

Letter to 2023 WHO Expert Committee on the Selection & Use of Essential Medicines:
Indications for GLP-1 Receptor Agonists

Dear WHO Expert Committee on the Selection & Use of Essential Medicines,

We recently submitted an application to consider the inclusion of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on the WHO Essential Medicines List (EML) for the indication of weight loss in obesity. The purpose of this letter is to clearly note that GLP-1 RAs are also indicated for the management of type 2 diabetes mellitus (T2DM); however the dosages for the indication of T2DM are different than those associated with weight loss in obesity and formulations for weight loss in obesity are not formally indicated for diabetes. Given the potential for GLP-1 RA use in T2DM, specifically in populations with established or at high risk of cardiovascular disease (CVD), and to avoid confusion, we caution against the inclusion of GLP-1 RA on the EML only at their typical doses for obesity without including the typical doses and requisite guidance for glycemic control for T2DM.

To that end, we have undertaken a detailed review for the T2DM indication and kindly summarize brief highlights in this letter for your comment and feedback and/or requests for a broader technical review to inform the assessment. We aim to submit a formal application to include GLP-1 RAs for the indication of T2DM in 2025. We plan on working closely with the appropriate technical unit (Non-communicable Diseases) and EML Secretariat prior to submitting the application.

[1] The evidence for the benefit of GLP-1 RA for those individuals with T2DM with established or at high risk of CVD has strengthened since the prior reviews by the WHO Expert Committee. GLP-1 RAs will enable more patients with T2DM to achieve glycemic control and cardiovascular (CV) and renal protection. 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% (1). 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 (2). GLP-1 RA provide clear alternatives to agents currently listed on the EML (3).

[2] We address the false dichotomy between SGLT-2 inhibitors and GLP-1 RAs. GLP-1 RAs have different and complementary benefits to SGLT2-inhibitors. GLP-1 RAs, in contrast to SGLT2-inhibitors which are already included on the WHO EML, provide reduction in fatal or non-fatal stroke, possess superior glycaemic efficacy, and do not require hepatic or renal dose adjustments (4–6). SGLT2-inhibitors have various contraindications and precautions to use, including avoiding use in patients with previous diabetic ketoacidosis (7). SGLT-2 inhibitors pose risk for genitourinary infections (8). Notably, GLP-1 RA and SGLT2-inhibitors showed an additive benefit when used in combination on heart failure hospitalizations compared to when either agent was used alone (9).

[3] Consultation with the humanitarian agency Médecins Sans Frontières (MSF) indicates that a once weekly dosing with an agent with CV benefit would be optimal in humanitarian settings. Subcutaneous liraglutide, semaglutide and dulaglutide have all been shown to provide CV benefits in this patient population(4). Only liraglutide and semaglutide compounds carry the formal dual indications for T2DM and obesity at this time. Liraglutide has the advantage of upcoming global patent expirations; however, the injectable agent is dosed daily which is less convenient for patients and less optimal for field based and global humanitarian settings. By contrast, semaglutide at typical diabetes dosing is dosed weekly with CV benefits based on 3-point MACE primary outcomes in trials for this indication.

[4] For low- and middle-income country (LMIC) settings where the introduction of insulin for people living with T2DM, including with obesity, is programmatically challenging and often stigmatizing, the use of GLP-1 RAs in combination with other oral agents, including SGLT2 inhibitors, may simplify service delivery in addition to their proven clinical benefits. GLP-1 RA therefore serve as likely insulin-sparing agents in areas where minimizing insulin use would be helpful. MSF plans to incorporate SGLT2 inhibitors and GLP-1 RA (weekly injectable semaglutide) within draft 2023 MSF treatment algorithms for pilot projects.

[5] Finally, we provide recent updates on cost. Recent and upcoming patent expirations for GLP-1 RA in manufacturing countries suggest greater opportunities for multi-source manufacturing and meaningful price reductions - similar to the implications of essential medicine status for insulin analogues and SGLT2 inhibitors. Two companies currently hold most of the market. Historically, a diverse and widening manufacturing base (including for biosimilars) has been critical for enabling global access to essential medicines (10–12). There is a concern for a “treatment paradox” wherein the most at risk individuals are least likely to be prescribed these agents (13) compounded by cost-related under use driven by high prices and high out of pocket costs (14). A 2023 unpublished analysis shows the following costs in USD per day of treatment (USD per WHO defined daily dose, DDD) in a range of countries across income status. The prices represent the lowest available cost across formulations and across public price databases for each country:

USD/DDD	liraglutide (SQ)	semaglutide (SQ)	dulaglutide (SQ)
Bangladesh	\$5.75	\$1.27	\$3.49
Brazil	\$2.62	\$3.17	\$1.91
El Salvador	\$11.07	n/a	\$5.01
France	\$3.79	\$4.54	\$0.74
India	\$4.63	n/a	\$2.77
Latvia	\$4.75	\$7.63	n/a
Philippines	\$4.66	n/a	\$2.94
South Africa	\$3.95	\$3.84	\$2.85
UK	\$3.95	\$2.42	\$0.79
USA	\$28.38	\$11.73	\$7.58

Prior reviews have raised concerns on global cost-effectiveness of GLP-1 RA. One 2021 study estimated that in LMICs, the price of GLP-1 agents would need to be dramatically reduced in order to meet cost-effectiveness thresholds versus sulfonylureas for T2DM. The study indicated that cost-effectiveness ratios for GLP-1 agents could be improved by targeting treatment to patients with T2DM who have comorbid CVD, heart failure, or chronic kidney disease (15). Notably, this analysis used a median GLP-1 RA price of \$12,378 USD annually (~34 USD/day) based on liraglutide 1.2mg /day. This price point is far higher than the ~5 USD/day in a range of countries, as presented. Thus, using today’s prices for GLP-1 RA could offer far improved cost-effectiveness than was found in the cited study to address possible concerns.

We thank you for your consideration and welcome any feedback by the WHO Expert Committee.

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