Journal of Endocrinology, Metabolism and Diabetes of South Africa 2021; 25(1):8-10

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

PRODUCT FOCUS

Focus on Saxenda® solution for injection

L Lambert

Amayeza Information Services, South Africa
Corresponding author, email: amayeza@amayeza-info.co.za

Introduction

The World Obesity Federation recognises obesity as a "chronic relapsing disease process", defined as having a body mass index (BMI) equal to or greater than 30 kg/m^2 and has been identified as a strong predictor of cardiovascular disease.[1,2] The challenge with weight loss is keeping it off because of changes in appetite-regulating hormones that occur after weight has been lost, leading to increased hunger and decreased satiety.[2]

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue which, by virtue of its mechanism of action, increases satiety and decreases hunger, leading to weight loss.[3]

Saxenda® solution for injection

Each ml of Saxenda® solution for injection contains 6 mg liraglutide, a human GLP-1 that is 97% structurally similar to natural GLP-1.[3]

Indications

Saxenda® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for medically supervised weight loss in adult patients with an initial BMI:[3]

- greater than or equal to 30 kg/m^2 (obese), or
- between 27 kg/m^2 and 30 kg/m^2 (overweight), with at least one weight-related comorbidity such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus [T2DM]), hypertension, dyslipidaemia, or obstructive sleep apnoea.

Dosing and administration

Saxenda® is available as a pre-filled multidose disposable pen. The starting dose of Saxenda® is 0.6 mg subcutaneously once daily at any time, independent of meals. The dose should be increased in increments (to improve gastrointestinal tolerability) of 0.6 mg at weekly intervals to 3.0 mg once daily.[3]

Important dosing considerations[3]

- If escalation to the next dose step is not tolerated for two consecutive weeks, discontinuation of treatment with Saxenda® should be considered.
- The interval between dose increases during dose escalation should not be less than one week.
- Daily doses higher than 3.0 mg are not recommended.

Table I: Dose escalation of Saxenda®[3]

Week 1	Starting dose of 0.6 mg, once daily
Week 2	Increase by 0.6 mg to 1.2 mg, once daily
Week 3	Increase by 0.6 mg to 1.8 mg, once daily
Week 4	Increase by 0.6 mg to 2.4 mg, once daily
Week 5	Increase by 0.6 mg to 3.0 mg, once daily, as the maintenance dose

- Saxenda® must not be administered intravenously or intramuscularly.

Mechanism of action

GLP-1 is a natural hormone that regulates appetite and is released after eating. Liraglutide is structurally similar to natural GLP-1 and works by interacting with GLP-1 receptors present in the brain. Liraglutide stimulates insulin secretion and lowers inappropriately high glucagon secretion in a glucose-dependent manner:

- 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 delay in gastric emptying. Saxenda® works in the hypothalamus, regulating appetite and food intake by increasing satiety and reducing hunger, thereby leading to weight loss through decreased food intake.[3]

Pharmacokinetics

After subcutaneous injection, liraglutide is slowly absorbed, reaching a maximum concentration in approximately 12 hours and has an absolute availability of approximately 15%. This, together with its half-life of 13 hours, makes liraglutide suitable for once-daily dosing.[3,4]

Liraglutide demonstrated a significant weight reduction compared to placebo and orlistat. Patients taking liraglutide lost weight and kept it off during a one-year trial. The benefits of liraglutide extended beyond weight loss by improving blood pressure and lowering the risk of T2DM.[5,6]

Efficacy

The first major phase III trial evaluated liraglutide's efficacy (at four individual doses) against placebo and orlistat (120 mg three times a day). Patients treated with liraglutide lost significantly more weight than patients treated with placebo and orlistat at the end of the 20-week study period.[5]

Table II: Weight loss after 20 weeks[5]

Liraglutide		Placebo	Orlistat
1.2 mg	4.8 kg	2.8 kg	4.1 kg
1.8 mg	5.5 kg		
2.4 mg	6.3 kg		
3.0 mg	7.2 kg		

A two-year extension of this study reported that patients taking liraglutide 3.0 mg lost a mean weight of 5.8 kg at the end of the first year. Furthermore, the prevalence of pre-diabetes and metabolic syndrome were significantly reduced compared to placebo.[5]

The efficacy of liraglutide was further evaluated in clinical trials that formed part of the Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) programme in non-diabetic and diabetic patients. The key results are summarised below:

- **The SCALE maintenance trial** compared the efficacy of liraglutide 3.0 mg with placebo. At the end of 56 weeks, patients in the liraglutide group lost significantly more weight than patients given placebo (6.2% vs 0.2%). A greater proportion of patients treated with liraglutide achieved at least 5% weight loss (50.5% vs 21.8%) and at least 10% weight loss (26.1% vs 6.3%) compared to placebo.[5]
- **The SCALE obesity and pre-diabetes trial** compared the efficacy of liraglutide 3.0 mg with placebo in 3 731 patients.[5]
  - Patients treated with liraglutide had a more significant loss in the mean body weight (8.0% vs 2.6%) than the placebo group.[5]
  - Additionally, a greater proportion of patients treated with liraglutide lost at least 5% (63.2% vs 27.1%) and 10% (33.1% vs 10.6%) of the initial body weight compared to placebo.[5]
  - Patients treated with liraglutide had a reduction in mean waist circumference of 8.2 cm vs 3.9 cm with placebo.[6]
  - Liraglutide also demonstrated significant decreases in mean BMI, waist circumference and blood pressure compared to placebo.[5]
  - The risk of pre-diabetic patients (at baseline) developing T2DM was reduced by 79% with liraglutide.[5]
- **The SCALE diabetes trial** compared the efficacy of liraglutide 3.0 mg, 1.8 mg and placebo.[5]
  - Patients in the liraglutide 3.0 mg, liraglutide 1.8 mg and placebo groups had a mean weight loss of 6.0% (6.4 kg), 4.7% (5.0 kg) and 2.0% (2.2 kg) respectively, at the end of 56 weeks.[5]
- Liraglutide 3.0 mg was also found to reduce apnoea-hypopnoea index (AHI) in patients with a BMI ≥ 30 kg/m^2 unwilling or unable to use continuous positive airway pressure (CPAP) treatment.[5]

Safety

Contraindications[3]

- Hypersensitivity to liraglutide or to any of the excipients contained in Saxenda®.
- Patients using Saxenda® who become or wish to become pregnant should discontinue treatment. Patients should not use Saxenda® while breastfeeding.
- Patients under 18 years of age should not use Saxenda®.

Precautions[3]

Saxenda® must not be used as a substitute for insulin. Saxenda® should be used with caution or avoided in patients:[3]

- with congestive heart failure.
- treated with other products for weight loss.
- with obesity secondary to endocrinological or eating disorders or treatment with medicinal products that may cause weight gain.
- with severe renal or hepatic impairment.
- 75 years and older.

Dehydration: Patients treated with Saxenda® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.[3]

Hypoglycaemia in overweight or obese patients with T2DM has been reported.[3]

Patients with T2DM using Saxenda® in combination with a sulphonylurea have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of the sulphonylurea. Blood glucose levels should be carefully monitored during treatment with Saxenda® in patients with T2DM.[3] Saxenda® should not be used in combination with another GLP-1 receptor agonist.[3]

Drug interactions

Due to the mechanism of action of liraglutide, delayed gastric emptying may affect the metabolism of other medications:[3]

- Patients on warfarin or other coumarin derivatives starting liraglutide require more frequent monitoring of international normalised ratio (INR).
- Liraglutide may affect the pharmacokinetic parameters of certain medications (listed below). However, no dose adjustment is necessary for the concomitant use of:
  - paracetamol
  - atorvastatin
  - griseofulvin
  - digoxin
  - lisinopril

Side effects

Gastrointestinal reactions were the most frequently reported adverse reactions during clinical trials. These include nausea, vomiting, diarrhoea and constipation. During clinical trials, most of these were mild to moderate in severity; nausea was transient and occurred mainly during the first four weeks of treatment, coinciding with dose escalation. Hypoglycaemia was reported more frequently with liraglutide compared to placebo.[3,5]

References

1. Bray GA, Kim KK, Wilding JPH, on behalf of the World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obesity Reviews. 2017;18(7):715-23. https://doi.org/10.1111/obr.12551.
2. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. Int J Obes. 2015;39(8):1188-96. https://doi.org/10.1038/ijo.2015.59.
3. Saxenda® Professional Information. South Africa. March 2020
4. Jacobsen LV, Flint A, Olsen AK, Ingwersen SH. Liraglutide in type 2 diabetes mellitus: clinical pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2016;55(6):657-72. https://doi.org/10.1007/s40262-015-0343-6.
5. Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. Obes Sci Pract. 2017;3(1):3-14. https://doi.org/10.1002/osp4.84.
6. Pi-Sunyer X, Astrup A, Fujioka K, et al; for the SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomised, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373(1):11-22. https://doi.org/10.1056/NEJMoa1411892.