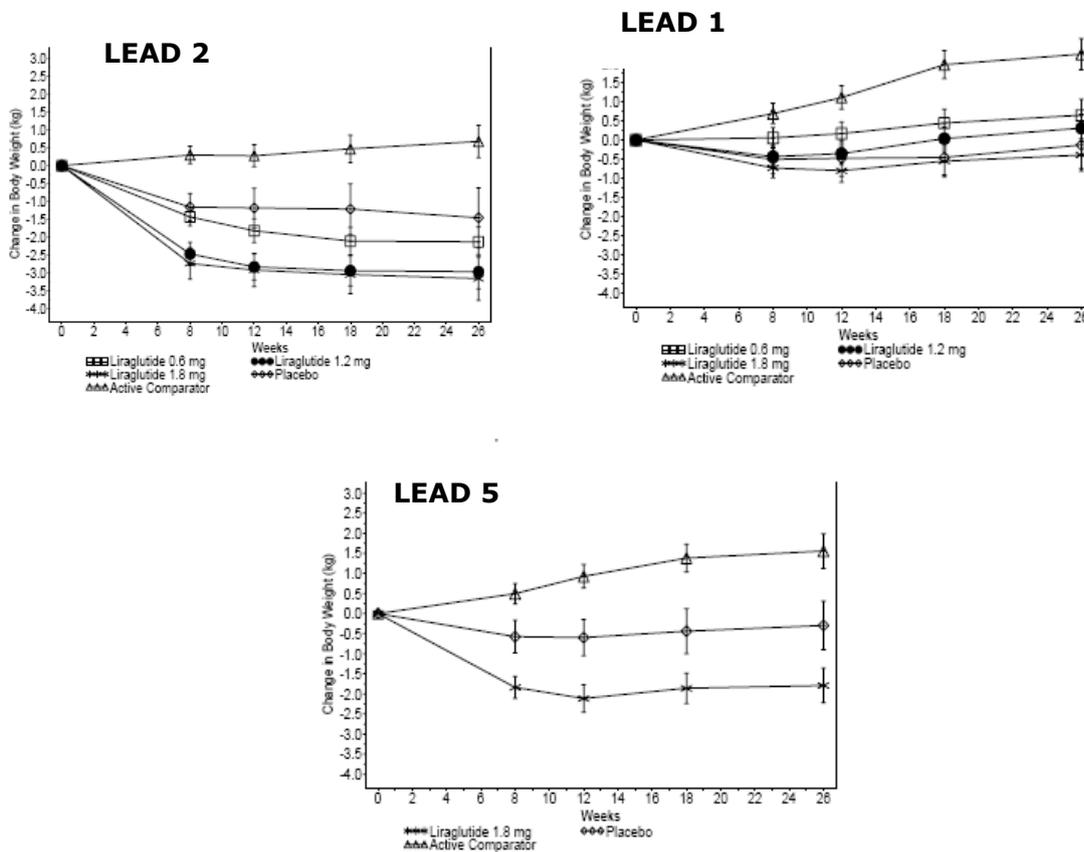
**Postprandial glucose**

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

**Body weight**

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 occurrence 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  $\pm$ 2 SEM

**Effect on 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.

**Effect on lipids**

Victoza showed no adverse effects on lipid parameters.

### ***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.

### ***Macrovascular outcomes***

There have been no clinical studies establishing conclusive evidence of the long-term benefits or adverse effects of Victoza on cardiovascular morbidity or mortality.

*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 5607 patients (3651 exposed to liraglutide), showed no increase in cardiovascular risk (incidence ratio of 0.75 (95% CI 0.35; 1.63) for the composite endpoint for liraglutide versus all comparators (metformin, glimepiride, rosiglitazone, insulin glargine, placebo). High-risk cardiovascular patients were excluded from the trials and the incidence rates of serious major cardiovascular events in the trials were low (6.02 per 1000 patient years in liraglutide-treated patients and 10.45 in all-comparator-treated patients), precluding firm conclusions.

### ***Use 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 insulin and/or OAD in patients with type 2 diabetes and moderate renal impairment, Victoza was superior to placebo treatment in reducing HbA<sub>1c</sub> after 26 weeks (-1.05% vs -0.38%, p<0.0001). Significantly more patients achieved HbA<sub>1c</sub> 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 (-2.4 kg vs -1.3 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. There have been no clinical trials to assess the long term (> 26 weeks) safety of liraglutide in renal impairment, nor the impact of liraglutide on the progression of pre-existing micro or macrovascular disease.

### ***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 subjects developed antibodies. Antibody formation has not been associated with reduced efficacy of Victoza.

### ***Other clinical data***

In an open label study comparing efficacy and safety of liraglutide (1.2 mg and 1.8 mg) and sitagliptin (a DPP-4 inhibitor, 100 mg) in patients inadequately controlled on metformin therapy (mean HbA<sub>1c</sub> 8.5%), Victoza at both doses was statistically superior to sitagliptin treatment in reducing HbA<sub>1c</sub> after 26 weeks (-1.24%, -1.50%, -0.90%, for liraglutide 1.2 mg, 1.8 mg and sitagliptin respectively; p<0.0001). Patients treated with liraglutide 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 liraglutide 1.2 mg, 1.8 mg and sitagliptin treatment groups, respectively, p<0.0001). Greater proportions of patients treated with liraglutide experienced transient nausea compared to patients treated with sitagliptin (20.8%, 27.1%, 4.6% in liraglutide 1.2 mg, 1.8 mg and sitagliptin treatment groups respectively). The reductions in HbA<sub>1c</sub> 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 liraglutide 1.2 mg, 1.8 mg and sitagliptin treatment groups respectively, p<0.0001).

In an open label study comparing efficacy and safety of liraglutide 1.8 mg once daily and exenatide 10 µg twice daily in patients inadequately controlled on metformin and/or sulphonylurea therapy (mean HbA<sub>1c</sub> 8.3%), liraglutide was statistically superior to exenatide treatment in reducing HbA<sub>1c</sub> 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<sub>1c</sub> 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.

## INDICATIONS

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

- in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy.
- in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.
- in combination therapy with basal insulin, with or without metformin.

## CONTRAINDICATIONS

Liraglutide is not to be used in:

- patients with hypersensitivity to liraglutide or any of its excipients.
- patients with a past history of GLP-1 analogue associated pancreatitis.

## 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 limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II, Victoza should therefore be used with caution in these patients. There is no experience in patients with congestive heart failure NYHA class III-IV, Victoza is therefore not recommended in these patients.

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

### ***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 have been no clinical trials to assess the long term (> 26 weeks) safety of Victoza in renal impairment. Caution is required in patients with pre-existing mild/moderate renal impairment. Victoza is not recommended for use in patients with severe renal impairment.

### ***Thyroid disease***

Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in clinical trials, in particular in patients with pre-existing thyroid disease, and liraglutide should therefore be used with caution in these patients.

### ***Pancreatitis***

Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. Acute pancreatitis was reported from clinical trials and marketed use. 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. Caution should be exercised in patients with a history of pancreatitis.

After initiation of Victoza, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting).

In completed 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.

### ***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 a basal insulin may have an increased risk of hypoglycaemia (see Table 5 in Adverse Effects). The risk of hypoglycaemia can be lowered by a reduction in the dose of sulfonylurea or basal 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 a basal 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  $\geq 1$  mg/kg/day (relative exposure based on plasma AUC,  $\geq 7.7$ ) and in rats at all doses tested ( $\geq 0.075$  mg/kg/day subcutaneously; relative exposure,  $\geq 0.5$ ). No tumours or other C-cell proliferative changes were seen in monkeys treated with liraglutide for 20 months ( $\leq 5$  mg/kg/day subcutaneously; relative exposure,  $\leq 64$ ). 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  $\leq 1$  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  $\geq 0.01$  mg/kg/day (relative exposure,  $\geq 0.2$ ), 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 ethinyloestradiol 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 ethinylloestradiol 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 ethinylloestradiol 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 INR (International Normalised Ratio) is recommended.

### *Insulin*

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

## **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 basal insulin. Major 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 4 lists adverse reactions reported in long-term phase 3 controlled studies and spontaneous (post-marketing) reports. Frequencies for related spontaneous reports (post-marketing) have been calculated based on their incidence in phase 3 clinical studies. 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) and rare (≥1/10,000 to <1/1000) and very rare (<1/10,000).

**Table 4 Adverse reactions reported in long-term phase 3 controlled studies and spontaneous (post-marketing) reports**

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

N=2501 Victoza-treated subjects

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

# See 'Precautions'

**Description of selected adverse events:**

*Hypoglycaemia*

Most episodes of confirmed hypoglycaemia in clinical studies were minor.

No episodes of major hypoglycaemia were observed in the study with Victoza used as monotherapy. Major hypoglycaemia may occur uncommonly and has primarily been observed when Victoza is combined with a 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.

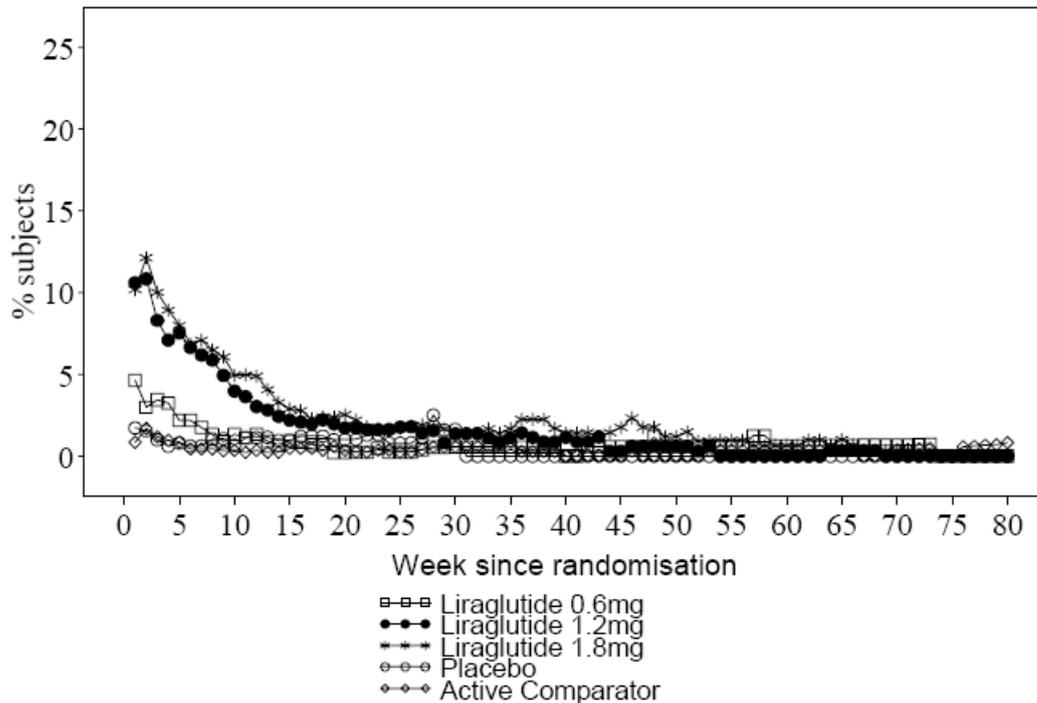
Table 5 presents the incidence of confirmed hypoglycaemic episodes (number of episodes divided by subject years of exposure).

**Table 5 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	
<b>Monotherapy (LEAD 3)</b>	<b>Liraglutide</b>	<b>Placebo + Sulfonylurea</b>
(52 week study)	0.27	1.70
<b>Combination with Metformin (LEAD 2)</b>	<b>Liraglutide + Metformin</b>	<b>Metformin + Sulfonylurea</b>
(26 week study)	0.05	0.87
<b>Combination with Sulfonylurea (LEAD 1)</b>	<b>Liraglutide + Sulfonylurea</b>	<b>Sulfonylurea + Rosiglitazone</b>
(26 week study)	0.43	0.14
<b>Combination with Metformin + Rosiglitazone (LEAD 4)</b>	<b>Liraglutide + Metformin + Rosiglitazone</b>	<b>Placebo + Metformin + Rosiglitazone</b>
(26 week study)	0.50	0.18
<b>Combination with Metformin + Sulfonylurea (LEAD 5)</b>	<b>Liraglutide + Metformin + Sulfonylurea</b>	<b>Insulin glargine + Metformin + Sulfonylurea</b>
(26 week study)	1.21	1.33

*Gastrointestinal adverse events*

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

#### *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 (<0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza (see Contraindications and Precautions). Pancreatitis was also reported from marketed use.

#### *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.

#### *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.

### *Increased heart rate*

Signs and symptoms of increased heart rate were reported with the use of Victoza. Mean increase in heart rate from baseline of 2 to 3 beats per minute has been observed with Victoza in long-term clinical trials. The long-term clinical effects of the increase in heart rate have not been established.

## **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 liraglutide 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 basal 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, a reduction in the dose of sulfonylurea 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.

When Victoza is added to an existing therapy with basal insulin, a reduction in the dose of the insulin should be considered to reduce the risk of 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 a basal insulin, blood glucose self-monitoring may become necessary to adjust the dose of the sulfonylurea or the basal 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. Therapeutic experience in patients  $\geq 75$  years of age is limited (see Pharmacokinetics).

### Patients with hepatic impairment

The therapeutic experience in patients with hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment (see Pharmacokinetics).

### Patients with renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance 60–90 mL/min and 30–59 mL/min, respectively). There is no therapeutic experience in patients with severe renal impairment (creatinine clearance below 30 mL/min). Victoza can currently not be recommended for use in patients with severe renal impairment including patients with end-stage renal disease (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***

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<sup>®</sup> 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**

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 overdose, 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 stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polyolefin and polyacetal.

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

Pack sizes of 1, 2, 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:**

17 January 2017