FOOD AND DRUGS AUTHORITY

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Victoza 6 mg/ml solution for injection in pre-filled pen
1 ml of solution contains 6 mg of liraglutide*. One pre-filled pen contains 18 mg liraglutide in 3 ml.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Victoza is indicated for the treatment of adults, adolescents and children aged 10 years and above with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
• as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
• in addition to other medicinal products for the treatment of diabetes.

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.
When Victoza is added to a sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see section 4.4).
Combination therapy with sulfonylurea is only valid for adult patients.
Self-monitoring of blood glucose is not needed in order to adjust the dose of Victoza.
Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Victoza therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

Special populations
Elderly (≥65 years old)
No dose adjustment is required based on age.

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.

Hepatic impairment
No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Victoza is not recommended for use in patients with severe hepatic impairment.

Paediatric population
No dose adjustment is required for adolescents and children aged 10 years and above. No data are available for children below 10 years of age.

Method of administration
Victoza must not be administered intravenously or intramuscularly.
Victoza is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Liraglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
Liraglutide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin.

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

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

Acute pancreatitis
Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued; if acute pancreatitis is confirmed, liraglutide should not be restarted (see sections 4.8 and 5.1).

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

Hypoglycaemia
Patients receiving liraglutide in combination with a sulfonylurea or insulin 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 sulfonylurea or insulin.

Dehydration
Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients treated with liraglutide. Patients treated with liraglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Excipients
Victoza contains less than 1 mmol sodium (23 mg) per dose, therefore the medicinal product is essentially 'sodium-free'.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 and therefore no dose adjustment is required. Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.

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

Paracetamol
Liraglutide did not change the overall exposure of paracetamol following a single dose of 1000 mg. Paracetamol Cmax was decreased by 31% and median tmax 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 Cmax was decreased by 38% and median tmax 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 Cmax increased by 37% while median tmax 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%; Cmax decreased by 31%. Digoxin median tmax was delayed from 1 h to 1.5 h. No adjustment of digoxin dose 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%; Cmax decreased by 27%. Lisinopril median tmax 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 ethinyloestradiol and levonorgestrel Cmax by 12 and 13%, respectively, following administration of a single dose of an oral contraceptive product. Tmax 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.

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.

Paediatric Population
Interaction studies have only been performed in adults.

4.6 Fertility, Pregnancy and lactation

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

Breast-feeding
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.

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

4.7 Effects on ability to drive and use machines

Victoza has no or negligible influence on the ability to drive and use machines.

Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza is used in combination with a sulfonylurea or insulin.

4.8 Undesirable effects

Summary of the safety profile

In five large long-term clinical phase 3a trials over 2,500 adult patients have received treatment with Victoza alone or in combination with metformin, a sulfonylurea (with or without metformin) or metformin plus rosiglitazone.

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 the 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 liraglutide is used in combination with a sulfonylurea. Severe hypoglycaemia has primarily been observed when combined with a sulfonylurea.

Tabulated list of adverse reactions

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

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, adverse reactions are presented in order of decreasing seriousness.

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

MedDRA system organ classes	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Nasopharyngitis Bronchitis			
Immune system disorders				Anaphylactic reactions	
Metabolism and nutrition disorders		Hypoglycaemia Anorexia Appetite decreased	Dehydration		
Nervous system disorders		Headache Dizziness			
Cardiac disorders		Increased heart rate			
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Dyspepsia Abdominal pain upper Constipation Gastritis Flatulence Abdominal distension Gastroesophageal reflux disease	Delayed gastric emptying	Intestinal obstruction	Pancreatitis (including necrotising pancreatitis)

		Abdominal discomfort Toothache			
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*			

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

Description of selected adverse reactions

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

Hypoglycaemia

Most episodes of confirmed hypoglycaemia in clinical trials were minor. No episodes of severe hypoglycaemia were observed in the trial with liraglutide used as monotherapy. Severe hypoglycaemia may occur uncommonly and has primarily been observed when liraglutide is combined with a sulfonylurea (0.02 events/patient year). Very few episodes (0.001 events/patient year) were observed with administration of liraglutide in combination with oral antidiabetics other than sulfonylureas. The risk of hypoglycaemia is low with combined use of basal insulin and liraglutide (1.0 events per patient year, see section 5.1). In the LEADER trial, severe hypoglycaemic episodes were reported at a lower rate with liraglutide vs placebo (1.0 vs 1.5 events per 100 patient years; estimated rate ratio 0.69 [0.51 to 0.93]) (see section 5.1). For patients treated with premix insulin at baseline and at least for the following 26 weeks, the rate of severe hypoglycaemia for both liraglutide and placebo was 2.2 events per 100 patient years.

Gastrointestinal adverse reactions

When combining liraglutide 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 liraglutide with a sulfonylurea, 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 and moderate renal impairment (creatinine clearance 60–90 ml/min and 30–59 ml/min, respectively) may experience more gastrointestinal effects when treated with liraglutide.

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 liraglutide. In the LEADER trial, the frequency of cholelithiasis and cholecystitis was 1.5% and 1.1% for liraglutide and 1.1% and 0.7% for placebo, respectively (see section 5.1).

Withdrawal
The incidence of withdrawal due to adverse reactions was 7.8% for liraglutide-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 liraglutide-treated patients were nausea (2.8% of patients) and vomiting (1.5%).

Injection site reactions
Injection site reactions have been reported in approximately 2% of patients receiving Victoza in long-term (26 weeks or longer) controlled trials. These reactions have usually been mild.

Pancreatitis
Few cases of acute pancreatitis (<0.2%) have been reported during long-term, controlled phase 3 clinical trials with Victoza. Pancreatitis was also reported from marketed use. In the LEADER trial, the frequency of acute pancreatitis confirmed by adjudication was 0.4% for liraglutide and 0.5% for placebo, respectively (see sections 4.4 and 5.1).

Allergic reactions
Allergic reactions including urticaria, rash and pruritus have been reported from marketed use of Victoza.
Few cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnoea and oedema have been reported with marketed use of Victoza.
Few cases (0.05%) of angioedema have been reported during all long-term clinical trials with Victoza.

Paediatric population
Overall, frequency, type and severity of adverse reactions in adolescents and children aged 10 years and above were comparable to that observed in the adult population. Rate of confirmed hypoglycaemic episodes was higher with liraglutide (0.58 events/patient year) compared to placebo (0.29 events/patient year). In patients treated with insulin prior to a confirmed hypoglycaemic episode the rate was higher with liraglutide (1.82 events/patient year) compared to placebo (0.91 events/patient years). No severe hypoglycaemic episodes occurred in the liraglutide treatment group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

From clinical trials and marketed use, overdoses have been reported of up to 40 times (72 mg) the recommended maintenance dose. Events reported included severe nausea, vomiting, diarrhoea and severe hypoglycaemia.
In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. The patient should be observed for clinical signs of dehydration and blood glucose should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Liraglutide is a 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 -4 (DPP-4) 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, GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear.

In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions involved in regulation of appetite, where liraglutide via specific activation of the GLP-1 receptor (GLP-1R) increased key satiety and decreased key hunger signals, thereby leading to lower body weight.

GLP-1 receptors are also expressed in specific locations in the heart, vasculature, immune system, and kidneys. In mouse models of atherosclerosis, liraglutide prevented aortic plaque progression and reduced inflammation in the plaque. In addition, liraglutide had a beneficial effect on plasma lipids. Liraglutide did not reduce the plaque size of already established plaques.

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 (mean body weight approximately 73 kg) 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 (mean body weight approximately 76 kg). The exposure of liraglutide decreases with increasing body weight. 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 affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. Insulin aspart has a low binding to plasma proteins (<10%), similar to that seen with regular human insulin.

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

Elimination
Following a [3H]-liraglutide dose, intact liraglutide was not detected in urine or faeces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or faeces (6% and 5%, respectively). The urine and faeces radioactivity was mainly excreted during the first 6–8 days, and corresponded to three minor metabolites, respectively.
The mean clearance following 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 patients
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 patients 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 patients with varying degree of hepatic impairment in a single-dose trial. Liraglutide exposure was decreased by 13–23% in patients with mild to moderate hepatic impairment compared to healthy subjects. Exposure was significantly lower (44%) in patients with severe hepatic impairment (Child Pugh score >9).

Renal impairment
Liraglutide exposure was reduced in patients with renal impairment compared to individuals with normal renal function. Liraglutide exposure was lowered by 33%, 14%,

27% and 26% in patients 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, respectively.
Similarly, in a 26-week clinical trial, patients with type 2 diabetes and moderate renal impairment (CrCL 30–59 ml/min, see section 5.1) had 26% lower liraglutide exposure when compared with a separate trial including patients with type 2 diabetes with normal renal function or mild renal impairment.

Paediatric population
Pharmacokinetic properties were assessed in clinical studies in the paediatric population with type 2 diabetes aged 10 years and above. The liraglutide exposure in adolescents and children was comparable to that observed in the adult population.

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

Victoza 6 mg/ml solution for injection in pre-filled pen
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 <and special equipment for use, administration or implantation>

Victoza 6 mg/ml solution for injection in pre-filled pen
3 mL solution in a cartridge (type 1 glass) with a plunger (halobutyl) and a laminate rubber sheet (halobutyl/polyisoprene) contained in a multidose disposable pre-filled pen made of polypropylene.
Pack sizes of 1 (with or without needles), 5 (without needles) and multipack containing 10 (2 packs of 5) (without needles) 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 or almost colourless.
Victoza should not be used if it has been frozen.
Victoza can be administered with needles up to a length of 8 mm and as thin as 32G. The pen is designed to be used with NovoFine or NovoTwist disposable needles.
Needles are not included.
The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the pen without an injection needle attached. This prevents contamination, infection and leakage. It also ensures that the dosing is accurate.

7. <SUPPLIER>

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

8. DATE OF PUBLICATION OR REVISION

Date of first authorisation: 30 June 2009
Date of latest renewal: 11 April 2014

1 APPENDIX

1.1 Change History

SN	Date	Ver. No.	Description of Change (section)
1.	Effective date	01	Initial issue