

Regulatory Operations

Insert: 2010-508x462-024
LIFT - Current 1

Professional

Colour:
PMS 280C +
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1. Name of the medicinal product

Saxenda®
6 mg/mL

Solution for injection in pre-filled pen

2. Qualitative and quantitative composition
1 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 the full list of excipients, see section 6.1.

3. Pharmaceutical form
Solution for injection.
Clear and colourless or almost colourless, isotonic solution; pH=8.15.

4. Clinical particulars

4.1 Therapeutic indications

Adults
Saxenda® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of:
• ≥30 kg/m² (obesity), or
• ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment with Saxenda® should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight†.

Adolescents (≥12 years)
Saxenda® can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:
• obesity (BMI corresponding to ≥30 kg/m² for adults by interventional cut-off points)† and
• body weight above 60 kg.

Treatment with Saxenda® should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.
*IOTM BMI cut-off points for obesity by sex between 12–18 years (see table 1).

Table 1 IOTM BMI cut-off points for obesity by sex between 12–18 years

| Age (years) | BMI corresponding to 30 kg/m ² for adults by interventional cut-off points | |
|-------------|---|---------|
| | Males | Females |
| 12 | 26.02 | 26.67 |
| 12.5 | 26.43 | 27.24 |
| 13 | 26.84 | 27.76 |
| 13.5 | 27.25 | 28.20 |
| 14 | 27.63 | 28.57 |
| 14.5 | 27.98 | 28.87 |
| 15 | 28.30 | 29.11 |
| 15.5 | 28.60 | 29.29 |
| 16 | 28.88 | 29.43 |
| 16.5 | 29.14 | 29.56 |
| 17 | 29.41 | 29.69 |
| 17.5 | 29.70 | 29.84 |
| 18 | 30.00 | 30.00 |

4.2 Posology and method of administration

Posology

Adults
The starting dose is 0.6 mg once daily. The dose should be increased to 1.0 mg once daily in increments of 0.6 mg with at least one week intervals to improve gastrointestinal tolerability (see table 2). If escalation to the next dose step is not tolerated for two consecutive weeks, consider discontinuing treatment. Daily doses higher than 3.0 mg are not recommended.

Table 2 Dose escalation schedule

| Dose | Weeks |
|------------------|--------|
| 0.6 mg | 1 |
| 1.2 mg | 1 |
| 1.8 mg | 1 |
| 2.4 mg | 1 |
| Maintenance dose | 3.0 mg |

Adolescents (≥12 years)
For adolescents from the age of 12 to below 18 years old a similar dose escalation schedule as for adults should be applied (see table 2). The dose should be increased until 3.0 mg (maintenance dose) or maximum tolerated dose has been reached. Daily doses higher than 3.0 mg are not recommended.

Missed doses

If a dose is missed within 12 hours from when it is usually taken, the patient should take the dose as soon as possible. If there is less than 12 hours to the next dose, the patient should not take the missed dose and resume the once-daily regimen with the next scheduled dose. An extra dose or increase in dose should not be taken to make up for the missed dose.

Patients with type 2 diabetes mellitus.

Saxenda® should not be used in combination with another GLP-1 receptor agonist. When initiating Saxenda®, it should be considered to reduce the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of insulin or insulin-secretagogues (see section 4.4).

Special populations

Elderly (≥65 years old)
No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited and use in these patients is not recommended (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance ≥30 mL/min). Saxenda® is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) including patients with end-stage renal disease (see sections 4.4, 4.8 and 5.2).

Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Saxenda® is not recommended for use in patients with severe hepatic impairment and should be used cautiously in patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

No dose adjustment is required for adolescents from the age of 12 years and above. The safety and efficacy of Saxenda® in children below 12 years of age has not been established (see section 5.1).

Method of administration

Saxenda® is for subcutaneous use only. It must not be administered intravenously or intramuscularly. Saxenda® is administered once daily at any time, independent of meals. It should be injected in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that Saxenda® 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 liraglutide or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

Patients with heart failure

There is no clinical 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.

Special populations

The safety and efficacy of liraglutide for weight management have not been established in patients:
– aged ≥75 years or more,
– treated with other products for weight management,
– with obesity secondary to endocrinological or eating disorders or to treatment with medicinal products that may cause weight gain, and
– with severe renal impairment.

Use in these patients is not recommended (see section 4.2). As liraglutide for weight management was not investigated in subjects with mild or moderate hepatic impairment, it should be used with caution in these patients (see sections 4.2 and 5.2).

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.

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 (i.e. pancreatitis is suspected, liraglutide should be discontinued; if acute pancreatitis is confirmed, liraglutide should not be restarted).

Cholelithiasis and cholecystitis

In clinical trials for weight management, a higher rate of cholelithiasis and cholecystitis was observed in patients treated with liraglutide than in patients on placebo. The fact that substantial weight loss can increase the risk of cholelithiasis and thereby cholecystitis only partially explained the higher rate with liraglutide. Cholelithiasis and cholecystitis may lead to hospitalisation and cholecystectomy. Patients should be informed of the characteristic symptoms of cholelithiasis and cholecystitis.

Thyroid disease

In clinical trials in type 2 diabetes, thyroid adverse events, such as goitre, have been reported in particular in patients with pre-existing thyroid disease. Liraglutide should therefore be used with caution in patients with thyroid disease.

Heart rate

An increase in heart rate was observed with liraglutide in clinical trials. In clinical trials, heart rate should be monitored at regular intervals consistent with usual clinical practice. Patients should be informed of the symptoms of increased heart rate (palpitations or feelings of a racing heartbeat while at rest). For patients who experience a clinically relevant sustained increase in resting heart rate, treatment with liraglutide should be discontinued.

Dehydration

Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients treated with GLP-1 receptor agonists. 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.

Hypoglycaemia in patients with type 2 diabetes mellitus
Patients with type 2 diabetes mellitus receiving liraglutide in combination with insulin and/or sulfonylurea may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of insulin and/or sulfonylurea.

Paediatric population
Episodes of clinically significant hypoglycaemia have been reported in adolescents (≥12 years) treated with liraglutide. Patients should be informed about the characteristic symptoms of hypoglycaemia and the appropriate actions.

Hypertension in insulin treated patients with diabetes mellitus
In patients with diabetes mellitus Saxenda® must not be used as a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

Excipients

Saxenda® contains less than 1 mmol sodium (23 mg) per dose, therefore the medicinal product is essentially sodium-free†.

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 (CYP) and P-glycoprotein (P-gp). 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.

Interaction studies have been performed with 1.8 mg liraglutide. The effect on rate of gastric emptying was equivalent between liraglutide 1.8 mg and 3.0 mg (paracetamol AUC_{0-12h}). 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 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 International Normalised Ratio (INR) is recommended.

Paracetamol (Acetaminophen)

Liraglutide did not change the overall exposure of paracetamol following a single dose of 1,000 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 following a 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 1.5 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 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% 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 ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Fertility
There are limited 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. If a patient wishes to become pregnant or pregnancy occurs, treatment with liraglutide 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, Saxenda® 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Saxenda® has no or negligible influence on the ability to drive and use machines. However, dizziness can be experienced mainly during the first 3 months of treatment with Saxenda®. Driving or use of machines should be exercised with caution if dizziness occurs.

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 group, adverse reactions are presented in order of decreasing seriousness.

| 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 Dysgeusia | | |
| Cardiac disorders | | | Tachycardia | |
| Gastrointestinal disorders | Nausea Vomiting Diarrhoea Constipation | Dry mouth Dyspeppia Gastritis Gastro-oesophageal reflux disease Abdominal pain Upper Flatulence Erectation Abdominal distension | Pancreatitis*** Delayed gastric emptying**** | |
| Hepatobiliary disorders | | Cholelithiasis*** | Cholecystitis*** | |
| Skin and subcutaneous tissue disorders | | | Urticaria | |
| Renal and urinary disorders | | | | Acute renal failure Renal impairment |
| General disorders and administration site conditions | | | | Malaise |
| Investigations | | Injection site reactions Asthenia Fatigue Increased lipase 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, 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 hypoglycaemic events (requiring third party assistance) were 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®.

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 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.

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: A10BD02

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
Liraglutide lowers body weight in humans mainly through loss of fat mass with relative reductions in visceral fat being greater than for subcutaneous fat loss. Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and hunger signals from the food compartment, thereby reducing food intake. Liraglutide does not increase energy expenditure compared to placebo.

Liraglutide stimulates insulin secretion and lowers glucose secretion in a glucose-dependent manner which results in a lowering of fasting and post-prandial glucose. The glucose-lowering effect is more pronounced in patients with prediabetes and diabetes compared to patients with normoglycaemia. Clinical trials suggest that liraglutide improves and sustains beta-cell function, according to HOMA-B and the proinsulin-to-insulin ratio.

Clinical efficacy and safety
The efficacy and safety of liraglutide for weight management in patients with reduced caloric intake and increased physical activity were studied in four phase 3 randomised, double-blind, placebo-controlled trials which included a total of 5,358 adult patients.

Trial 1 (SCALE Obesity & Pre-Diabetes - 1839): A total of 3,731 patients with obesity (BMI ≥30 kg/m²) and/or overweight (BMI ≥27 kg/m²) with dyslipidaemia and/or hypertension were stratified into overweight or prediabetes status at screening and BMI at baseline (≥30 kg/m² or <30 kg/m²). All 3,731 patients were randomised to 56 weeks of treatment and the 2,254 patients with prediabetes at screening were randomised to 160 weeks of treatment. Both treatment periods were followed by a 12-week off drug/placebo observational follow-up period. Lifestyle intervention in the form of an energy-restricted diet and exercise counseling was background therapy for all patients.

The 56-week part of trial 1 assessed time to onset of type 2 diabetes in the 2,254 randomised patients with prediabetes (1,128 completers). **Trial 2 (SCALE Diabetes- 1922):** A 56-week trial assessing body weight in 846 randomised (628 completers) obese and overweight patients with insufficiently controlled type 2 diabetes mellitus (HbA_{1c} range 7–10%). The background treatment at trial start was either diet and exercise alone, metformin, a sulfonylurea, a glitazone as single agents or any combination thereof.

Trial 3 (SCALE Sleep Apnoea - 3970): A 32-week trial assessing sleep apnoea severity and body weight loss in 359 randomised (276 completers) obese patients with moderate or severe obstructive sleep apnoea. **Trial 4 (SCALE Maintenance - 1923):** A 56-week trial assessing body weight maintenance and weight loss in 422 randomised (305 completers) obese and overweight patients with hypertension or dyslipidaemia after a preceding weight loss of ≥5% induced by a low-calorie diet.

Body weight
Superior weight loss was achieved with liraglutide compared to placebo in obese/overweight patients in all groups studied. Across the trial populations, greater proportions of the patients achieved ≥5% and ≥10% weight loss with liraglutide than with placebo. In the 160-weeks part of trial 1, the weight loss occurred mainly in the first year and was sustained throughout 160 weeks.

• In trial 1, mean change from baseline in body weight at week 56 was -6.4% (-4.4 kg) for liraglutide vs -2.6% (-2.8 kg) for placebo (estimated treatment difference (ETD) (mean change in kg): -5.495%CI [-5.8; -5.0], p<0.0001, ETD (mean change in kg): -5.3%CI [-5.0; -5.1], p<0.0001). The proportion of patients losing 5% and 10% weight loss at week 56 was 63.5% and 32.8% respectively for liraglutide vs 26.6% and 10.1% respectively for placebo (estimated odds ratio (of losing ≥5% body weight): 3.895%CI [4.1; 5.6], p<0.0001, estimated odds ratio (of losing >10% body weight): 4.395%CI [3.5; 5.3], p<0.0001).

• In trial 1, mean change from baseline in body weight at week 160 was -6.2% (-4.5 kg) for liraglutide vs -2.8% (-2.8 kg) for placebo (estimated treatment difference (ETD) (mean change in kg): -4.395%CI [-4.

Liraglutide significantly reduced the rate of major adverse cardiovascular events (primary endpoint events, MACE) vs placebo (3.41 vs 3.90 per 100 patient years of observation in the liraglutide and placebo groups, respectively) with a risk reduction of 13%, HR 0.87, [0.78, 0.97] (95% CI) (p=0.005) (see figure 4).

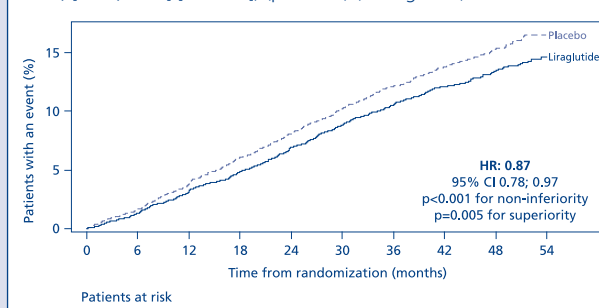


Figure 4 Kaplan Meier plot of time to first MACE - FAS population

In a double-blind trial comparing the efficacy and safety of Saxenda® versus placebo on weight loss in adolescent patients aged 12 years and above with obesity, Saxenda® was superior to placebo in weight reduction (evaluated as BMI Standard Deviation Score) after 56 weeks of treatment (table 4). A greater proportion of the patients achieved ≥5% and ≥10% reductions in BMI with liraglutide than with placebo, as well as greater reductions in mean BMI and body weight (table 4). After 26 weeks of off-trial product follow-up period, weight regain was observed with liraglutide vs placebo (table 4).

Table 4 Trial 4180: Changes from baseline in body weight and BMI at week 56 and change in BMI SDS from week 56 to week 82

| | Saxenda® (N=125) | Placebo (N=126) | Saxenda® vs. placebo |
|---|------------------|-----------------|------------------------|
| BMI SDS | | | |
| Baseline, BMI SDS (SD) | 3.14 (0.65) | 3.20 (0.77) | -0.22* |
| Mean change at week 56 (95% CI) | -0.23 | 0.00 | -0.22* (-0.37; -0.08) |
| Week 56, BMI SDS (SD) | 2.88 (0.94) | 3.14 (0.98) | |
| Mean change from week 56 to week 82, BMI SDS (95% CI) | 0.22 | 0.07 | 0.15** (0.07; 0.23) |
| Body weight | | | |
| Baseline, kg (SD) | 99.3 (19.7) | 102.2 (21.6) | - |
| Mean change at week 56, % (95% CI) | -2.65 | 2.37 | -5.01** (-7.63; -2.39) |
| Mean change at week 56, kg (95% CI) | -2.26 | 2.25 | -4.50** (-7.17; -1.84) |
| BMI | | | |
| Baseline, kg/m ² (SD) | 35.3 (5.1) | 35.8 (5.7) | - |
| Mean change at week 56, % (95% CI) | -1.39 | 0.19 | -1.58** (-2.47; -0.69) |
| Mean change at week 56, kg/m ² (95% CI) | -1.39 | 0.19 | -1.58** (-2.47; -0.69) |
| Proportion of patients with ≥5% reduction in baseline BMI at week 56, % (95% CI) | 43.25 | 18.73 | 3.31** (1.78; 6.16) |
| Proportion of patients with ≥10% reduction in baseline BMI at week 56, % (95% CI) | 26.08 | 8.11 | 4.00** (1.81; 8.83) |

Full Analysis Set. For BMI SDS, body weight and BMI, baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For BMI SDS, value at week 56 are means, changes from week 56 to week 82 are estimated means (least-squares) and treatment contrasts at week 82 are estimated treatment differences. For the proportions of patients losing ≥5%/≥10% baseline BMI, estimated odds ratios are presented. Missing observations were imputed from the placebo arm based on a jump to reference multiple (x100) imputation approach. *p<0.01, **p<0.001, CI=confidence interval, SD=standard deviation. Based on tolerability, 103 patients (82.4%) escalated and remained on dose of 3.0 mg, 11 patients (8.8%) escalated and remained on

dose of 2.4 mg, 4 patients (3.2%) escalated and remained on dose of 1.8 mg, 4 patients (3.2%) escalated and remained on dose of 1.2 mg and 3 patients (2.4%) remained on dose of 0.6 mg. No effects on growth or pubertal development were found after 56 weeks of treatment.

A 16-week double-blind, 36 week open-label study was conducted to evaluate the efficacy and safety of Saxenda® in paediatric patients with Prader-Willi Syndrome and obesity. The study included 32 patients between 12 to <18 years of age (part A) and 24 patients between 6 to <12 years of age (part B). Patients were randomized 2:1 to receive Saxenda® or placebo. Patients with a body weight less than 45 kg started dose escalation at a lower dose, 0.3 mg instead of 0.6 mg and were escalated to a maximum dose of 2.4 mg. The estimated treatment difference in mean BMI SDS at 16 weeks (part A: -0.20 vs -0.13, part B: -0.50 vs -0.44) and 52 weeks (part A: -0.31 vs -0.17, part B: -0.73 vs -0.67) were similar with Saxenda® and placebo.

5.2 Pharmacokinetic concerns
Absorption
The absorption of liraglutide following subcutaneous administration was slow, reaching maximum concentration approximately 11 hours post dosing. The average liraglutide steady state concentration (AUC₀₋₂₄) reached approximately 31 nmol/L in obese (BMI 30-40 kg/m²) patients following administration of 3 mg liraglutide. Liraglutide exposure increased proportionally with dose. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution
The mean apparent volume of distribution after subcutaneous administration is 20-25 L (for a person weighing approximately 100 kg). Liraglutide is extensively bound to plasma protein (>98%).
Biotransformation
During 24 hours following administration of a single [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).

Elimination
Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of 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 liraglutide is approximately 0.9-1.4 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 population pharmacokinetic analysis of data from overweight and obese patients (18 to 82 years). No dosage adjustment is required based on age.

Gender: Based on the results of population pharmacokinetic analysis, females have 24% lower weight adjusted clearance of liraglutide compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.

Ethnic origin: Ethnic origin had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic analysis which included overweight and obese patients of White, Black, Asian and Hispanic/non-Hispanic groups.
Body weight: The exposure of liraglutide decreases with an increase in baseline body weight. The 3.0 mg daily dose of liraglutide provided adequate systemic exposures over the body weight range of 60-234 kg evaluated for exposure response in the clinical trials. Liraglutide exposure was not studied in patients with body weight >234 kg.

Hepatic impairment: The pharmacokinetics of liraglutide was evaluated in patients with varying degree of hepatic impairment in a single-dose trial (0.75 mg). 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 in a single-dose trial (0.75 mg). Liraglutide exposure was lowered by 33%, 14%, 27% and 26%, respectively, 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.

Paediatric population: Pharmacokinetic properties for liraglutide 3.0 mg were assessed in clinical studies for adolescent patients with obesity aged 12 to less than 18 years (134 patients, body weight 62-178 kg).

The liraglutide exposure in adolescents (age 12 to less than 18 years) was similar to that in adults with obesity. Pharmacokinetic properties were also assessed in a clinical pharmacology study in the paediatric population with obesity aged 7-11 years (13 patients, body weight 54-87 kg) respectively. Exposure associated with 3.0 mg liraglutide was found to be comparable between the children aged 7 to 11, adolescents and adults with obesity, after correction for body weight.

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

Non-lethal thyroid C-cell tumours were seen in two-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 liraglutide during mid-gestation caused a reduction in maternal weight and foetal growth with equivalent effects on ribs in rats and skeletal variation in the rabbit. Neonatal growth was reduced in rats while exposed to liraglutide 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. In juvenile rats, liraglutide caused delayed sexual maturation in both males and females at clinical relevant exposures. These delays had no impact upon fertility and reproductive capacity of either sex, or on the ability of the females to maintain pregnancy.

6. Pharmaceutical particulars
6.1 List of excipients
Disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injections.

6.2 Incompatibilities
Substances added to Saxenda® 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
Expiry date is stated on the pen label and carton after 'Expiry'. 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 20°C or store in a refrigerator (2°C-8°C). 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 laminate rubber sheet (bromobutyl/polypropylene) contained in a pre-filled multidose disposable pen made of polypropylene, polyacetal, polycarbonate and acrylonitrile butadiene styrene. Each pen contains 3 mL solution and is able to deliver doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg. Pack sizes of 1, 3 or 5 pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
The solution should not be used if it does not appear clear and colourless or almost colourless. Saxenda® should not be used if it has been frozen. The pen is designed to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm and as thin as 32G. Needles are not included. The patient should be advised to discard the injection needle 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. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Produced by
Novo Nordisk A/S, Novo Allé, DK-2880 Bagsvaerd, Denmark

Instructions on how to use Saxenda® 6 mg/mL solution for injection in pre-filled pen

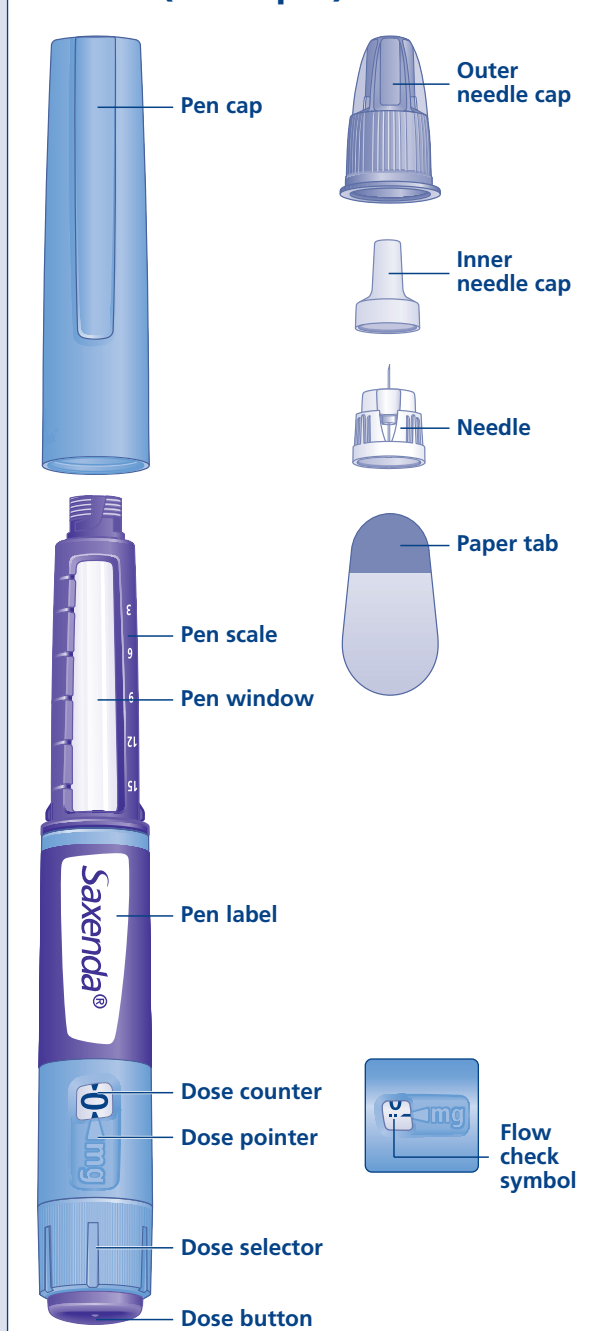
Please read these instructions carefully before using your Saxenda® pre-filled pen. Do not use the pen without proper training from your doctor or nurse.

Start by checking your pen to make sure that it contains Saxenda® 6 mg/mL, then look at the illustrations below to get to know the different parts of your pen and needle.

If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Saxenda® pre-filled pen. Your pen is a pre-filled dial-a-dose pen. It contains 18 mg of liraglutide and delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg. Your pen is designed to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm and as thin as 32G. Needles are not included in the pack.

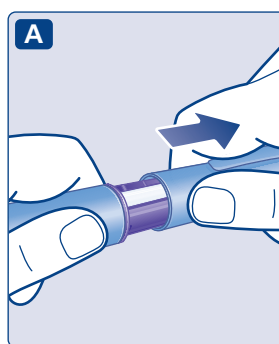
Important information
Pay special attention to these notes as they are important for safe use of the pen.

Saxenda® pre-filled pen and needle (example)

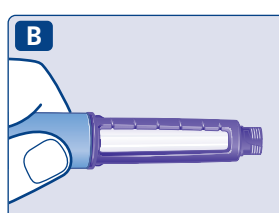


1. Prepare your pen with a new needle

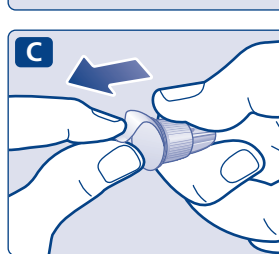
- Check the name and coloured label of your pen, to make sure that it contains Saxenda®. This is especially important if you take more than one type of injectable medicine. Using the wrong medicine could be harmful to your health.
- Pull off the pen cap.



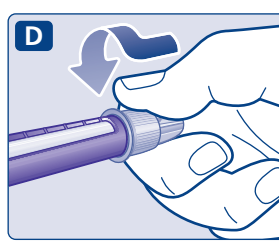
- Check that the solution in your pen is clear and colourless. Look through the pen window. If the solution looks cloudy, do not use the pen.



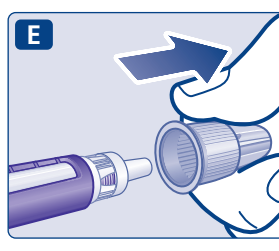
- Take a new needle and tear off the paper tab.



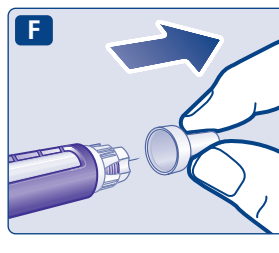
- Push the needle straight onto the pen. Turn until it is on tight.



- Pull off the outer needle cap and keep it for later. You will need it after the injection, to safely remove the needle from the pen.



- Pull off the inner needle cap. If you try to put it back on, you may accidentally stick yourself with the needle. A drop of solution may appear at the needle tip. This is normal, but you must still check the flow if you use a new pen for the first time.



Do not attach a new needle to your pen until you are ready to take your injection.

- Always use a new needle for each injection. This may prevent blocked needles, contamination, infection and inaccurate dosing.

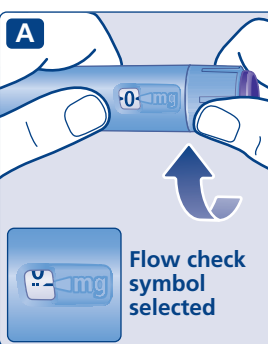
- Never use a bent or damaged needle.

Further important information

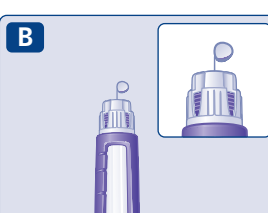
- Always keep your pen and needles out of sight and reach of others, especially children.
- Never share your pen or your needles with other people.
- Caregivers must be very careful when handling used needles to prevent needle injury and cross-infection.

2. Check the flow

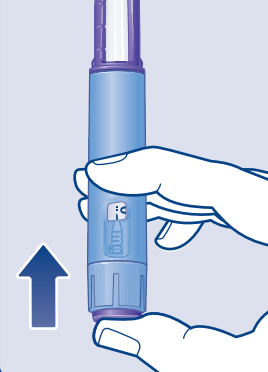
- Before your first injection with each new pen, check the flow. If your pen is already in use, go to step 3 'Select your dose'.
- Turn the dose selector until the dose counter shows the flow check symbol (↔ =).



- Hold the pen with the needle pointing up. Press and hold in the dose counter returns to 0. The 0 must line up with the dose pointer.



- A drop of solution should appear at the needle tip. A small drop may remain at the needle tip, but it will not be injected. If no drop appears, repeat step 2. Check the flow up to 6 times. If there is still no drop, change the needle and repeat step 2. Check the flow once more. If a drop still does not appear, dispose of the pen and use a new one.

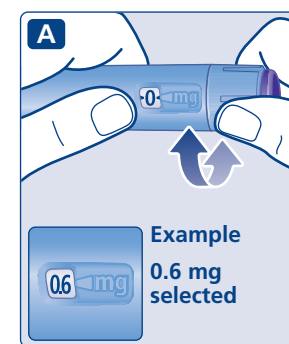


- Always make sure that a drop appears at the needle tip before you use a new pen for the first time. This makes sure that the solution flows. If no drop appears, you will not inject any medicine, even though the dose counter may move. This may indicate a blocked or damaged needle.

If you do not check the flow before your first injection with each new pen, you may not get the prescribed dose and the intended effect of Saxenda®.

3. Select your dose

- Turn the dose selector until the dose counter shows your dose (0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg). If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose. The pen can dial up to a maximum of 3.0 mg.



The dose selector changes the dose. Only the dose counter and dose pointer will show how many mg you select per dose. You can select up to 3.0 mg per dose. When your pen shows less than 3.0 mg the dose counter stops before 3.0 is shown.

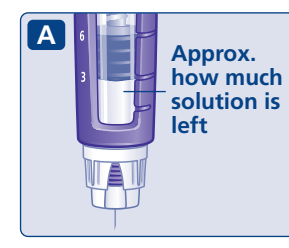
The dose selector clicks differently when turned forwards, backwards or past the number of mg left. Do not count the pen clicks.

- Always use the dose counter and the dose pointer to see how many mg you have selected before injecting this medicine. Do not count the pen clicks. It only shows approximately how much solution is left in your pen.

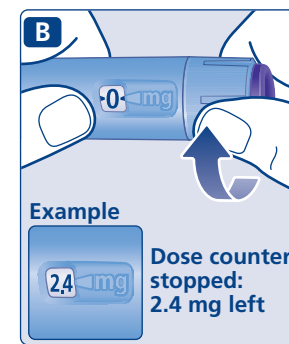
Only doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg must be selected with the dose selector. The selected dose must line up precisely with the dose pointer to ensure that you get a correct dose.

How much solution is left?

- The pen scale shows you approximately how much solution is left in your pen.



- To see precisely how much solution is left, use the dose counter. Turn the dose selector until the dose counter stops.



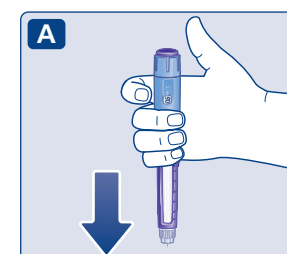
If it shows 3.0, at least 3.0 mg are left in your pen. If the dose counter stops before 3.0 mg, there is not enough solution left for a full dose of 3.0 mg.

If you need more medicine than what is left in your pen Only if trained or advised by your doctor or nurse, you may split your dose between your current pen and a new pen. Use a calculator to plan the doses as instructed by your doctor or nurse.

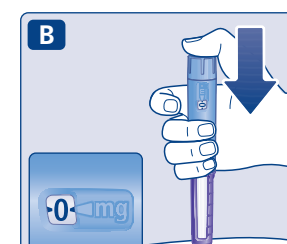
- Be very careful to calculate correctly. If you are not sure how to split your dose using two pens, then select and inject the dose you need with a new pen.

4. Inject your dose

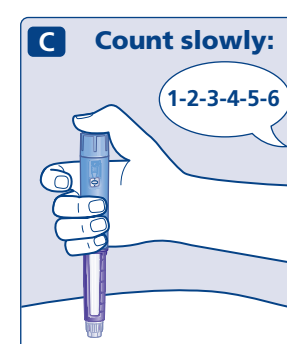
- Insert the needle into your skin as your doctor or nurse has shown you.
- Make sure you can see the dose counter. Do not cover it with your fingers. This could interrupt the injection.



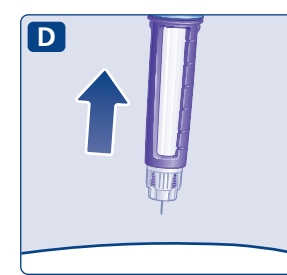
- Press and hold down the dose button until the dose counter shows 0. The 0 must line up with the dose pointer. You may then hear or feel a click.



- Keep the needle in your skin after the dose counter has returned to 0 and count slowly to 6. If the needle is removed earlier, you may see a stream of solution coming from the needle tip. If so, the full dose will not be delivered.



- Remove the needle from your skin. If blood appears at the injection site, press lightly. Do not rub the area. You may see a drop of solution at the needle tip after injecting. This is normal and does not affect your dose.



- Always watch the dose counter to know how many mg you inject. Hold the dose button down until the dose counter shows 0.

- How to identify a blocked or damaged needle? If 0 does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle.

- In this case - you have not received any medicine - even though the dose counter has moved from the original dose that you have set.

How to handle a blocked needle?
Change the needle as described in step 5 'After your injection' and repeat all steps starting with step 1 'Prepare your pen with a new needle'. Make sure you select the full dose you need.

Never touch the dose counter when you inject.
This can interrupt the injection.

Caring for your pen

- Do not leave the pen in a car or other place where it can get too hot or too cold.
- Do not inject Saxenda® which has been frozen. If you do that, you may not get the intended effect of this medicine.
- Do not expose your pen to dust, dirt or liquid.
- Do not wash, soak or lubricate your pen. If necessary, clean it with a mild detergent on a moistened cloth.

- Do not drop your pen or knock it against hard surfaces. If you drop it or suspect a problem, attach a new needle and check the flow before you inject.
- Do not try to refill your pen. Once empty, it must be disposed of.
- Do not try to repair your pen or pull it apart.