## 4.8 Undesirable effects

Summary of the safety profile:

Saxenda was evaluated for safety in 5 double-blind, placebo-controlled trials that enrolled 5,813 adult patients with overweight or obesity with at least one weight-related comorbidity. Overall, gastrointestinal reactions were the most frequently reported adverse reactions during treatment (67.9%) (see section 'Description of selected adverse reactions').

Tabulated list of adverse reactions

Table 3 lists adverse reactions reported in adults. Adverse reactions are listed by system organ class and frequency. Frequency categories 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 3 Adverse reactions reported in adults**

| **MedDRA system organ classes** | **Very common** | **Common** | **Uncommon** | **Rare** |
|---|---|---|---|---|
| Immune system disorders | | | | Anaphylactic reaction |
| Metabolism and nutrition disorders | | Hypoglycaemia* | Dehydration | |
| Psychiatric disorders | | Insomnia** | | |
| Nervous system disorders | Headache | Dizziness<br>Dysgeusia | | |
| Cardiac disorders | | | Tachycardia | |
| Gastrointestinal disorders | Nausea<br>Vomiting<br>Diarrhoea<br>Constipation | Dry mouth<br>Dyspepsia<br>Gastritis<br>Gastro-oesophageal reflux disease<br>Abdominal pain upper<br>Flatulence<br>Eructation<br>Abdominal distension | Pancreatitis***<br>Delayed gastric emptying**** | |
| Hepatobiliary disorders | | Cholelithiasis*** | Cholecystitis*** | |
| Skin and subcutaneous tissue disorders | | | Urticaria | |
| Renal and urinary disorders | | | | Acute renal failure<br>Renal impairment |
| General disorders and administration site conditions | | Injection site reactions<br>Asthenia<br>Fatigue | Malaise | |
| Investigations | | Increased lipase<br>Increased amylase | | |

*Hypoglycaemia (based on self-reported symptoms by patients and not confirmed by blood glucose measurements) reported in patients without type 2 diabetes mellitus treated with Saxenda in combination with diet and exercise. Please see section 'Description of selected adverse reactions' for further information.
**Insomnia was mainly seen during the first 3 months of treatment.
***See section 4.4.
****From controlled phase 2, 3a and 3b clinical trials.

Description of selected adverse reactions:

*Hypoglycaemia in patients without type 2 diabetes mellitus*

In clinical trials in overweight or obese patients without type 2 diabetes mellitus treated with Saxenda in combination with diet and exercise, no severe hypoglycaemic events (requiring third party assistance) were reported. Symptoms of hypoglycaemic events were reported by 1.6 % of patients treated with Saxenda and 1.1% of patients treated with placebo; however, these events were not confirmed by blood glucose measurements. The majority of events were mild.

*Hypoglycaemia in patients with type 2 diabetes mellitus*

In a clinical trial in overweight or obese patients with type 2 diabetes mellitus treated with Saxenda in combination with diet and exercise, severe hypoglycaemia (requiring third party assistance) was reported by 0.7% of patients treated with Saxenda and only in patients concomitantly treated with sulfonylurea. Also, in these patients documented symptomatic hypoglycaemia was reported by 43.6% of patients treated with Saxenda and in 27.3% of patients treated with placebo. Among patients not concomitantly treated with sulfonylurea, 15.7% of patients treated with Saxenda and 7.6% of patients treated with placebo reported documented symptomatic hypoglycaemic events (defined as plasma glucose ≤3.9 mmol/L accompanied by symptoms).

*Hypoglycaemia in patients with type 2 diabetes mellitus treated with insulin*

In a clinical trial in overweight or obese patients with type 2 diabetes mellitus treated with insulin and liraglutide 3.0 mg/day in combination with diet and exercise and up to 2 OADs, severe hypoglycaemia (requiring third party assistance) was reported by 1.5% of patients treated with liraglutide 3.0 mg/day. In this trial, documented symptomatic hypoglycaemia (defined as plasma glucose ≤3.9 mmol/L accompanied by symptoms) was reported by 47.2% of patients treated with liraglutide 3.0 mg/day and by 51.8% of patients treated with placebo. Among patients concomitantly treated with sulfonylurea, 60.9% of patients treated with liraglutide 3.0 mg/day and 60.0% of patients treated with placebo reported documented symptomatic hypoglycaemic events.

*Gastrointestinal adverse reactions*

Most episodes of gastrointestinal events were mild to moderate, transient and the majority did not lead to discontinuation of therapy. The reactions usually occurred during the first weeks of treatment and diminished within a few days or weeks on continued treatment.

Patients ≥65 years of age may experience more gastrointestinal effects when treated with Saxenda.

Patients with mild or moderate renal impairment (creatinine clearance ≥30 ml/min) may experience more gastrointestinal effects when treated with Saxenda.

*Acute renal failure*

In patients treated with GLP-1 receptor agonists, there have been reports of acute renal failure. A majority of the reported events occurred in patients who had experienced nausea, vomiting or diarrhoea leading to volume depletion (see section 4.4).

*Allergic reactions*

Few cases of anaphylactic reactions with symptoms such as hypotension, palpitations, dyspnoea and oedema have been reported with marketed use of liraglutide. Anaphylactic reactions may potentially be life threatening. If an anaphylactic reaction is suspected, liraglutide should be discontinued and treatment should not be restarted (see section 4.3).

*Injection site reactions*

Injection site reactions have been reported in patients treated with Saxenda. These reactions were usually mild and transitory and the majority disappeared during continued treatment.

*Tachycardia*

In clinical trials, tachycardia was reported in 0.6% of patients treated with Saxenda and in 0.1% of patients treated with placebo. The majority of events were mild or moderate. Events were isolated and the majority resolved during continued treatment with Saxenda.

Paediatric population

In a clinical trial conducted in adolescents of 12 years to less than 18 years with obesity, 125 patients were exposed to Saxenda for 56 weeks.
Overall, the frequency, type and severity of adverse reactions in the adolescents with obesity were comparable to that observed in the adult population. Vomiting occurred with a 2-fold higher frequency in adolescents compared to adults.
The percentage of patients reporting at least one episode of clinically significant hypoglycaemia was higher with liraglutide (1.6%) compared to placebo (0.8%). No severe hypoglycaemic episodes occurred in the trial.

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 post-marketing use of liraglutide overdoses have been reported up to 72 mg (24 times the recommended dose for weight management). Events reported included severe nausea, severe vomiting 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 an acylated human glucagon-like peptide-1 (GLP-1) analogue with 97% amino acid sequence homology to endogenous human GLP-1. Liraglutide binds to and activates the GLP-1 receptor (GLP-1R).

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-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.

Pharmacodynamic effects