SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Victoza ▼6 mg/ml solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 6 mg of liraglutide*. One pre-filled pen contains 18 mg liraglutide in 3 ml.

* human glucagon-like peptide-1 (GLP-1) analogue produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (injection).
Clear, colourless, isotonic solution; pH=8.15.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Victoza is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:
In combination with:
– Metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea.
In combination with:
– Metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

4.2 Posology and method of administration

Posology
To improve gastro-intestinal tolerability, the starting dose is 0.6 mg liraglutide daily. After at least one week, the dose should be increased to 1.2 mg. Some patients are expected to benefit from an increase in dose from 1.2 mg to 1.8 mg and based on clinical response, after at least one week the dose can be increased to 1.8 mg to further improve glycaemic control. Daily doses higher than 1.8 mg are not recommended.

Victoza can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione can be continued unchanged.

Victoza can be added to existing sulphonylurea or to a combination of metformin and sulphonylurea therapy. When Victoza is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia (see section 4.4).

Self-monitoring of blood glucose is not needed in order to adjust the dose of Victoza. However, when initiating treatment with Victoza in combination with a sulphonylurea, blood glucose self-monitoring may become necessary to adjust the dose of the sulphonylurea.

Special populations
Elderly (>65 years old): No dose adjustment is required based on age. Therapeutic experience in

patients ≥75 years of age is limited (see section 5.2).

Renal impairment: No dose adjustment is required for patients with mild renal impairment (creatinine clearance ≤60-90 ml/min). There is very limited therapeutic experience in patients with moderate renal impairment (creatinine clearance of 30-59 ml/min) and 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 moderate and severe renal impairment including patients with end-stage renal disease (see section 5.2).

Hepatic impairment: The therapeutic experience in patients with all degrees of hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment (see section 5.2).

Paediatric population: Victoza is not recommended for use in children below 18 years of age due to lack of data on its safety and efficacy.

Method of administration
Victoza should **not** be administered intravenously or intramuscularly.

Victoza is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that Victoza is injected around the same time of the day, when the most convenient time of the day has been chosen. For further instructions on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

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

There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV.

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

Use of other GLP-1 analogues has been associated with the risk of pancreatitis. There have been few reported events of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Victoza and other potentially suspect medicinal products should be discontinued.

Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in clinical trials in particular in patients with pre-existing thyroid disease (see section 4.8).

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

4.5 Interaction with other medicinal products and other forms of interaction

In vitro, liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 and plasma protein binding.

The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption. Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.

Paracetamol
Liraglutide did not change the overall exposure of paracetamol following a single dose of 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 clinical relevant degree following single dose administration of atorvastatin 40 mg. Therefore, no dose adjustment of atorvastatin is required when given with liraglutide. Atorvastatin C_{max} was decreased by 38% and median t_{max} was delayed from 1 h to 3 h with liraglutide.

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

Lisinopril and digoxin
Single dose administration of lisinopril 20 mg or digoxin 1 mg with liraglutide showed a reduction of lisinopril and digoxin AUC by 15% and 16%, respectively; C_{max} decreased by 27% and 31%, respectively. Lisinopril median t_{max} was delayed from 6 h to 8 h with liraglutide; whereas digoxin median t_{max} was delayed from 1 h to 1.5 h. No adjustment of lisinopril or digoxin dose is required based on these results.

Oral contraceptives
Liraglutide lowered ethinyloestradiol and levonorgestrel C_{max} by 12 and 13%, respectively, following administration of a single dose of an oral contraceptive product. T_{max} was delayed by 1.5 h with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinyloestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

Warfarin
No interaction study has been performed. A clinically relevant interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin cannot be excluded. Upon initiation of liraglutide treatment in patients on warfarin more frequent monitoring of INR (International Normalised Ratio) is recommended.

Insulin
Combination of liraglutide with insulin has not been evaluated and is therefore not recommended.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of Victoza in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Victoza should not be used during pregnancy, and the use of insulin is recommended instead. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Victoza should be discontinued.

Lactation

It is not known whether liraglutide is excreted in human milk. Animal studies have shown that the transfer of liraglutide and metabolites of close structural relationship into milk is low. Non-clinical studies have shown a treatment-related reduction of neonatal growth in suckling rat pups (see section 5.3). Because of lack of experience, Victoza should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza is used in combination with a sulphonylurea.

4.8 Undesirable effects

In five large long-term clinical trials over 2500 patients have received treatment with Victoza alone or in combination with metformin, a sulphonylurea (with or without metformin) or metformin plus rosiglitazone.

Frequencies are defined as: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequently reported adverse reactions during clinical trials were gastrointestinal disorders: nausea and diarrhoea were very common, whereas vomiting, constipation, abdominal pain, and dyspepsia were common. At the beginning of Victoza therapy, these gastrointestinal adverse reactions may occur more frequently. These reactions usually diminish within a few days or weeks on continued treatment. Headache and nasopharyngitis were also common. Furthermore, hypoglycaemia was common, and very common when Victoza is used in combination with a sulphonylurea. Major hypoglycaemia has primarily been observed when combined with a sulphonylurea.

Table 1 lists related adverse reactions identified from Phase III combination-studies with Victoza. The table presents adverse reactions that occurred with a frequency >5% if the frequency was higher among Victoza-treated patients than patients treated with comparator. The table also includes adverse reactions with a frequency ≥2% if the frequency was >2 times the frequency for comparator-treated subjects.

Table 1 Adverse reactions identified from long-term controlled phase III studies

Adverse reaction	**Frequency of adverse reaction by treatment group**			
	Liraglutide with metformin	**Liraglutide with glimepiride**	**Liraglutide with metformin and glimepiride**	**Liraglutide with metformin and rosiglitazone**
Infections and infestations				
Nasopharyngitis		Common		Common
Bronchitis			Common	
Metabolism and nutrition disorders				
Hypoglycaemia		Common	Very common	Common
Anorexia	Common	Common	Common	Common
Appetite decreased	Common			Common
Nervous system disorders				
Headache	Very common		Common	Common
Dizziness	Common			

Adverse reaction	Frequency of adverse reaction by treatment group			
	Liraglutide with metformin	**Liraglutide with glimepiride**	**Liraglutide with metformin and glimepiride**	**Liraglutide with metformin and rosiglitazone**
Gastrointestinal disorders				
Nausea	Very common	Common	Very common	Very common
Diarrhoea	Very common	Common	Very common	Very common
Vomiting	Common	Common	Common	Very common
Dyspepsia	Common	Common	Common	Common
Abdominal pain upper			Common	
Constipation		Common	Common	Common
Gastritis	Common			
Flatulence				Common
Abdominal distension				Common
Gastroesophageal reflux disease				Common
Abdominal discomfort		Common		
Toothache			Common	
Gastroenteritis viral				Common
General disorders and administration site conditions				
Fatigue				Common
Pyrexia				Common

In a clinical trial with Victoza as monotherapy rates of hypoglycaemia reported with Victoza were lower than rates reported for patients treated with active comparator (glimepiride). The most frequently reported adverse events were gastrointestinal and infections and infestations.

Hypoglycaemia
Most episodes of confirmed hypoglycaemia in clinical studies were minor. No episodes of major hypoglycaemia were observed in the study with Victoza used as monotherapy. Major hypoglycaemia may occur uncommonly and has primarily been observed when Victoza is combined with a sulphonylurea (0.02 events/subject year). Very few episodes (0.001 events/subject year) were observed with administration of Victoza in combination with oral antidiabetics other than sulphonylureas.

Gastrointestinal adverse reactions
When combining Victoza with metformin, 20.7% of patients reported at least one episode of nausea, and 12.6% of patients reported at least one episode of diarrhoea. When combining Victoza with a sulphonylurea, 9.1% of patients reported at least one episode of nausea and 7.9% of patients reported at least one episode of diarrhoea. Most episodes were mild to moderate and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea.

Patients >70 years may experience more gastrointestinal effects when treated with liraglutide. Patients with mild renal impairment (creatinine clearance ≤60-90 ml/min) may experience more

gastrointestinal effects when treated with liraglutide.

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

Immunogenicity
Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop anti-liraglutide antibodies following treatment with Victoza. On average, 8.6% of patients developed antibodies. Antibody formation has not been associated with reduced efficacy of Victoza.

Few cases (0.05%) of angioedema have been reported during all long-term clinical trials with Victoza.

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

Pancreatitis
Few cases (<0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza. A causal relationship between Victoza and pancreatitis can neither be established nor excluded.

Thyroid events
The overall rates of thyroid adverse events in all intermediate and long-term trials are 33.5, 30.0 and 21.7 events per 1000 subject years of exposure for total liraglutide, placebo and total comparators; 5.4, 2.1 and 0.8 events, respectively concern serious thyroid adverse events.
In liraglutide-treated patients, thyroid neoplasms, increased blood calcitonin and goiters are the most frequently thyroid adverse events and were reported in 0.5%, 1% and 0.8% of patients respectively.

4.9 Overdose

In a clinical study of Victoza, one patient with type 2 diabetes experienced a single overdose of 17.4 mg subcutaneous (10 times the maximal recommended maintenance dose of 1.8 mg). Effects of the overdose included severe nausea and vomiting, but not hypoglycaemia. The patient recovered without complications.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other blood glucose lowering drugs, excl. insulins. ATC code: A10BX07

Mechanism of action
Liraglutide is a GLP-1 analogue with 97% sequence homology to human GLP-1 that binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in humans suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption; binding to

albumin; and higher enzymatic stability towards the dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidase (NEP) enzymes, resulting in a long plasma half-life.

Liraglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Liraglutide stimulates insulin secretion in a glucose-dependent manner. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying. Liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake.

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

Clinical efficacy
Five double-blind, randomised, controlled clinical trials were conducted to evaluate the effects of Victoza on glycaemic control. Treatment with Victoza produced clinically and statistically significant improvements in glycosylated haemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose and post-prandial glucose compared with placebo.

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

There was an additional open-label randomised controlled study comparing liraglutide with exenatide.

Glycaemic control
Victoza in combination therapy, for 26 weeks, with metformin, glimepiride or metformin and rosiglitazone resulted in statistically significant ($p<0.0001$) and sustained reductions in HbA_{1c} compared with patients receiving placebo (Tables 2 and 3).

Table 2 Results of two 26 week trials. Victoza in combination with metformin and Victoza in combination with glimepiride.

Metformin add-on therapy	1.8 mg liraglutide + metformin[3]	1.2 mg liraglutide + metformin[3]	placebo + metformin[3]	Glimepiride[2] + metformin[3]
N	242	240	121	242
Mean HbA_{1c} (%)				
Baseline	8.4	8.3	8.4	8.4
Change from baseline	-1.00	-0.97	0.09	-0.98
Patients (%) achieving HbA_{1c} <7%				
All patients	42.4	35.3	10.8	36.3
Previous OAD monotherapy	66.3	52.8	22.5	56.0
Mean body weight (kg)				
Baseline	88.0	88.5	91.0	89.0
Change from baseline	-2.79	-2.58	-1.51	0.95

Glimepiride add-on therapy	**1.8 mg liraglutide + glimepiride[2]**	**1.2 mg liraglutide + glimepiride[2]**	**Placebo + glimepiride[2]**	**rosiglitazone[1] + glimepiride[2]**
N	234	228	114	231
Mean HbA_{1c} (%)				
Baseline	8.5	8.5	8.4	8.4
Change from baseline	-1.13	-1.08	0.23	-0.44

Patients (%) achieving HbA_{1c} <7%				
All patients	41.6	34.5	7.5	21.9
Previous OAD monotherapy	55.9	57.4	11.8	36.1
Mean body weight (kg)				
Baseline	83.0	80.0	81.9	80.6
Change from baseline	-0.23	0.32	-0.10	2.11

[1] Rosiglitazone 4 mg/day; [2] glimepiride 4 mg/day; [3] metformin 2000 mg/day

Table 3 Results of two 26 week trials. Victoza in combination with metformin + rosiglitazone and Victoza in combination with glimepiride + metformin.

Metformin + rosiglitazone add-on therapy	1.8 mg liraglutide + metformin[2] + rosiglitazone[3]	1.2mg liraglutide + metformin[2] + rosiglitazone[3]	placebo + metformin[2] + rosiglitazone[3]	N/A
N	178	177	175	
Mean HbA_{1c} (%)				
Baseline	8.56	8.48	8.42	
Change from baseline	-1.48	-1.48	-0.54	
Patients (%) achieving HbA_{1c} <7%				
All patients	53.7	57.5	28.1	
Mean body weight (kg)				
Baseline	94.9	95.3	98.5	
Change from baseline	-2.02	-1.02	0.60	
Metformin + glimepiride add-on therapy	**1.8 mg liraglutide + metformin[2] + glimepiride[4]**	**N/A**	**Placebo + metformin[2] + glimepiride[4]**	**insulin glargine[1] + metformin[2] + glimepiride[4]**
N	230		114	232
Mean HbA_{1c} (%)				
Baseline	8.3		8.3	8.1
Change from baseline	-1.33		-0.24	-1.09
Patients (%) achieving HbA_{1c} <7%				
All patients	53.1		15.3	45.8
Mean body weight (kg)				
Baseline	85.8		85.4	85.2
Change from baseline	-1.81		-0.42	1.62

[1] The dosing of insulin glargine was open-labelled and was applied according to the following titration guideline. Titration of the insulin glargine dose was managed by the patient after instruction by the investigator.

Guideline for titration of insulin glargine

Self-measured FPG	Increase in insulin glargine dose (IU)
≤5.5 mmol/l (≤100 mg/dl) Target	No adjustment
>5.5 and <6.7 mmol/l (>100 and <120 mg/dl)	0 – 2 IU[a]
≥6.7 mmol/l (≥120 mg/dl)	2 IU

[a] According to the individualised recommendation by the investigator at the previous visit for example depending on whether subject has experienced hypoglycaemia.

[2] Metformin 2000 mg/day; [3] rosiglitazone 4 mg twice daily; [4] glimepiride 4 mg/day.

Proportion of patients achieving reductions in HbA_{1c}

Victoza in combination with metformin, glimepiride, or metformin and rosiglitazone resulted in a

statistically significant ($p \leq 0.0001$) greater proportion of patients achieving an $HbA_{1c} \leq 6.5\%$ at 26 weeks compared with patients receiving these agents alone.

Fasting plasma glucose
Treatment with Victoza alone or in combination with one or two oral antidiabetic drugs resulted in a reduction in fasting plasma glucose of 13-43.5 mg/dl (0.72-2.42 mmol/l). This reduction was observed within the first two weeks of treatment.

Post-prandial glucose
Victoza reduces post-prandial glucose across all three daily meals by 31-49 mg/dl (1.68-2.71 mmol/l).

Beta-cell function
Clinical studies with Victoza indicate improved beta-cell function based on measures such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio. Improved first and second phase insulin secretion after 52 weeks treatment with Victoza was demonstrated in a subset of patients with type 2 diabetes (N=29).

Body weight
Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies in a range from 1.0 kg to 2.8 kg.

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

Blood pressure
Over the duration of the studies Victoza decreased the systolic blood pressure on average of 2.3 to 6.7 mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5 mmHg

5.2 Pharmacokinetic properties

Absorption
The absorption of liraglutide following subcutaneous administration is slow, reaching maximum concentration 8-12 hours post dosing. Estimated maximum liraglutide concentration was 9.4 nmol/l for a subcutaneous single dose of liraglutide 0.6 mg. At 1.8 mg liraglutide, the average steady state concentration of liraglutide ($AUC_{\tau/24}$) reached approximately 34 nmol/l. Liraglutide exposure increased proportionally with dose. The intra-subject coefficient of variation for liraglutide AUC was 11% following single dose administration.
Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution
The apparent volume of distribution after subcutaneous administration is 11-17 l. The mean volume of distribution after intravenous administration of liraglutide is 0.07 l/kg. Liraglutide is extensively bound to plasma proteins (>98%).

Metabolism
During 24 hours following administration of a single radiolabelled [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (≤9% and ≤5% of total plasma radioactivity exposure). Liraglutide is metabolised in a similar manner to large proteins without a specific organ having been identified as major route of elimination.

Elimination
Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or faeces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or faeces (6% and 5%, respectively). The urine and faeces radioactivity was mainly excreted during the first 6-8 days, and corresponded to three minor metabolites, respectively.

The mean clearance following subcutaneous administration of a single dose liraglutide is

approximately 1.2 l/h with an elimination half-life of approximately 13 hours.

Special populations

Elderly: Age had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results from a pharmacokinetic study in healthy subjects and population pharmacokinetic data analysis of patients (18 to 80 years).

Gender: Gender had no clinically meaningful effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic data analysis of male and female patients and a pharmacokinetic study in healthy subjects.

Ethnic origin: Ethnic origin had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic analysis which included subjects of White, Black, Asian and Hispanic groups.

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

Hepatic impairment: The pharmacokinetics of liraglutide was evaluated in subjects with varying degree of hepatic impairment in a single-dose trial. Liraglutide exposure was decreased by 13-23% in subjects with mild to moderate hepatic impairment compared to healthy subjects.
Exposure was significantly lower (44%) in subjects with severe hepatic impairment (Child Pugh score >9).

Renal impairment: Liraglutide exposure was reduced in subjects with renal impairment compared to individuals with normal renal function. Liraglutide exposure was lowered by 33%, 14%, 27% and 28%, respectively, in subjects with mild (creatinine clearance, CrCL 50-80 ml/min), moderate (CrCL 30-50 ml/min), and severe (CrCL <30 ml/min) renal impairment and in end-stage renal disease requiring dialysis.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, or genotoxicity.

Non-lethal thyroid C-cell tumours were seen in 2-year carcinogenicity studies in rats and mice. In rats, a no observed adverse effect level (NOAEL) was not observed. These tumours were not seen in monkeys treated for 20 months. These findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot be completely excluded. No other treatment-related tumours have been found.

Animal studies did not indicate direct harmful effects with respect to fertility but slightly increased early embryonic deaths at the highest dose. Dosing with Victoza during mid-gestation caused a reduction in maternal weight and foetal growth with equivocal effects on ribs in rats and skeletal variation in the rabbit. Neonatal growth was reduced in rats while exposed to Victoza, and persisted in the post-weaning period in the high dose group. It is unknown whether the reduced pup growth is caused by reduced pup milk intake due to a direct GLP-1 effect or reduced maternal milk production due to decreased caloric intake.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dihydrate

Propylene glycol
Phenol
Water for injections

6.2 Incompatibilities

Substances added to Victoza may cause degradation of liraglutide. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months.

After first use: 1 month

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store away from the freezer compartment.

After first use: Store below 30°C or store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the cap on the pen in order to protect from light.

6.5 Nature and contents of container

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

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

Pack sizes of 1, 2, 3, 5 or 10 pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Victoza should not be used if it does not appear clear and colourless.
Victoza should not be used if it has been frozen.

Victoza can be administered with needles up to a length of 8 mm and as thin as 32G. The pen is designed to be used with NovoFine or NovoTwist disposable needles.
Injection needles are not included.

The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the Victoza pen without an injection needle attached. This prevents contamination, infection, and leakage. It also ensures that the dosing is accurate.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/529/001
EU/1/09/529/002
EU/1/09/529/003
EU/1/09/529/004
EU/1/09/529/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 June 2009

10. DATE OF REVISION OF THE TEXT

06/2009

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.