COMMENTS FROM THE DEPARTMENT OF NONCOMMUNICABLE DISEASES, REHABILITATION AND DISABILITY (NCD) ON THE PROPOSAL FOR ADDITION OF GLP-1 RECEPTOR AGONISTS TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF ADULTS WITH TYPE 2 DIABETES MELLITUS AND ESTABLISHED OR HIGH RISK CARDIOVASCULAR DISEASE

The application was submitted by Sanjana Garimella et al. and was developed with a brief consultation with the WHO Department of Noncommunicable Diseases, Rehabilitation and Disability ahead of submission.

The technical unit supports the application to add GLP-1 receptor agonists (GLP-1RAs) to the 24th WHO Model List of Essential Medicines with the following additions:

- GLP-1RAs are an option to include add-on glucose lowering therapy when sodium-glucose co-transporter-2 (SGLT-2) inhibitors are not tolerated, cause side effects or are ineffective.
- add dulaglutide on EML as therapeutic equivalents.

The application for consideration is:

- semaglutide, injection (subcutaneous), 0.25 mg, 0.50 mg, 1.0 mg, 2.0 mg

Target population of the application includes non-pregnant adults 18 years and older with type 2 diabetes (T2DM) and:

- established cardiovascular disease (CVD); or
- estimated to be at high-risk of developing CVD.

Current WHO recommendations

The *WHO Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus*, published in 2018, have not included GLP-1RA. When the evidence for those guidelines was being reviewed in 2015-2016, the guidelines group concluded that there were too few trials of GLP-1RA to issue a recommendation.

Effectiveness

- The application adequately address effectiveness.
- GLP-1RAs are an established and effective treatment for T2DM, with moderate to high-quality evidence in the studied populations. The evidence primarily supports the use of GLP-1RAs as an add-on to usual care, including other glucose-lowering medications.
- Compared to placebo, several randomised clinical trials have shown that GLPA-1RAs added to usual care significantly reduce premature mortality, CVD and adverse renal

outcomes in people with T2DM. They have also been shown to reduce hospitalizations for heart failure, although specific studies in T2DM patients with heart failure are lacking.

- A recent systematic review demonstrated that over a median follow-up of 25.2 months, GLP-1RAs reduced composite kidney outcomes by 18%, kidney failure by 16%, major adverse cardiovascular events (MACE) by 13% and all-cause mortality by 12% (Badve SV et al. (2025)). GLP-1RA (and SGLT-2 inhibitors) have no demonstrated benefit on diabetes microvascular complications of retinopathy and neuropathy.
- Limited randomized controlled trial (RCT) data are available from low- and middle-income countries (LMICs), which can be relevant due to differences in T2DM phenotypes in populations without obesity, where decreased insulin secretion predominates over insulin resistance.
- No RCTs have evaluated GLP-1RAs as first-line agents or conducted head-to-head with other glucose-lowering medications.

Summary of effectiveness: The evidence supports the benefits of GLP-1RAs in people with T2DM or at high risk of CVD complications. Data from LMICs remain limited as most studies have been conducted in higher-income countries.

Adverse effects

- The application adequately addresses safety and adverse effects.
- A recent systematic review found no difference in the risk of serious adverse effects, including acute pancreatitis and severe hypoglycaemia. However, treatment discontinuation due to adverse effects occurred 51% more frequently with GLPA-1Ras (Badve SV et al. (2025)).
- The most common adverse effect of GLP-1 RA is gastrointestinal side effects. The application states that “those who have significant gastrointestinal symptoms may be at increased risk for dehydration in the setting of diarrhea or vomiting. Thus, kidney function should be checked within 4 weeks of starting the medication and 2-3 months after any dose increase” (page 12). This monitoring requirement may be challenging in settings with limited health resources.
- Healthcare providers must be well-versed in the medication, dosage, injection device, administration procedure and dose titration to minimise and control gastrointestinal side effects.

Summary of adverse effects: The well-known risk is gastrointestinal side effects, which healthcare providers should monitor.

Affordability

- GLP-1RAs are currently less available in most LMICs, and even better resourced health systems struggle with affordability and most place restrictions on their use.

- It is questionable if the GLP-1RAs fulfil the criteria of a WHO essential medicine as stated in the EML - *"Essential medicines are those that satisfy the priority health care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness. They are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford".* At present they are not medications that LMIC health systems and most individuals can afford and even better resourced health systems struggle with affordability and most have placed restrictions on their use.
- Cost is a major issue with GLP-1 RAs and there are a lack of studies showing favourable cost-effectiveness analyses, even in well-resourced setting, even in well-resourced settings. Prior reviews have raised concerns on global cost-effectiveness of GLP-1 RAs.
- There is an expectation (hope) that the costs of GLP-1RAs will come down as patents expire and biosimilar equivalents enter the market. Programmes, such as WHO prequalification, may assist with biosimilar GLP-1RA.
- Challenges also include industry intervention to protect market share and prevent price dilution that would increase access, availability and affordability in LMIC. The generic SGLT-2 inhibitor global market could still advance more. Also access to insulin remains a challenge after 100 years despite biosimilar insulins.
- Obesity/overweight in people with T2DM may not be an issue in many LMIC populations. Considering affordability and that GLP-1RA is administered by injection, the most likely place of GLP-1RA in LMICs in the diabetes treatment algorithm is as an option when SGLT-2 inhibitors are not tolerated, cause side effects or are ineffective.

Regulatory consideration

This medicine has been approved by several regulatory authorities, including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the UK Medicines and Healthcare Products Regulatory Agency (MHRA).

There are no major regulatory limitations on the availability of the proposed medicines, as they are approved in multiple countries. While only two primary manufacturers exist, the product will be off-patent by 2026 and expected to increase global availability, with generic and biosimilar production already in progress. This expansion is anticipated to improve market affordability.

Other clinical considerations

- GLP-1RA is a newer class of blood glucose-lowering medications that is mostly injectable. GLP-1RA can be used with other blood glucose-lowering medications listed in the 23rd WHO Model List of Essential Medicines (2023). It is usually used in combination with metformin, and most guidelines recommend its use when metformin is already being

used unless metformin is contraindicated. This application does not propose GLP-1RAs as first-line agents.

- GLP-1RAs should not be used with DPP-4 inhibitors. Dose adjustments for other glucose-lowering medications, especially sulfonylureas and insulin, may be required to reduce the risk of hypoglycaemia if blood glucose control improves.
- SGLT-2 inhibitors offer a cost-effective alternative to GLP-1RAs with similar or better outcomes for heart failure. They are a cheaper alternative with equivalent (or better in relation to heart failure) outcomes. In LMICs, where cost and the injectable method of GLP-1RAs may limit their use, GLP-1RAs are an option when SGLT-2 inhibitors are not tolerated, cause side effects or are ineffective.
- The application states that *"When considering indication, GLP-1 RAs are to be considered in patients who have established or are at high risk of cardiovascular disease whereas SGLT2-inhibitors are typically considered for patients with established heart failure or chronic kidney disease"* (page 8). This is not consistent with current guidelines which recommend SGLT-2 inhibitors for people with T2DM with or at high risk of CVD.
- The application refers to the potential for combination SGLT-2i and GLP-1 RA treatment. However, it should be noted that:
    - No clinical trial has studied combinations of SGLT-2i and GLP-1 RA on cardio-renal outcomes in people with T2DM.
    - The application cites an opinion review (Reference 9) which included an analysis of pooled data from five CVD outcome trials and reported a similar reduction in MACE with GLP1-RA plus SGLT-2i combination therapy compared to GLP-1 RA or SGLT-2i alone, against placebo. The only difference with combination therapy, based on two RCTs, was an additive benefit on heart failure hospitalizations compared to when either agent was used alone.
- Adherence and perseverance with GLP-1 RA treatment in clinical practice is also a challenge and the real-world experience differs from clinical trial data.

The application supports adding semaglutide as a square box symbol in the WHO's EML. If GLP-1RAs are included in the WHO EML, dulaglutide and other "therapeutic equivalents" with similar evidence should be included, anticipating the future availability of biosimilars.

- Given that the evidence for dulaglutide is comparable to that for semaglutide, it should also be considered a therapeutic alternative. Both products are used in health settings where they are approved. If a listing for GLP-1RA is approved, it would be appropriate to include dulaglutide in the EML, as well as "therapeutic equivalents," in anticipation of the availability of approved biosimilar substitutes.
- Since this application was submitted, some additional studies have been published, but they have not substantially changed the conclusions of the available evidence.

Conclusion

GLP-1RAs are an effective treatment option with established cardiovascular benefits for T2DM. They have a good safety profile apart from their known gastrointestinal side effects. Most of the clinical evidence involves their use alongside other CVD therapies (e.g. statins, aspirin, ACEI/ARBs), and their effectiveness without these additional treatments remains uncertain. In addition, evidence from LMICs is limited. This may be particularly relevant in the context of studies which have highlighted differences in T2DM phenotype in populations without obesity.

Due to the costs, GLP-1RAs are currently unaffordable in many low-resourced health systems. Shortages and increasing financial burden on health systems and individuals have been reported even in high income settings. However, it is hoped that their accessibility and affordability will change when they come off-patent. SGLT-2 inhibitors, which are already listed in the EML, can be a cheaper alternative with comparable or even better outcomes, particularly in heart failure.

Although GLP-1RAs are not included in current WHO guidelines for T2D management, these guidelines are being updated. The exact role (if any) of GLP-1RA is undetermined at the moment, but due to the costs of the medicine and the infrastructure required for its use, SGLT-2 inhibitors, which are already listed in the EML, would likely be the preferred treatment in high-risk CVD groups.

It would seem appropriate to include dulaglutide in the EML if a listing for GLP-1RA is approved, as well as “therapeutic equivalents” in anticipation of the availability of approved biosimilar substitutes.