Liraglutide

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 18. Medicines for endocrine disorders

ATC codes: A10BJ02

Indication	Obesity ICD11 code: 5B81.Z
INN	Liraglutide
Medicine type	Chemical agent
List type	Core
Formulations	Parenteral > General injections > SC: 6 mg per mL in 3 mL pre-filled pen
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	Medicines within the same pharmacological class can be used
Therapeutic alternatives limitations	Therapeutic alternatives are medicines in the 4th level ATC chemical subgroup: A10BJ Glucagon-like peptide-1 (GLP-1) analogues
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Liraglutide
DrugBank	Liraglutide

Expert Committee recommendation

The Expert Committee noted that the prevalence of overweight and obesity continues to increase in adults and children and has grown to epidemic proportions, with more than 4 million people having died in 2017 because of being overweight or obese according to the Global Burden of Disease Study. Overweight and obesity, as well as their associated noncommunicable diseases such as arterial hypertension, type 2 diabetes, hyperlipidaemia and breathing problems, are largely preventable. The Committee recognized however that when lifestyle modifications such as reduced calorie diet and regular physical activity are not sufficient, people with obesity may require pharmacological or surgical treatments. The Committee noted that GLP-1 receptor agonists have been shown to reduce weight and BMI in the short term compared with placebo. However, evidence about the efficacy in different populations (e.g. with regard to ethnicity and age) is lacking. The optimal duration of treatment has also not been defined since maintenance of weight reduction once the therapy is stopped seems to be rare. Furthermore, to date, it is unclear whether treatment of overweight and obesity with GLP-1 receptor agonists affects long-term clinically important outcomes such as hypertension, hyperglycaemia, osteoarthritis and mortality. The Committee also noted that the use of GLP-1 receptor agonists was associated with an increased frequency of adverse events such as nausea, vomiting, constipation and diarrhoea compared with placebo, although these were usually manageable and self-limiting. The Committee stressed the importance of long-term safety data, which are currently lacking, given the potential need for long-term administration of these medicines to maintain weight loss. The Committee noted that prices of these medicines were currently high and treatments were unlikely to be cost-effective in several regions of the world. The Committee also noted that the current application focused on weight loss in people with obesity,

while GLP-1 receptor agonists are licensed and widely used for the treatment of type 2 diabetes. In that context, the Committee noted that the applicant already proposed to submit a new application in 2025 to evaluate GLP-1 receptor agonists for the treatment of type 2 diabetes. The Expert Committee therefore did not recommend inclusion of GLP-1 receptor agonists to the core list of the EML for weight loss in people with obesity because of uncertain long-term clinical benefit and safety in this population. The Committee noted the advice from the applicants of a planned submission to the 2025 Expert Committee meeting for consideration of GLP-1 receptor agonists for use in the treatment of type 2 diabetes.

Background

Medicines for the treatment of obesity are currently not included on the WHO Model Lists and have not been assessed by previous Expert Committees. In 2017, the Expert Committee considered a review of medicines for second-line therapy for type 2 diabetes, including (but not limited to) GLP-1 receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors, based on an update of the 2013 review by the Canadian Agency for Drugs and Technologies in Health. The Committee did not recommend the inclusion of second-line medicines for type 2 diabetes on the EML and confirmed the role of sulfonylureas as one of the most cost-effective treatments for intensification therapy of type 2 diabetes. However, the Committee noted that SGLT2 inhibitors had shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality. The Committee considered that this finding needed to be confirmed with data from other trials before this class of medicines could be supported for inclusion on the EML (1). In 2021, the Expert Committee reviewed an application presenting new evidence which confirmed the positive effect of SGLT2 inhibitors compared with placebo on all-cause mortality, cardiovascular outcomes (cardiovascular mortality, non-fatal myocardial infarction and hospital admission for unstable angina), renal outcomes (kidney failure, end-stage renal disease and renal death), body weight and haemoglobin A1c (HbA1c). The Committee noted that the situation was less clear when comparing SGLT2 inhibitors with GLP-1 receptor agonists, although the SGLT2 inhibitors seemed to be the preferred option as they were consistently associated with favourable results for most cardiovascular outcomes and were administered orally in contrast to GLP-1 receptor agonists that needed to be injected. For SGLT2 inhibitors, the Committee considered that there was high-quality evidence showing clinically beneficial effects in patients with type 2 diabetes who had not achieved appropriate glycaemic control with metformin or a sulfonylurea, particularly in those at high risk of cardiovascular events and/or diabetic nephropathy, and there was a reasonable safety profile. The Expert Committee therefore recommended the inclusion of SGLT2 inhibitors on the core list of the EML as a second-line therapy. GLP-1 receptor agonists were not recommended for inclusion for second-line therapy for type 2 diabetes at that time (2).

Public health relevance

Obesity is associated with numerous complications such as ischaemic heart disease, stroke, diabetes mellitus, chronic kidney disease, hypertensive heart disease and lower back pain. Obesity is also associated with increased health care-related costs both for society as well as for people with obesity and their families. The overall medical cost due to obesity in adults in the United States was estimated to be US$ 260.6 billion in 2016 (3). Obesity was once considered to be a problem of high-income countries but has now become an increasingly important problem in low- and middle-income countries The global age-standardized prevalence of obesity increased from 0.7% (95% credibility interval (CrI) 0.4% to 1.2%) in 1975 to 5.6% (95% CrI 4.8% to 6.5%) in 2016 in girls aged 5–19 years, and from 0.9% (95% CrI 0.5% to 1.3%) in 1975 to 7.8% (95% CrI 6.7% to 9.1%) in 2016 in boys aged 5–19 years (4). A high prevalence of obesity (> 20%) was not only observed in high-income countries but also in several countries in Polynesia and Micronesia, the Middle East and north Africa, and the Caribbean. Overall, it was estimated that in 2016 more than 1.9 billion adults were overweight, of whom 650 million were obese (i.e. with a body mass index (BMI) of at least 30 kg/m2) (5). The increase in the global prevalence of overweight and obesity has been accompanied by a substantial increase in global deaths attributable to a high BMI (≥ 25 kg/m2) between 1990 and 2017. According to an analysis of the Global Burden of Disease study, the global deaths attributable to high BMI have increased from 1.2 million (95% uncertainty interval (UI) 0.7 to 1.8 million) in 1990 to 2.4 million (95% UI 1.6 to 3.4 million) in 2017 for females, and from 1.0 million (95% UI 0.5 to 1.6 million) in 1990 to 2.3 million (95% UI 1.4 to 3.4 million) in 2017 for males. Over the same time, the global number of high BMI-related disability-adjusted life years (DALYs) has more than doubled for both sexes (6).

Benefits

GLP-1 is one of two main incretin hormones (the other one being gastric inhibitory polypeptide). GLP-1 is secreted by the

gastrointestinal tract on ingestion of glucose or other nutrients. GLP-1 stimulates insulin secretion from pancreatic beta cells and inhibits gastric emptying and release of the hormone glucagon. Liraglutide is a long-acting analogue of GLP 1 and mimics the effects of the naturally occurring hormone, stimulating the secretion of insulin, decreasing glucagon secretion, slowing gastric motility and decreasing appetite via an anorectic effect in the arcuate nucleus of the brain (7). Liraglutide was first approved as a medicine for the treatment of type 2 diabetes in 2009 in Europe and in 2010 in the United States (8). In 2014, the United States Food and Drug Administration approved liraglutide for the treatment of obese adults (BMI ≥ 30 kg/m2) and overweight adults (BMI ≥ 27 kg/m2) with at least one weight related condition. The European Medicines Agency approved a similar indication in 2015. Both regulatory authorities emphasize that liraglutide should be used in addition to a reduced-calorie diet and physical activity. Several phase III studies of liraglutide in the treatment of type 2 diabetes showed that liraglutide treatment was associated with weight loss in diabetic patients (9–12). In these studies, the mean reduction in body weight was 1–3 kg with the 1.2 mg daily dose and 2–3.4 kg with a 1.8 mg daily dose (7). The first study to assess the efficacy of liraglutide for the treatment of obesity in patients without type 2 diabetes was an industry-sponsored randomized, placebo-controlled, double-blind study in 19 sites in eight European countries in 2007 (13). Patients were randomized 1:1:1:1:1:1 to one of four doses of liraglutide (1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg subcutaneously once a day), placebo or open-label orlistat (an orally administered lipase inhibitor). Participants in all groups were also assigned to a 500 kcal energy-deficient diet and an increase in physical activity. The primary outcome was weight change during the 20-week study period. Overall, the group on liraglutide lost significantly more weight than patients in the placebo or orlistat groups, specifically losing on average 2.1 kg (95% confidence interval (CI) 0.6 to 3.6 kg) to 4.4 kg (CI 6.9 to 6.0 kg) more weight than the placebo group. The weight loss experienced with liraglutide was dose dependent with the highest weight loss occurring in the highest dose group (3 mg once a day). A 2022 systematic review and meta-analysis of 12 randomized trials (8249 participants) assessed the efficacy of liraglutide versus placebo on BMI and weight loss in obese adults without diabetes (14). Overall, liraglutide showed a statistically larger effect on BMI (mean difference (MD) −1.45 kg/m2, 95% CI −1.98 to −0.90 kg/m2) and body weight (MD −3.35 kg, 95% CI −4.65 to −2.05 kg) than placebo. Liraglutide also reduced systolic and diastolic blood pressure compared with placebo (MD −3.07 mmHg, 95% CI −3.66 to −2.48 mmHg and MD −1.01 mmHg, 95% CI −1.55 to −0.47 mmHg, respectively). Seven randomized controlled trials were judged to be of high risk of bias and the quality of evidence was assessed as low or very low for most outcomes. Another 2022 systematic review and meta-analysis of 12 randomized trials assessed the effect of GLP-1 receptor agonists (semaglutide 2.4 mg weekly (two trials, 2262 participants); semaglutide 0.05 0.4 mg daily (one trial, 957 participants); liraglutide 3.0 mg daily (five trials, 7306 participants); liraglutide 1.8 mg daily (one trial, 68 participants); exenatide 10 micrograms twice daily (two trials, 193 participants); and efpeglenatide 6 mg weekly (one trial, 295 participants)) on weight loss in obese adults without diabetes (15). The overall MD in weight loss between GLP-1 receptor agonist and control groups was −7.1 kg (95% CI −9.2 to −5.0 kg). Secondary outcomes assessed showed improved glycaemic control without hypoglycaemic events and improved blood pressure and lipid levels (low-density lipoprotein, high-density lipoprotein and triglycerides) with GLP-1 receptor agonists compared with control. Subgroup analyses compared once-weekly semaglutide 2.4 mg with once-daily liraglutide 3 mg. The treatment effect comparison showed greater weight loss with semaglutide (overall MD −12.4 kg, 95% CI −13.2 to −11.5 kg) than with liraglutide (overall MD −5.3 kg, 95% CI −5.9 to −4.7 kg). A 2012 systematic review and meta-analysis of 25 randomized trials assessed the effect on weight loss of GLP-1 receptor agonists compared with placebo, third-generation sulphonylureas, insulin, dipeptidyl peptidase 4 inhibitors, thiazolidinediones, or metformin in overweight and obese adults with and without diabetes (16). The included trials evaluated exenatide 5 to 10 micrograms twice daily (13 trials, 3566 participants), liraglutide 1.2 or 1.8 mg daily (eight trials, 5512 participants) and exenatide 2 mg once weekly (four trials, 1052 participants). Two trials directly compared exenatide twice daily with exenatide once weekly, and one trial directly compared twice daily exenatide with liraglutide. A statistically significant greater weight loss was seen with GLP-1 receptor agonists than in the control groups (weighted MD −2.9 kg, 95% CI −3.6 to −2.2 kg). The mean reduction of body weight for those on a GLP-1 receptor agonist ranged from −7.2 to −0.2 kg. Subgroup analysis showed that weight loss was greater with higher doses of GLP-1 receptor agonists. Weight loss was seen both in patients with diabetes (−2.8 kg, 95% CI −3.4 to −2.3 kg) and without diabetes (−3.2 kg, 95% CI −4.3 to −2.1 kg). Another 2022 systematic review and meta-analysis of 14 randomized trials assessed the efficacy of liraglutide 3 mg compared with placebo in overweight (BMI ≥ 27 kg/m2) and obese (BMI ≥ 30 kg/m2) adult patients (with and without diabetes) (17). Liraglutide therapy resulted in a significant change in body weight from baseline compared with placebo (MD −4.91 kg, 95% CI −5.43 to −4.39 kg) both in patients without diabetes (MD −5.04 kg, 95% CI −5.60 to −4.49 kg) and in those with diabetes (MD −4.14 kg, 95% CI −4.95 to −3.32). Liraglutide therapy also resulted in a significant reduction in waist circumference from baseline in both groups (MD −3.64 cm (95% CI −4.43 to −2.85 cm) in patients without diabetes and −3.11 cm (95% CI −3.88 to −2.34 cm) in patients with diabetes). BMI was also significantly reduced from baseline in the liraglutide group both in patients

without diabetes (MD −1.95 kg/m2, 95% CI −2.22 to −1.68 kg/m2) and in those with diabetes (MD −1.40 kg/m2, (95% CI −1.73 to −1.07 kg/m2). Liraglutide therapy resulted in a higher proportion of patients with a weight loss of at least 5% (risk ratio (RR) 2.23, 95% CI 1.98 to 2.52) or 10% (RR 3.28, 95% CI 2.23 to 4.83) from baseline compared to placebo in patients with or without diabetes. A 2016 systematic review and meta-analysis evaluated the effect on weight loss of five pharmacological treatments approved by the United States Food and Drug Administration (including liraglutide) for obese (BMI > 30 kg/m2) and overweight (BMI > 27 kg/m2) adult patients (18). The review included 28 randomized controlled trials (all considered at high risk of bias) of which three trials (about 4500 participants) assessed the effects of liraglutide: two versus placebo and one versus orlistat, a lipase inhibitor. In the network meta-analysis, compared with placebo, liraglutide was associated with an odds ratio (OR) of 5.54 (95% CrI 4.16 to 7.78) of achieving at least 5% weight loss and OR 4.99 (95% CrI 3.67 to 7.48) of achieving at least 10% weight loss. Among patients treated with liraglutide, a weight loss of at least 5% was achieved in 63% of participants (23% with placebo) and at least 10% in 34% of participants (9% with placebo). Liraglutide was also associated with an excess weight loss compared with placebo of 5.3 kg (95% CrI −6.06 to −4.52 kg). In the direct meta-analysis, liraglutide was associated with higher odds of 5% weight loss compared with placebo (OR 5.09, 95% CI 4.07 to 6.37) and orlistat (OR 3.66, 95% CI 1.79 to 7.46) and higher odds of 10% weight loss compared with placebo (OR 4.36, 95% CI 3.61 to 5.26) and orlistat (OR 3.87, 95% CI 1.65 to 9.04). A 2021 systematic review and meta-analysis of 64 randomized trials (27 018 participants) assessed the effectiveness on weight loss of seven GLP-1 receptor agonists (including liraglutide) compared with placebo in obese or overweight adults with a BMI > 25 kg/m2 (or > 23 kg/m2 in Asian patients) (19). Liraglutide was assessed in 29 of the included trials. Adults with or without diabetes or with non-alcoholic fatty liver disease were included. For liraglutide, the meta-analysis showed a statistically significant greater weight reduction over placebo with liraglutide ≤ 1.8 mg (20 trials) (weighted MD −2.72 kg, 95% CI −3.35 to −2.09 kg) and with liraglutide > 1.8 mg (nine trials) (weighted MD −4.49 kg, 95% CI −5.26 to −3.72 kg). Across all included GLP-1 receptor agonists, treatment with liraglutide > 1.8 mg (and semaglutide 2.4 mg and < 2.4 mg) were associated with the highest weight losses over placebo.

Harms

The safety of liraglutide 3 mg versus placebo was assessed in a 2022 systematic review and meta-analysis in overweight and obese adults with (12 trials) and without (2 trials) type 2 diabetes (17). The safety outcome measures looked at the proportion of adults who experienced adverse events, serious adverse events and treatment discontinuation due to adverse events (TDAEs). Of the 14 studies, 11 included the proportion of participants with adverse events or serious adverse events and five included TDAEs. In adults without diabetes, the pooled estimate of nine studies showed a significantly higher proportion in the liraglutide group experienced adverse events compared with the placebo group (RR 1.11, 95% CI 1.04 to 1.18). For serious adverse events, liraglutide 3.0 mg had a similar risk of compared with placebo (RR 1.12, 95% CI 0.89 to 1.40). Of the five studies including TDAEs, the risk of TDAEs was similar in both treatment groups (RR 1.14, 95% CI 0.50 to 2.60). A 2019 systematic review and meta-analysis of five randomized trials (4754 participants) investigated the safety of liraglutide in obese individuals without diabetes (20). Four trials (4703 participants) reported the proportion of participants who had withdrawn due to adverse events: 202/2972 in the liraglutide group and 36/1731 in the placebo group (OR 2.85, 95% CI 0.84 to 9.62). In addition, nausea was significantly more common in the liraglutide group than the placebo group (1189/2982 and 236/1731 patients, respectively, OR 5.04, 95% CI 3.34 to 7.60). A 2016 systematic review and meta-analysis assessed adverse events of multiple pharmacological treatments for obesity (orlistat, lorcaserin, naltrexone bupropion, phentermine-topiramate or liraglutide) in overweight and obese adults who were being treated for at least 1 year (18). Compared with placebo, liraglutide (OR 2.95, 95% CI 2.11 to 4.23; surface under the cumulative rankings score 0.20) and naltrexone-bupropion (OR 2.64, 95% CI 2.10 to 3.35; surface under the cumulative ranking (SUCRA) score 0.23) had the highest probability of TDAEs. SUCRA scores (from 0 to 1) determined the probability of each agent having the fewest TDAEs, with higher scores indicating a lower probability. A 2021 systematic review and network meta-analysis of 64 randomized trials (27 018 participants) also assessed adverse events of GLP-1 receptor agonists in obese participants (19). Compared with placebo, taspoglutide (relative risk (RR) 3.87 (95% CI 1.44 to 10.35; SUCRA score 15.1) and liraglutide > 1.8 mg (RR 2.32, 95% CI 1.49 to 3.63; SUCRA score 28.3) had the highest probability of TDAEs. SUCRA scores (from 0 to 100) determined the probability of each agent having the fewest TDAEs, with higher scores indicating a lower probability. GLP-1 agonists or analogues were associated with significantly increased risks of nausea (RR 2.75, 95% CI 2.44 to 3.09) and vomiting (RR 3.22, 95% CI 2.74 to 3.78).

Cost / cost effectiveness

Several studies on the cost–effectiveness of liraglutide and semaglutide for the treatment of obesity are available. This literature

is, however, smaller than the literature examining the cost–effectiveness of GLP-1 receptor agonists for the treatment of type 2 diabetes. Furthermore, the available cost–effectiveness analyses are limited to high-income countries. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) published a technology appraisal of liraglutide for managing obesity, focusing on the subgroup of patients with BMI ≥ 35 kg/m2, prediabetes (non-diabetic hyperglycaemia) and a high risk of cardiovascular disease (21). At the chosen threshold of £20 000 per quality-adjusted life year (QALY) gained, the report concluded that liraglutide was cost-effective for the management of obesity. Specifically, the base-case incremental cost–effectiveness ratio for liraglutide plus diet and exercise compared with diet and exercise alone was £13 569 per QALY gained. NICE also published a technology appraisal on semaglutide for managing obesity (22). For the population of people with a BMI ≥ 30 kg/m2 with at least one weight-related comorbidity, the base-case incremental cost–effectiveness ratio for semaglutide plus diet and exercise was £16 337 per QALY gained compared to diet and exercise alone. In comparison with liraglutide, the base-case incremental cost–effectiveness ratio was £600 per QALY gained. A report by the Canadian Agency for Drugs and Technologies in Health (CADTH) found that compared with standard care, the incremental cost–effectiveness ratio for liraglutide compared with diet and exercise was Can$ 196 876 per QALY gained, and that the price of liraglutide would need to decrease by at least 62% to achieve cost–effectiveness at a Can$ 50 000 per QALY threshold (23). In the United States context, the Institute for Clinical and Economic Review published a report on the effectiveness and value of medications for obesity management (24). The report concluded that prices would need to decrease for semaglutide and liraglutide to meet cost–effectiveness benchmarks. Specifically, to achieve incremental cost–effectiveness ratios between US$ 100 000 and US$ 150 000 per QALY or equal value life year gained, the health-benefit price benchmark range for semaglutide would require a discount of 28-45% from the current wholesale acquisition cost. A cost–effectiveness analysis of GLP-1 receptor agonists for treatment of obesity in a United States setting, using a willingness-to-pay threshold of US$ 195 000 found that exenatide, dulaglutide and semaglutide were not cost-effective (25). Compared with exenatide as the reference strategy, semaglutide was the most cost-effective strategy with an incremental cost–effectiveness ratios of US$ 135 467 per QALY gained. A manufacturer-sponsored cost–effectiveness analysis reported that semaglutide 2.4 mg was cost-effective at a willingness-to-pay threshold of US$ 150 000 compared with no treatment, diet and exercise alone, and other anti-obesity medicines (liraglutide 3 mg, phentermine-topiramate and naltrexone-bupropion) over a 30-year time horizon, with the incremental cost per QALY gained ranging from US$ 23 556 to US$ 144 296 (26). Cost–effectiveness studies to date have been based on prices of the branded product without generic competition. Patents for liraglutide have begun to expire (see section on availability) and biosimilar versions of liraglutide are expected to lead to price reductions and improve cost–effectiveness.

WHO guidelines

WHO guidelines for the management of overweight and obesity are not currently available.

Availability

Liraglutide has been approved by the United States Food and Drug Administration as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. As of the date of the application at the end of 2022, liraglutide was also available in Canada, Denmark, France, Germany, Indonesia, Italy, Japan, Malaysia, the Netherlands (Kingdom of the), Singapore, Sweden, and the United States. According to a report released by the manufacturer, the drug compound patent for liraglutide has expired in China and Japan as of February 2022 and is set to expire in 2023 in the United States and Germany. The manufacturer reports that generic versions of liraglutide could be available in the United States from June 2024 (27).

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