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. According to WHO, in 2022, 1 in 8 people globally were living with obesity, cutting across LMIC to HIC (with LMIC projected to report more (79%) by 2023. The economic impact of obesity is profound, representing about 2.8% GDP (2 T USD). Obesity-related comorbidities add to its public health relevance. There convincing data in support of benefits over harms, overall health outcomes (including co-morbidities), and cost-effectiveness. This is clearly so for Semaglutide subcut, Semaglutide oral, Tirzepatide, and Liraglutide. Availability of medicines is currently mostly in high income settings. An inclusion in EML would facilitate access in other settings. I am supportive of the proposal for Semaglutide subcut, Semaglutide oral, Tirzepatide, and Liraglutide.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (https://list.essentialmeds.org/) An application submitted in 2023 (for Liraglutide) was not favourable; due to uncertain long-term clinical benefit (including on non-weight loss outcomes) and safety; the Committee also noted high prices and uncertainty regarding international cost-effectiveness. The current application has met tis gap (to an extent).	☒ 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;) **There is adequate evidence on effectiveness (moderate to high) of the representative medicine (semaglutide subcutaneous) but also for other square boxed medicines (Semaglutide (oral), Tirzepartide, and Liraglutide) (as shown in table below and GRADE analysis). Other medicines were not so promising (Exenatide, Beinaglutide, and Dulaglutide) and life style modifications are more promising.**	☒ Yes ☐ No ☐ Not applicable

Interventions	Percent bodyweight change from baseline, MD (95%CI)	Participants with bodyweight reduction ≥ 5%, RR (95%CI)	Participants with bodyweight reduction ≥ 10%, RR (95%CI)	Participants with bodyweight reduction ≥ 15%, RR (95%CI)	Participants with bodyweight reduction ≥ 20%, RR (95%CI)	Absolute waist circumference change from baseline, MD (95%CI)	Quality-of-life score, SMD (95% CI)	Percent fat mass change from baseline, MD (95%CI)	Percent lean mass change from baseline, MD (95%CI)	Discontinuations due, adverse events, RR (95%CI)	Participants with,total gastrointestinal events, IRR (95%CI)	Participants with gallbladder-related disorders, RR (95%CI)	Participants with fatigue, RR (95%CI)
Tirzepatide	**-15.15 (-16.28, -14.03)**	**3.34 (2.78, 4.03)**	**6.98 (5.39, 9.04)**	**16.69 (11.06, 25.15)**	**21.47 (15.21, 30.31)**	**-11.58 (-13.02, -10.13)**	**0.45 (0.24, 0.65)**	**-25.70 (-31.53, -19.87)**	**-8.30 (-12.45, -4.15)**	**1.91 (1.41, 2.58)**	**3.08 (2.49, 3.81)**	1.71 (0.81, 3.61)	**2.09 (1.09, 4.01)**
Semaglutide (oral)	**-12.70 (-15.89, -9.51)**	**3.53 (2.12, 5.88)**	**6.27 (3.21, 12.23)**	**9.31 (3.44, 25.14)**	**12.45 (6.18, 25.08)**	**-10.00 (-13.42, -6.58)**	**0.56 (0.17, 0.95)**	—	—	1.63 (0.72, 3.70)	**2.96 (1.65, 5.32)**	**3.24 (1.07, 9.84)**	**2.39 (1.16, 4.93)**
Semaglutide (subcutaneous)	**-8.48 (-10.24, -6.72)**	**2.60 (2.28, 2.95)**	**5.11 (4.26, 6.13)**	**7.72 (5.79, 10.29)**	**16.10 (13.10, 19.79)**	**-7.71 (-8.66, -6.75)**	**0.28 (0.13, 0.42)**	**-18.63 (-24.21, -13.05)**	**-7.57 (-11.57, -3.57)**	**1.88 (1.51, 2.33)**	**2.78 (2.35, 3.29)**	**1.24 (1.05, 1.46)**	**1.83 (1.41, 2.39)**
Liraglutide	**-4.96 (-5.64, -4.28)**	**2.28 (1.98, 2.61)**	**3.06 (2.47, 3.78)**	**3.03 (2.10, 4.36)**	**2.50 (1.66, 3.76)**	**-3.22 (-4.07, -2.36)**	**0.28 (0.09, 0.48)**	**-7.99 (-11.30, 4.67)**	**-1.89 (-3.70, -0.09)**	**2.43 (1.91, 3.08)**	**2.82 (2.45, 3.25)**	**2.20 (1.23, 3.94)**	**1.58 (1.27, 1.97)**
Exenatide	**-3.58 (-4.78, -2.37)**	**1.86 (1.18, 2.93)**	2.09 (0.90, 4.86)	1.38 (0.06, 31.51)	4.81 (0.14, 168.82)	**-3.63 (-5.60, -1.65)**	—	-4.19 (-11.07, 2.69)	-2.18 (-7.65, 3.30)	1.28 (0.57, 2.87)	**1.79 (1.26, 2.55)**	—	0.79 (0.02, 33.24)
Beinaglutide	**-3.27 (-5.67, -0.87)**	**2.29 (1.31, 4.00)**	**4.19 (1.61, 10.91)**	**6.12 (1.15, 32.58)**	5.39 (0.30, 96.83)	-1.09 (-3.47, 1.29)	—	—	—	5.32 (0.87, 32.41)	**1.77 (1.03, 3.06)**	—	2.66 (0.85, 8.27)
Dulaglutide	-1.38 (-3.81, 1.06)	0.71 (0.28, 1.82)	0.35 (0.13, 0.91)	0.30 (0.05, 1.80)	0.43 (0.05, 3.35)	-1.80 (-4.51, 0.90)	—	—	—	1.02 (0.44, 2.40)	1.64 (0.97, 2.79)	0.34 (0.02, 7.80)	0.30 (0.01, 6.18)
Lifestyle modification alone	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference

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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;) There exists adequate evidence for safety and harms (from 184 studies). Most harms are no more than in life-style changes. Tirzepatide, semaglutide subcutaneous, and Liraglutide however reported more GI related events than lifestyle changes.	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? **Tirzepatide, semaglutide (oral), semaglutide (subcutaneous), and Liraglutide provide a meaningful and favorable balance of benefits to harms.**	☒ 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) No	☐ Yes ☒ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? 1. **Cost Implications: Semaglutide offers greater health benefits but incurs higher costs compared to conventional interventions like diet and exercise (D&E) and some surgical options. Tirzepatide, though it offers greater health benefits in terms of weight loss and potential for substantial health benefits, has limited cost effectiveness.** 2. **Economic Models: Incremental cost-effectiveness ratios (ICERs) often exceed willingness-to-pay (WTP) thresholds, especially in comparisons with surgical interventions** 3. **Research Gaps: There is limited data on long-term cost-effectiveness and outcomes in diverse populations**	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) **GLP-1 RAs are more accessible in high-income countries (HICs) with established pharmaceutical distribution systems and coverage through insurance or public health. In LMICs (Low- and Middle-Income Countries), limited access may be due to:** • **High cost** • **Limited health insurance coverage** • **Lack of regulatory approvals or registration** • **Low prioritization for type 2 diabetes management compared to other pressing health needs**	☐ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval? **All 3 promising medicines remain under patent protection in the US and Europe (unclear what is the status in other regions). Patent expires in 2026 for Liraglutide, 2030 for Tirzepatide, and 2032 for semaglutide.**	☒ Yes, for the proposed indication ☒ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable