A.18	Glucagon-like peptide-1 receptor agonists – weight loss in obesity – EML
Draft recommendation	☐ Recommended ☒ Not recommended **Justification:** Obesity is a long-term condition like hypertension and diabetes. Currently, little is known as to the optimal duration of treatment. A short treatment duration would not be suitable to address the clinical need to reduce weight and maintain it. Moreover, the majority of patients will regain weight after the drug is discontinued or develop a weight loss plateau after a few years. In most studies, liraglutide has been compared with a placebo and orlistat. There is little evidence about its effectiveness in comparison to other pharmacological agents licensed for treatment of obesity. The safety and efficacy of co-administration of liraglutide with other weight loss agents have not been studied as yet. Gastrointestinal adverse events are quite commonly observed with liraglutide, therefore it may not be suitable for all patients. In an everyday obesity care setting, achievements with liraglutide may clash with confounding factors (comorbidities, other drugs etc). Practical difficulties like storage of medication and injectable mode of delivery may limit patients' compliance with liraglutide. Adherence to treatment will also be challenged due to patients' expectations of a 'quick fix' for such a chronic condition.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable **Comments:** Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. The worldwide prevalence of obesity nearly tripled between 1975 and 2016.In 2019, an estimated 38.2 million children under the age of 5 years were overweight or obese. Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings. In Africa, the number of overweight children under 5 has increased by nearly 24% percent since 2000. Almost half of the children under 5 who were overweight or obese in 2019 lived in Asia. Obesity impacts an individual's health by increasing complications such as prediabetes, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, metabolic syndrome, cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), cancers (eg endometrial), and obstructive sleep apnea (OSA).

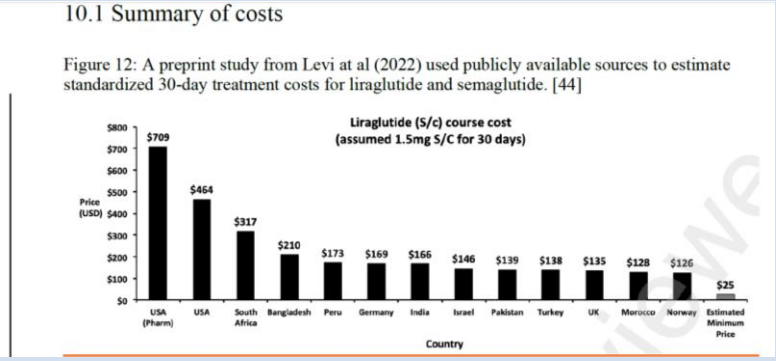
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☒ No ☐ Not applicable **Comments**: Further studies are needed in large and diverse populations with varying race/ethnicities to establish the long-term effectiveness of liraglutide, as currently the appropriate duration for which patients need treatment is not well established. Currently, little is known as to the optimal duration of treatment. In most studies, liraglutide has been compared with a placebo and orlistat. There is little evidence about its effectiveness in comparison to other pharmacological agents licensed for treatment of obesity. The safety and efficacy of co-administration of liraglutide with other weight loss agents have not been studied as yet. NICE also suggested that liraglutide for weight management should be prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service. NICE didn't recommend for its use in the full population covered by the marketing authorisation as evidence provided by the company (Novo Nordisk) was only for people with BMI ≥35kg/m2 with prediabetes and high risk for CVD.18 The Scottish Medicines Consortium (SMC) has not recommended the use of liraglutide for the management of obesity in NHS Scotland as yet. Several studies were conducted in a large population of subjects with diabetes to evaluate liraglutide as a treatment for diabetes and found that it improved glycemic control and produced significant body weight loss.[1] Liraglutide was firstly approved for the treatment of diabetes, and several studies were then conducted to evaluate it as a therapy for obesity. The 56 weeks SCALE Diabetes trial which included 846 participants with body mass index of 27 or greater demonstrated that both the 3.0 and 1.8 mg subcutaneous doses of liraglutide performed better than placebo, with percentage body weight reduction of 6%, 5% and 2%, respectively. A total of 50% of individuals on 3.0 mg liraglutide showed ≥5.0% of body weight reduction, compared with 36% in individuals on the lower dose and 14% on the placebo. A total of 23%, 14% and 4% of participants lost >10% body weight in the three arms, respectively.[2] The SCALE Obesity and Prediabetes trial involving 3731 patients showed that the once-daily subcutaneous dose of 3.0 mg liraglutide, when **used as an adjunct** to a reduced-calorie diet and increased physical activity, was associated with significant weight reduction in adult with overweight or obesity who did not have diabetes. The response to liraglutide was similar in subjects with prediabetes versus one without prediabetes, and was similar across baseline Body mass index (BMI) categories. The mean weight change with liraglutide was 8 kg and was generally maintained for 1 year, **as long as the patients continued treatment** and weight regain usually follows after treatment discontinuation.[3]

[1] Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013;381(9861):117–124. doi:10.1016/S0140-6736(12)61267-7

[2] Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA. 2015;314(7):687–699. doi:10.1001/jama.2015.9676

[3] Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373(1):11–22. doi:10.1056/NEJMoa1411892

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable **Comments:** The only strict contraindications to liraglutide are prior serious hypersensitivity to liraglutide, a personal or family history of medullary thyroid cancer, a personal history of multiple endocrine neoplasia syndrome type 2 (MEN2), and pregnancy.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable **Comments:** Side effects of liraglutide include hypoglycemia (in 2% of adults without T2DM and 13-28% in adults with other treatment for T2DM), increased heart rate of >10 beats per minute (34%), local injection site reactions (1-14%) and most commonly, GI disturbance. The most common side effect is nausea (39-42%) followed by diarrhea (21-22%).
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable **Comments:** In most clinical trials, gastrointestinal adverse effects were observed among participants receiving liraglutide, therefore initiation, maintenance and dose titration should be carefully supervised at frequent intervals and added caution should be utilised in patients with a previous history of gastroparesis, pancreatitis and renal impairment. When a patient is initiated on liraglutide, heart rate, renal function, plasma glucose, a lipid panel, signs of pancreatitis and gall bladder disease, signs of worsening depression, and body weight should be checked. Follow up body weight at the twelve and sixteen week mark should also be checked to determine continuity of the medication.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☐ No ☐ Not applicable **Comments:** Liraglutide is expensive.  A report by the Canadian Agency for Drugs and Technologies in Health (CADTH) found that compared to standard care, the ICER for liraglutide was $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 $50,000 per QALY threshold. In the US context, the Institute for Clinical and Economic Review released a report on the effectiveness and value of medications for obesity management in October 2022. The report concluded that U.S. prices would need to decrease for semaglutide and liraglutide to meet costeffectiveness benchmarks. Specifically, to achieve ICERs between $100,000 and $150,000 perQALY or evLY gained, the health-benefit price benchmark range for semaglutide was estimated as $7500 - $9800 per year, which would require a discount of 28-45% from the current US net price. NICE concluded that liraglutide is cost-effective for the management of obesity. Specifically, the ICER for liraglutide plus diet and exercise compared with diet and exercise alone was £11,293- £13,569 per QALY gained. NICE also published a report on semaglutide for obesity treatment in June 2022. For the population of people with a BMI of 30 or higher with at least one weight-related comorbidity, semaglutide was cost-effective with an ICER estimated at £14,827- £16,337 per QALY gained.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable **Comments:** Available in U.S.; Canada; UK; Germany; France; Italy; Spain; Australia; China; Japan; South Korea; Brazil; Mexico; Argentina; South Africa; Saudi Arabia; Denmark; the Netherlands; Sweden; Indonesia, Malaysia and Singapore. Generic versions of liraglutide could be available in the United States from June 2024
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: