A.15 Glucagon-like peptide-1 receptor agonists – type 2 diabetes – EML

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Overall, GLP-1 receptor agonists have a favorable and meaningful balance of benefits to harm. Robust evidence shows clear long-term benefits in patients- important outcomes.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☒ 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 robust, high-quality evidence from large randomized controlled trials and meta-analyses supporting the effectiveness of GLP-1 RAs (mainly semaglutide) for the treatment of T2DM with established or high-risk CVD. • The GLP-1 RAs, especially semaglutide, reduce major adverse cardiovascular events (MACE), stroke, and composite kidney events. • Benefits have also been seen in in reducing HbA1c, body weight, and improving cardiovascular outcomes. • In patients with high cardiovascular risk, semaglutide, liraglutide, and others significantly reduced all-cause mortality and cardiovascular death.	☒ 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;) Available evidence shows that while GLP-1 RAs have known and manageable adverse effects, their safety profile is well-characterized and generally favorable. Unfortunately, there is limited information regarding potential side effects associated with extended use. Common adverse events of GLP-1 RAs include: • Gastrointestinal side effects (nausea, vomiting, diarrhea), which are usually dose-dependent and tend to improve over time. • Low risk of hypoglycemia Serious but rare risks include: • Potential increased risk of medullary thyroid carcinoma (seen in rodents but not confirmed in humans), so caution is recommended in individuals with a personal or family history of medullary thyroid cancer. • Acute pancreatitis was a concern. Large trials have not confirmed a strong link. • Semaglutide has been associated with increased odds of diabetic retinopathy.	☒ Yes ☐ No ☐ Not applicable

25th WHO Expert Committee on Selection and Use of Essential Medicines
Expert review

Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? GLP-1 receptor agonists have a favorable and meaningful balance of benefits to harm. The cardiovascular and glycemic benefits significantly outweigh the risks, particularly in patients with type 2 diabetes and established or high risk of cardiovascular disease.	☒ 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) Monitoring and adjustment: • Monitor for gastrointestinal side effects (nausea, vomiting) especially during dose escalation. • Monitor for signs of diabetic retinopathy progression, especially in patients with pre-existing retinopathy. • Monitor for hypoglycemia when used in combination with insulin or sulfonylureas. Training and healthcare system needs: • Subcutaneous injection training is necessary. • Cold chain storage is required before first. • Providers should be trained to counsel patients about recognizing symptoms of pancreatitis and when to seek medical advice. Medication-specific considerations: • Avoid combination with DPP-4 inhibitors.	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? GLP-1 RAs, including semaglutide, are expensive, especially compared to older diabetes medications. This is a barrier to widespread use, particularly in LMICs. Cost-effectiveness: • In high-income countries, semaglutide is considered cost-effective for patients with T2DM and high cardiovascular risk because it reduces costly events like heart attacks and strokes. • In lower-resource settings, cost-effectiveness is less certain, mainly because of the high drug price and limited health budgets. It is important to highlight that prices are expected to fall significantly with patent expirations and the entry of generic/biosimilar versions.	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) Semaglutide and other GLP-1 receptor agonists are available and accessible in many countries, but access remains uneven across the world. True accessibility (especially in LMICs) is still limited due to high costs.	☐ Yes ☒ No ☐ Not applicable

Does the medicine have wide regulatory approval? Approved by major regulatory agencies across high-, middle-, and some low-income countries	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable