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

Reviewer summary	☒ Supportive of the proposal (**with inclusion of oral semaglutide**) ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Worldwide, over 415 million people live with diabetes and an additional 193 million are thought to have undiagnosed diabetes. The proposal to include GLP-1 receptor agonists, specifically semaglutide, in the WHO Model List of Essential Medicines is well-supported. Evidence from major trials (e.g., SUSTAIN-6) and meta-analyses shows that semaglutide reduces cardiovascular events, stroke, mortality, and improves glycemic control with minimal hypoglycemia risk. It offers advantages over insulin and complements SGLT2 inhibitors already on the EML. Once-weekly subcutaneous dosing improves adherence and is suitable for LMICs. While costs are currently high, estimates suggest generic versions could reduce prices to under $1/month following patent expirations in 2026. Regulatory approval is widespread, and guidelines from ADA, EASD, and others recommend its use for patients with type 2 diabetes and established or high-risk cardiovascular disease. Inclusion in the EML could catalyze price reductions, improve access, and guide health systems to adopt more effective, life-saving diabetes treatment strategies. The clinical and policy rationale is strong for supporting its addition to the WHO EML.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**) 9 medicines and 5 therapeutic equivalents including Insulin, Metformin, Gliclazide, tolbutamide, dapagliflozin, canagliflozin, empagliflozin etc.	☒ 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;) The evidence for the benefit of GLP-1 RA for individuals with T2DM with established or at high risk of CVD has strengthened since the prior reviews by the WHO Expert Committee. Evidence suggests that GLP-1 RAs will enable more patients with T2DM to achieve glycemic control and cardiovascular (CV) and renal protection (2 major risks for individuals with T2DM).	☒ Yes ☐ No ☐ Not applicable

Interventions	All cause death (OR, 95%CI)	Cardiovascular death (OR, 95%CI)	Non-fatal myocardial infarction (OR, 95%CI)	Non-fatal stroke (OR, 95%CI)	Admission to hospital for heart failure (OR, 95%CI)	End stage kidney disease* (OR, 95%CI)	Health related quality of life score (OR, 95%CI)	Severe hypoglycaemia (OR, 95%CI)	Drug specific adverse events (OR, 95%CI)
SGLT-2 inhibitors	0.88 (0.83 to 0.94)	0.86 (0.80 to 0.94)	0.90 (0.82 to 0.98)	0.99 (0.88 to 1.11)	0.66 (0.60 to 0.73)	0.61 (0.55 to 0.67)	0.30 (0.10 to 0.49)	0.90 (0.79 to 1.02)	Genital infection 3.30 (2.88 to 3.78) Amputation 1.27 (1.01 to 1.61) Ketoacidosis 2.07 (1.44 to 2.98)
GLP-1 receptor agonists	0.88 (0.82 to 0.93)	0.87 (0.81 to 0.94)	0.91 (0.85 to 0.98)	0.85 (0.77 to 0.94)	0.91 (0.83 to 0.99)	0.83 (0.75 to 0.92)	0.17 (0.07 to 0.27)	0.98 (0.90 to 1.06)	Severe gastrointestinal events 1.97 (1.39 to 2.80)

HbA1c improvement

The SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) trials suggest that the mean HbA1c decreased from baseline by 1.2–1.5% with semaglutide 0.5 mg and 1.5–1.8% with semaglutide 1.0 mg, vs. < 0.1–0.4% with placebo and 0.5–1.4% with full doses of active comparators including sitagliptin, exenatide ER, insulin glargine, dulaglutide.

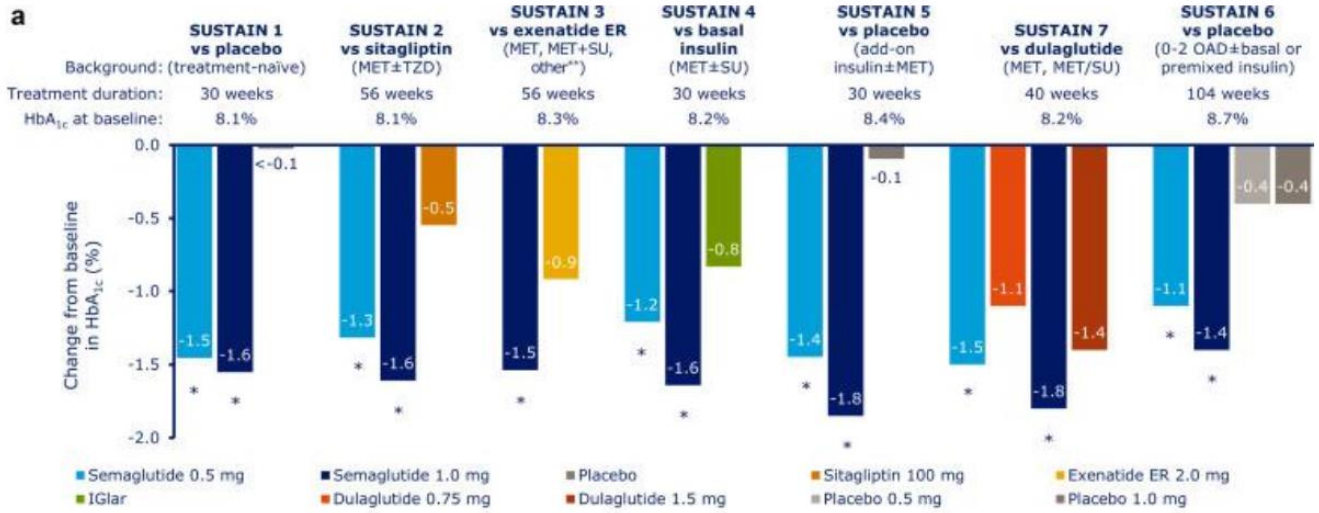

Figure 4. Semaglutide vs competitors in the SUSTAIN trials 1-7 on mean change in HbA1c [42].

There is a reported reduced risk of hypoglycemia in GLP-1 RAs compared to other classes such as insulin and sulfonylureas. In fact, Semaglutide 0.5 mg showed a decrease in incidence of hypoglycemia compared to any other agent.

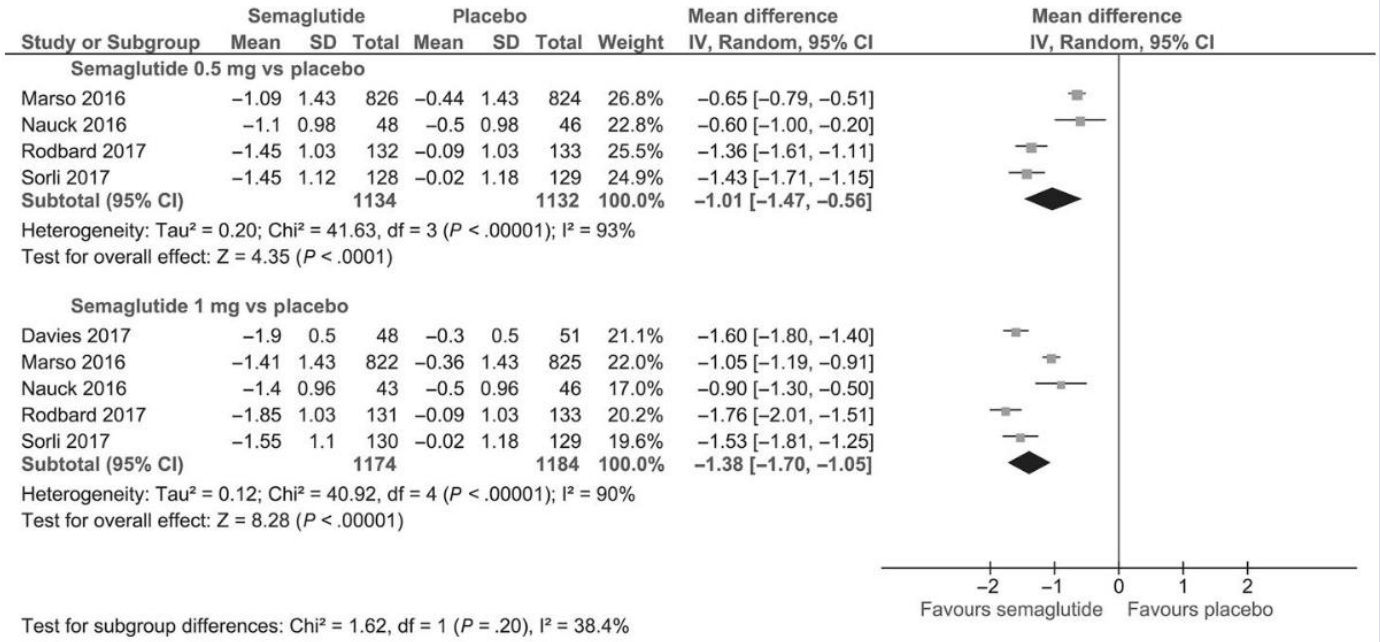

Figure 6. Weighted mean difference in change in HbA1c for Semaglutide vs placebo [44].

Cardioprotection

Against a placebo, semaglutide has been found to reduce blood pressure by 1.31 mmHg at the 0.5 mg dose ((95% CI, 0.07-2.56) and 3.05 mmHg at the 1.0 mg dose (95% CI, −4.63 to −1.47)

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;) **Yes,** adequate evidence exists for the safety and harms of GLP-1 receptor agonists, particularly semaglutide. Multiple high-quality randomized controlled trials and meta-analyses have consistently evaluated the safety profile of semaglutide. Key findings include: • Low risk of hypoglycemia when used without insulin or sulfonylureas. In monotherapy trials, severe hypoglycemia was rare (0%) a.15_glp-1-diabetes. • Common adverse effects are gastrointestinal (nausea, vomiting, diarrhea), generally mild to moderate and transient. Rates of discontinuation due to these events are low in trialsa.15_glp-1-diabetes. • Pancreatitis risk is low (0.3 cases per 100 patient-years) and primarily among those with previous history; patients with prior pancreatitis were excluded from trialsa.15_glp-1-diabetes. • Retinopathy concerns exist, especially with rapid A1c reduction, though evidence is mixed and may be confounded by baseline riska.15_glp-1-diabetes. • Thyroid C-cell tumors are extremely rare; semaglutide is contraindicated in patients with a personal/family history of medullary thyroid carcinoma or MEN2a.15_glp-1-diabetes. • GLP-1 RAs are now featured in multiple guidelines and standards of care and are shown to have a mean relative risk reduction in major adverse CV events (three point major adverse cardiovascular events (MACE) - CV death, non-fatal MI and non-fatal stroke) by 12%, all-cause/overall mortality by 12%, stroke by 16% and composite kidney events by 17%. These agents are associated with a low risk of hypoglycemia, reduce A1c significantly and directly target obesity resulting in weight loss, an important modifier of diabetes control and CV risk. **Overall, the safety profile is well-characterized and acceptable for the indicated population.**	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? **Yes, semaglutide has a favorable and meaningful balance of benefits to harms for adults with type 2 diabetes and established or high-risk cardiovascular disease.** **Overall, the proposed medicine has a favourable and meaningful balance of benefits to harms especially compared to other medicines on the EML.** **Benefits**	☒ Yes ☐ No ☐ Not applicable

• Cardiovascular Protection: Reduces 3-point MACE (CV death, MI, stroke) by 26% (SUSTAIN-6 trial)a.15_glp-1-diabetes. • Glycemic Control: Reduces HbA1c by 1.2–1.8%, outperforming many other agentsa.15_glp-1-diabetes. • Weight Loss: Associated with significant body weight reduction, improving metabolic outcomes. • Renal Protection: Reduces progression of kidney disease by 17% in meta-analysesa.15_glp-1-diabetes. • Low Hypoglycemia Risk: Particularly when not combined with insulin or sulfonylureas. **Harms** • Mostly gastrointestinal (nausea, vomiting) — generally transient and mild. • Rare risks include retinopathy progression (linked to rapid glucose lowering), pancreatitis, and thyroid C-cell tumors (in genetically predisposed individuals)a.15_glp-1-diabetes. **Conclusion** **Given the significant reductions in mortality and morbidity, especially cardiovascular events, alongside a manageable and well-characterized safety profile, the benefits of semaglutide clearly outweigh the harms for the indicated population.**	

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, there are some special requirements to ensure the safe, effective, and appropriate use of sub cutaneous semaglutide, but these are relatively minimal and suitable for primary care settings, including in low-resource environments. **A best option for temparature related stability is the inclusion of oral semaglutide.**
 	
Requirements for Safe and Effective Use
 	
1. Patient Assessment (Before Initiation)
• Medical history review to rule out contraindications:
  ○ Personal/family history of medullary thyroid cancer or MEN 2A/2B
  ○ History of pancreatitis
• Thyroid exam: Optional physical examination to assess thyroid nodules (precautionary).
2. Diagnostic and Monitoring Tests
• HbA1c testing: Every 3–6 months if available, to assess glycemic control.
• Kidney function tests (eGFR):
  ○ At baseline.
  ○ 4 weeks after initiation and 2–3 months after dose escalation—especially in patients with GI side effects (to monitor for
	☒ Yes ☐ No ☐ Not applicable

dehydration-related renal risk). • No need for daily glucose monitoring unless combined with insulin or sulfonylureas. **3. Healthcare Provider Training** • Basic training sufficient: Semaglutide can be safely prescribed by general practitioners. • No specialized endocrinology input required, but patient counseling on: o Proper injection technique (subcutaneous, once weekly) o Dose titration (0.25 mg → 0.5 mg → 1.0 mg as needed) o Recognition of side effects and what to report **4. Storage and Handling** • Cold chain required before first use (2–8°C). • Once in use, pens can be stored at room temperature (15–30°C) for up to 56 days, making it feasible in many LMICs. • **Consider inclusion of oral semaglutide to cater for challenges with cold chains in LMICs and humanitarian settings.**	
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? Yes, this medicine is still too expensive for LMICs	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) The availability and accessibility of semaglutide (GLP-1 receptor agonist) varies significantly across countries, with high availability in high-income settings and limited access in many low- and middle-income countries (LMICs). However, accessibility is expected to improve in the near future due to regulatory changes, patent expirations, and generic production efforts. **1. Current Global Availability** • Widely available in high-income countries (HICs): o Approved by regulatory agencies in the USA, EU, UK, Canada, Japan, Australia, China, and South Africa. o Listed on formularies and reimbursed in many HICs for T2DM with CVD. • Limited or absent registration in many LMICs: o Not registered in some African countries like Kenya at time of applicationa.15_glp-1-diabetes. o Registration is progressing in countries like India and China for generic versions.	☒ Yes ☐ No ☐ Not applicable

2. Supply and Market Conditions

- Brand-name injectable semaglutide (Ozempic) is in shortage in some markets (e.g., US) due to rising demand and supply chain constraints. (FDA)
- Compounded semaglutide is permitted in the US under specific regulations during shortage periods (FDA).

3. Pipeline for Generic and Biosimilar Versions

- Patent expirations for injectable semaglutide in March 2026, expected to open the market for biosimilars and generics.
- Generic production underway:
    - Indian companies (e.g., Natco Pharma, Zydus, Sun Pharma) are developing semaglutide generics, aiming for 2026 launch.
    - China also progressing toward domestic generic production pending court decisions.

4. Price and Affordability

- Prices vary drastically:
    - From $1.27/day (Bangladesh) to $11.73/day (USA)a.15_glp-1-diabetes.
- Estimated cost-based price: as low as $0.89/month, suggesting significant potential for cost reductions with generic competition.
- Price remains a key barrier to accessibility, especially in public sector procurement in LMICs.

5. Access Advocacy and Policy Levers

- Supported by:
    - MSF Access Campaign (Defeating the Double Standard in Diabetes Care)
    - Medicines Patent Pool (MPP)
    - Access to Medicine Foundation
- These organizations advocate for:
    - Voluntary licensing,
    - Compulsory licenses where applicable,
    - Use of TRIPS flexibilities to improve access in LMICs.

Conclusion: Semaglutide is available in many HICs but not yet widely accessible in LMICs. However, availability is improving due to:

- Ongoing generic development,
- Approaching patent expirations (2024–2026),
- International pressure for equitable access.

Inclusion in the WHO Model List of Essential Medicines could accelerate registration, affordability, and public procurement, particularly for populations with the highest unmet need.

Does the medicine have wide regulatory approval? **Yes,** semaglutide has wide regulatory approval across many countries and regions, particularly for the treatment of type 2 diabetes mellitus (T2DM) with or without cardiovascular risk. Its approval status strengthens the case for its inclusion on the WHO Model List of Essential Medicines. **Regulatory Approvals Globally** Semaglutide (as Ozempic for injectable and Rybelsus for oral) is approved for T2DM treatment in the following major regulatory jurisdictions including United States, European Union, United Kingdom, Canada, Japan, China, Australia, South Africa, Brazil. **Registration Status in LMICs** • South Africa: Registered with SAHPRA (South African Health Products Regulatory Authority)a.15_glp-1-diabetes. • India and China: Generic versions of semaglutide and liraglutide are under development or registration by local manufacturers in anticipation of patent expiration. • Kenya and other countries: Not yet registered, but WHO EML inclusion could facilitate accelerated review and regulatory approval. **Patent Landscape and Future Access** • Basic patents on semaglutide expire in 2026, opening the door to biosimilar and generic production. • Companies in India and China are preparing to launch generic versions once patents expire **Shortages and Temporary Measures** • In the USA, semaglutide (Ozempic/Wegovy) has appeared on the FDA Drug Shortage List, prompting temporary approval for compounded versions under specific conditions **Conclusion** Semaglutide has widespread regulatory approval in high- and upper-middle-income countries, and expanding regulatory submissions and patents expiring in 2026 are expected to increase access in LMICs. This global regulatory footprint supports its candidacy for inclusion on the WHO Model List of Essential Medicines.	☒ Yes, for the proposed indication ☒ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable
In Additio! Oral semaglutide is an emerging option within the GLP-1 receptor agonist class, offering potential advantages in terms of ease of administration and thermostability for use in low-resource settings. However, several important considerations—both from the application and external sources—should be taken into account when evaluating its inclusion in essential medicines or use in programs. **1. Evidence of Efficacy and Cardiovascular Benefit** • Top-line results from the SOUL trial suggest that oral semaglutide reduces cardiovascular events in adults with type 2 diabetes and high cardiovascular risk. At the time of the application, full peer-reviewed results were not yet publisheda.15_glp-1-diabetes. • The oral formulation has shown comparable glycemic and weight loss effects to injectable semaglutide at equivalent doses in the	

PIONEER trials:
- *PIONEER 6* demonstrated non-inferiority to placebo in cardiovascular outcomes (CV death, nonfatal MI/stroke) (Kristensen et al., 2019†Lancet Diabetes Endocrino).
- *PIONEER 4* showed significant HbA1c reduction and weight loss versus liraglutide (Aroda et al., 2019†Diabetes Obes Metab)

2. Administration Challenges
- Oral semaglutide has strict administration requirements:
  - Must be taken on an empty stomach with no more than 120 mL (4 oz) of plain water.
  - Requires a 30-minute wait before eating, drinking anything else, or taking other medicationsa.15_glp-1-diabetes.
- These requirements may limit its feasibility in low-literacy or food-insecure settings where fasting conditions are difficult to ensure.

3. Storage and Stability
- Oral semaglutide is thermostable, making it advantageous for settings lacking cold-chain capacity.
- Labeled storage: 20–25°C (68–77°F), with short excursions allowed (FDA Label, Rybelsus).
- This feature may be especially beneficial in humanitarian settings or rural areas of LMICs.

4. Cost and Access
- Oral semaglutide remains expensive, and no generics are yet available as of 2024.
- Cost-based price estimates range between $38.62–$72.49/month, which is significantly higher than injectable semaglutide's estimate of $0.89–$4.73/month
- Patents on oral formulations are expected to expire after 2030, limiting near-term generic production.

5. WHO and Guidelines Perspective
- This application prioritizes injectable semaglutide for EML inclusion due to:
  - Stronger evidence base (SUSTAIN-6)
  - More convenient once-weekly administration
  - Lower cost and more imminent generic competition
- Oral semaglutide may be considered in the future for contexts where:
  - Injection hesitancy is high,
  - Cold chain is a barrier,
  - And patients can reliably adhere to fasting requirements.

Rationale Behind MSF's Support
- Semaglutide provides:
  - Dual benefit: glycemic control and cardiovascular risk reduction.
  - Once-weekly administration, ideal for humanitarian settings.

• MSF aligns with the EML's equity goals, pushing for affordable access through:
  ○ Generic competition
  ○ Patent flexibility tools (TRIPS flexibilities, voluntary licenses)
  ○ Pooled procurement for diabetes care in LMICs
 	
Conclusion: Although this application did not primarily apply for oral semaglutide for T2DM due to challenges with administration, this medicine should be considered within this application or a separate application requested. Oral semaglutide shows promise but is not currently recommended as the lead agent for EML inclusion due to higher cost, stricter administration protocol, and limited comparative outcome data. However, it could be important in the future for non-injectable delivery in low-resource or humanitarian contexts if prices drop and trial evidence matures.	