A.14 Glucagon-like peptide-1 receptor agonists – obesity – EML

Reviewer summary	☐ Supportive of the proposal ☒ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Obesity is a significant public health challenge with substantial implications for health systems and society. However, according to the World Obesity Atlas, by 2035, it is anticipated that 79% of adults and 88% of children with overweight and obesity will reside in low- and middle-income countries (LMICs). Although GLP-1 receptor agonists have been shown to reduce weight and BMI, the majority of included studies were at high risk of bias due to deviations from the intended interventions and missing outcome data, as well as measurement issues related to outcomes of adverse events. Effect on long-term outcomes such as mortality, non-fatal MI and non-fatal stroke is still comparable with life-style modification alone. The evidence of effectiveness is only from one trial (SELECT trial). The cost is still very high even compare to surgical options. Class listing (square-boxing using EML jargon) is also not quite appropriate because at least two/three of the drugs in the class (beinaglutide, dulaglutide and exenetide) show no better results compare to life-style modification alone.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**) There are currently no medications included on the Essential Medicines List for obesity management.	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) Shown effectiveness on percentages of body weight change, absolute waist circumference change, body weight reduction up to ≥20% (tirzepatide, semaglutide, liraglutide and orforglipron), percentage mean fat changes and QOL. Median proportion of females included was 69%. The majority of included studies were at high risk of bias due to deviations from the intended interventions and missing outcome data, as well as measurement issues related to outcomes of adverse events. Effect on long-term outcomes such as mortality, non-fatal MI and non-fatal stroke is still comparable with life-style modification alone. The evidence of effectiveness is only from one trial (SELECT trial).	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) AEs include GI, gall-bladder, biliary tract disorders and fatigue. Those with better effectiveness have higher risk of AEs. Liraglutide (high certainty), oral semaglutide (moderate certainty), subcutaneous	☐ Yes ☒ No ☐ Not applicable

semaglutide (high certainty) and tirzepatide (moderate certainty) all increased the risk of discontinuation due to AEs. Low or very low certainty evidence existed for other GLP-1 receptor analogues. Higher risk but non-significant AEs include Erectile dysfunction, pancreatitis, thyroid cancer, suicidal.	
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? Inadequate evidence for effectiveness for long-term outcomes and higher risk for AEs in the long-term.	☐ Yes ☒ No ☐ Not applicable
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) When initiating or adjusting GLP-1 receptor agonists, measurement of serum creatinine and estimated glomerular filtration rate should be considered to evaluate kidney function. Baseline and serial monitoring of HbA1c and other glycemic parameters should be considered. No other close diagnostic work-up or monitoring is warranted. Treatment may be self-administered by patients in the community and does not require specific healthcare personnel or medical setting.	☐ Yes ☒ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? According to the World Obesity Atlas, by 2035, it is anticipated that 79% of adults and 88% of children with overweight and obesity will reside in low- and middle-income countries (LMICs). The cost is still very high even compare to surgical options.	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) Semaglutide has widespread market availability in North America, Europe, Asia, and Australia. Liraglutide is widely available in North America, Europe, and parts of Asia. However Semaglutide (2032), Liraglutide (2026) and Tirzepatide (2030) are all still under patent protection.	☐ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval? Subcutaneous semaglutide was approved by the United States Food and Drug Administration (FDA) in June 2021 for chronic weight management and is indicated for a body mass index of 30 kg/m² or higher; or a body mass index of 27 kg/m² or higher (overweight) with at least one weight-related condition (e.g., hypertension, type 2 diabetes, dyslipidemia, or obstructive sleep apnea. Liraglutide was approved by the FDA in December 2014 for chronic weight management with similar criteria.	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable