A.18	Glucagon-like peptide-1 receptor agonists – weight loss in obesity – EML
Draft recommendation	☐ Recommended ☒ Not recommended Justification: Although the body of evidence suggest that liraglutide and other GLP-1 RAs probably results in a reduction in BMI, weight, and more weight loss when compared to placebo, the clinical meaningfulness of these reductions on weight loss are still uncertain. Furthermore, there is still a paucity of evidence regarding its effects on other clinically important outcomes such as the development of hypertension, T2DM, osteoarthritis, cardiovascular effects, etc. The use of GLP-1 RA present also more frequency of adverse events, although these are usually manageable and self-limited. The price and ICER calculated for these medications may still be considered above the ICER thresholds of some countries.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Obesity is a condition with high-cost consequences, a health burden, and the indirect cause of other ailments such as cardiovascular disease, diabetes type 2, among other non-communicable diseases around the world. Overall, 39% of adults over the age of 18 were overweight with 13% of adults considered to be obese. The number of global deaths attributed to BMI has substantially increased from 1990 to 2017.
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: The body of evidence on the treatment of obesity with glucagon-like peptide 1 receptor antagonists (GLP-1 RAs) consists of several systematic reviews of RCTs. One review from 2022 with more than 7300 patients concludes that liraglutide may reduce BMI by a mean difference -1.45 (95% confidence interval (CI), -1.98 to -0.9) and may reduce body weight by 3.35 kg fewer (95% CI 4.65 fewer to 2.05 fewer). A second review (11,400 participants) included liraglutide, semaglutide, efpeglenatide, and exenatide, suggests that these interventions may improve weight loss as compared to control groups (by 7.1 kg fewer [95%CI from 9.2 fewer to 5.0 fewer]). A third review showed a difference of 3.2 fewer kg, 95% CI 4.3 fewer to 2.1 fewer with liraglutide. Overall, these bodies of evidence had some limitations due to risk of bias in some of the included studies and concerns of heterogeneity, hence the certainty was deemed low to moderate.

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: Several syntheses have looked at the harm outcome measures among patients using liraglutide. The first, with 11 studies in nondiabetic patients, the pooled estimate of nine studies revealed a significant proportion of patients experiencing adverse events in the liraglutide 3.0 mg group (RR = 1.11, 95% CI= 1.04 to 1.18) when compared to placebo. For serious adverse events, liraglutide 3.0 mg had a similar risk of compared to placebo (RR = 1.12, 95% CI = 0.89 to 1.40). Another review shows discontinuations due to AEs with OR 2.85 (95% CI= 0.84 to 9.62) and nausea events (OR 5.04, 95% CI =3.34 to 7.6). Overall, the body of evidence suggests that liraglutide may increase the number of adverse events and discontinuations due to adverse events, although these are generally self-limited and manageable.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Hypoglycemia and neoplasms are mentioned as adverse events of special interest to follow and monitor in patients receiving this therapy.
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: This treatment might require clinicians or health professionals with expertise in the treatment and monitoring of patients with obesity.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: In Canada, the ICER for liraglutide is calculated at $196,876 CAD per QALY gained. In other countries the situation is similar, for example, in the UK is at £14,827-£16,337 per QALY gained, and $135,467 USD in the US. All these ICER seem plausible to be above most countries ICER thresholds (around 50,000 USD).
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: The manufacturer reports that 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: Not found in the current repository of WHO clinical guidelines