ADVANCE NOTICE: Liraglutide has received a product license for the treatment of obesity but is not yet available in the UK for this indication

MTRAC
Midlands Therapeutics Review and Advisory Committee

On the Horizon: Liraglutide 3.0 mg/day *(Saxenda®▼)*

For the treatment of overweight and obesity

Commissioning considerations:

When making a decision about the use of liraglutide, commissioners may wish to consider the following:

- How the use of liraglutide as an aid to weight loss fits in with local commissioning arrangements for lifestyle weight management services and the need to work closely with local authority commissioners of weight management services.
- The availability of local weight-management clinics and services; in the trials, participants were supported to follow a 500 kcal/day deficit diet and encouraged to increase activity levels. Similar support may be necessary in wider non-trial use to enable the achievement of similar results.
- The agreement of appropriate stopping criteria for patients that do not achieve target weight loss.
- The NICE guideline on the assessment of obesity (CG189), suggested that drug treatment is an option (following diet and lifestyle advice) in people who are obese (Body Mass index, BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with comorbidities (type 2 diabetes, hypertension, cardiovascular disease, osteoarthritis, dyslipidaemia and sleep apnoea).
- The potential increased drug acquisition costs associated with commissioning liraglutide as an aid to weight loss; given the current cost per year of £1,432 for the liraglutide 1.8 mg daily dose as Victoza ®. If the price of liraglutide remains the same, the estimated yearly cost of the liraglutide 3.0 mg/day dose as Saxenda ® would be £2,387 (excluding VAT).
- A potential safety signal relating to an increased incidence of pancreatitis and pancreatic cancer with the use of GLP-1-based therapies exists and is being monitored by the EMA.

Strength of the evidence

The committee considered the evidence for liraglutide to be relatively strong. Four published randomised controlled trials (RCTs) evaluated liraglutide 3.0 mg/day as a weight loss treatment using patient-oriented outcomes, one of the trials including orlistat as an active comparator. The trials were well reported, with a low risk of bias. Limitations of the trials were the low numbers of male participants (29%), the small proportion of participants with a BMI < 30 kg/m^2, and low numbers of patients having experienced long-term use of the treatment e.g. 47 participants in the Astrup trial completed two years of treatment with liraglutide 3.0 mg/day.

Description of technology

Liraglutide 3.0 mg/day has European Medicines Agency (EMA) marketing approval as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial BMI of:

- ≥ 30 kg/m^2 (obese), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea

Liraglutide is administered as a once-daily subcutaneous injection. The recommended starting dose is 0.6 mg daily, increasing to 3.0 mg daily by 0.6 mg/week increments. Treatment with liraglutide 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 (EMA Summary of Product Characteristics). MTRAC guidance on liraglutide 1.8 mg/day for type 2 diabetes is available separately.

Background

In the UK, the prevalence of obesity increased from 13% of men in 1993 to 26% of men in 2013 and from 16% of women in 1993 to 24% of women in 2013.[1] NHS costs attributable to overweight and obesity are projected to reach £9.7 billion by 2050, with wider costs to society estimated to reach £49.9 billion per year.[1]

National guidance on the treatment of obesity focusses on weight loss due to diet and lifestyle interventions. The NICE clinical guideline 189[2] states that orlistat (only current pharmacologic treatment available at the time of publication) should only be available as part of an overall plan for managing obesity in adults who meet one of the following BMI criteria:

- ≥ 28 kg/m^2 with associated risk factors
- ≥ 30 kg/m^2

The prescribing of orlistat therapy should only be continued beyond 3 months if the person has lost at least 5% of their initial body weight since starting drug treatment. Orlistat is also available as a lower 60 mg/day over the counter medicine and can be supplied within the terms of the marketing authorisation to adults over the age of 18 with a BMI ≥ 28 kg/m^2.

Clinical evidence for efficacy and safety

Three peer-reviewed RCTs evaluated liraglutide in participants who were overweight (+ comorbidities) or

obese; a fourth trial evaluated liraglutide in participants with diabetes who were overweight or obese, and data from a trial in sleep apnoea sufferers was available from the European public assessment report for liraglutide[3]. Of the published trials, one active-comparator, 20-week trial compared liraglutide (1.2 to 3.0 mg daily) with placebo or orlistat[4] (120 mg/day) and reported a two-year extension phase[5]. The SCALE obesity & prediabetes trial measured weight loss in 3,731 participants taking liraglutide 3.0 mg or placebo over 56 weeks[6], and the SCALE maintenance trial evaluated liraglutide as a weight loss maintenance treatment over 56 weeks in participants who had achieved ≥ 5% weight loss on a low calorie diet during screening.[7] The SCALE diabetes trial evaluated weight loss over 56 weeks in 846 overweight or obese participants with diabetes taking liraglutide 3.0 mg or 1.8 mg, *vs*. placebo.[8]

Weight loss: significantly greater weight decreases were reported with liraglutide treatment than placebo or orlistat in the three trials that evaluated initial weight loss.[4,6,8] Two-year data from the active comparator trial, showed that participants treated with liraglutide 2.4 mg or 3.0 mg had a mean weight loss of 5.3 kg *vs*. 2.3 kg in orlistat-treated participants ($p < 0.001$).[5] In the 56-week SCALE obesity and prediabetes trial, participants had a mean weight loss of 8.4 kg (8% reduction from baseline) *vs*. 2.8 kg (1.6%) in placebo-treated participants (treatment difference [TD] -5.6 kg [95% CI -6.0 to -5.1]; $p < 0.001$). Proportions of participants losing ≥ 5% weight were 63.2% with liraglutide treatment *vs*. 27.1% with placebo ($p < 0.001$). Weight loss results in the 56-week SCALE diabetes trial were 6.4 kg or 6% (TD *vs*. placebo -4 kg [95% CI -5.1 to -2.0]; $p < 0.001$), 5.0 kg or 4.7% (TD *vs*. placebo -2.71 kg [95% CI -4.0 to -1.42]; $p < 0.001$) and 2.2 kg or 2%, in participants receiving liraglutide 3.0 mg, liraglutide 1.8 mg, or placebo, respectively.

Maintenance of weight loss: The SCALE-maintenance trial evaluated participants who achieved ≥ 5% weight loss during a 4-12 week, low-calorie diet screening period;[7] 422 of 551 participants achieved the target weight loss and were randomised to treatment. The percentage change in weight post-randomisation and the proportions of participants maintaining weight loss were co-primary outcomes. After 56 weeks, liraglutide-treated participants had an additional mean weight loss of 6.2% of randomisation weight *vs.* 0.2% in placebo-treated participants (both groups lost about 6% weight during run in). Significantly more liraglutide than placebo-treated participants maintained the ≥ 5% weight loss achieved during the screening period (81.4% *vs*. 48.9%, $p < 0.0001$).[7]

Cardiometabolic outcomes: the trials all reported significantly greater improvements in waist circumference and systolic blood pressure (SBP) with liraglutide-treated participants *vs*. placebo ($p < 0.05$).[4,6-8] The SCALE obesity and prediabetes trial also reported significantly greater improvement in diastolic BP *vs*. placebo ($p < 0.001$).[6]

The 32-week SCALE-sleep apnoea trial was described in the European Public Assessment report for liraglutide[3]. The population assessed was the same as the other SCALE trials with the additional requirement for moderate or severe sleep apnoea. The main outcome was change from baseline in the hourly rate of apnoea/hypopnoea events (AHI), which decreased by 6 events/hour with liraglutide *vs*. placebo ($p = 0.015$).[3] The difference in weight loss between liraglutide and placebo treatment was 4 kg (95% CI -5.21 to -3.09); $p < 0.001$.

Adverse events

The most common adverse event with liraglutide treatment was nausea, the incidence of which decreased during the first four weeks of treatment. Other common gastrointestinal events were vomiting, constipation and/or diarrhoea.[4,5,7,8]

Pancreatitis risk: the There was one case of acute pancreatitis reported in the Astrup trial[4] and none in the Wadden trial (SCALE-maintenance).[7] The EMA and FDA have not stated any final conclusions about the potential for a causal relationship between incretin-based drugs and pancreatitis, and pancreatitis will continue to be considered a risk associated with these drugs until more data are available.[9]

Considerations for cost impact

- According to 2009 mid-year population estimates for the West Midlands,[10] there are approximately 1.1 million obese adults and 1.6 million overweight adults.

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