M E M O R A N D U M

From:	Director, NFS	**To:**	Director, HPS	**Date: 23 April 2025**
Our ref:		**Attention:**		
Your ref:	EML	**Through:**		
Originator:	HEP/NFS	**Subject:**	REQUEST FOR INPUT AND COMMENTS FROM WHO TECHNICAL DEPARTMENTS, 25TH EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES	

In response to:

1. **The Essential Medicines List Application for Addition of Glucagon-Like Peptide-1 (GLP-1) receptor agonists to the WHO model list of essential medicines for the treatment of adults with obesity, it is noted that:**

The application was submitted by MAGIC Evidence Ecosystem Foundation, Oslo, Norway. The NFS department was consulted at the beginning of the process but not involved in the development of the application.

The technical unit supports the application to add GLP-1 receptor agonists (GLP-1RAs) to the 24th WHO Model List of Essential Medicines for the treatment of obesity in adults ≥ 19 years.
As the application recommends adding the class of medicines to the Essential Medicine List, the technical unit recommends the definition of 'GLP-1 RA and GLP-1 RA/GIP dual agonists' as class added to the Essential Medicine List.

Target population of the application includes adults with obesity. The technical unit recommends adding the following WHO definitions: Adults ≥ 19 years of age, and Obesity when BMI ≥30 kg/$m^{2.}$

Current WHO recommendations:
WHO is currently developing living guidelines on the use of, and indications for GLP-1 RA and GLP-1 RA/GIP dual agonists in the treatment of adults living with obesity. The WHO Secretariat convened the guidelines development group (GDG) earlier than planned on 7-9 April 2025, to be able to inform the 25th Expert Committee on Selection and Use of Essential Medicines. Three GLP-1 RA and GLP-1 RA/GIP dual agonists were evaluated for the purpose of this recommendation, including liraglutide, semaglutide, and tirzapatide. The critical outcomes that informed this decision are weight, quality of life, adverse events, major adverse cardiovascular events (MACE), and mortality.

The GDG made a conditional recommendation for the use of GLP-1 RA and GLP-1 RA/GIP dual agonists in the treatment of adults with obesity with due consideration to a series of critical elements such as:

- Need of longer-term studies on impact of GLP-1 RAs and GLP-1/GIP dual agonists discontinuation and maintenance doses on BMI and co-morbidities in people living with obesity and cost-effectiveness and budget impact of GLP-1 RAs and GLP-1/GIP dual agonists in people living with obesity across settings including LMICs.
- Effectiveness of GLP-1 RA and GLP-1 RA/GIP dual agonists in treating obesity which currently represent the only treating option for the disease with high morbidity and mortality across settings and populations. Of note, people living with obesity voted for a strong

recommendation also as a measure to increase access to treatment and equity especially in LMIC.
- The recommendation included an implementation consideration on how governments may want to prioritize the rollout of GLP-1 RAs and GLP-1/GIP dual agonists first for those with higher risk such as the presence of co-morbidities and higher BMIs), while ensuring health equity across population and settings. However, the research need to determine potential priority populations for the use of GLP-1 RAs and GLP-1/GIP dual agonists among all people with BMI ≥30 kg was also taken into consideration.

Effectiveness
- The application adequately addresses effectiveness.
- The data from randomized controlled trials include medium-term effects (6 months to less than 24 months) and long-term effects (24 or more months) of the GLP-1 RA and GLP-1 RA/GIP dual agonists, with stronger evidence for the medium-term effects.
- Tirzepatide and subcutaneous semaglutide are among the most effective in reducing fat mass (high certainty). Liraglutide is less effective but with probably larger effect on fat mass than lifestyle modification alone (moderate certainty).
- Estimates for exenatide were informed by very low certainty evidence.
- Tirzepatide and subcutaneous semaglutide led to reductions in lean mass (high certainty), whereas liraglutide (high certainty) and exenatide (very low certainty) resulted in little or no effect, or effects were very uncertain.
- Cardiovascular benefits of GLP-1 RA and GLP-1 RA/GIP dual agonists in people with obesity have been found, specifically HFpEF for semaglutie and tirzepatide and MACE for semaglutide. but without diabetes have only been demonstrated for subcutaneous semaglutide.
- Long term cardiovascular disease (CVD) and chronic kidney disease (CKD) benefits of GLP-1 RA in patients with type 2 diabetes are well established, supported by moderate to high certainty evidence from recent systematic reviews and network meta-analysis.
- However, there is a need to identify higher risk populations (either by BMI or co-morbidities) to target treatments to those most likely to benefit.

Adverse effects
- The application adequately addresses safety and adverse effects.
- The most common adverse effect of liraglutide, oral semaglutide, subcutaneous semaglutide and tirzepatide (moderate to high certainty) is gastrointestinal side effects.
- Healthcare providers must be well-versed in the medication, dosage, injection device, administration procedure and dose titration to minimise and control gastrointestinal side effects and support adherence
- There is a need to conduct systematic assessments of rare adverse events and long-term harms in people living with obesity.

Affordability
- Current costs of GLP-1 RAs and dual GLP-1/GIP dual agonists remain highly inadequate to meet the current population-level needs.
- There is limited data on long-term cost-effectiveness and outcomes in diverse populations and on budget impact of GLP-1 RAs and GLP-1/GIP dual agonists in people living with obesity across settings including LMICs.
- Primary patents on semaglutide expiring in 2026 have been filed or granted in few LMICs and several companies are planning to launch to launch a generic/biosimilar version of semaglutide in 2026.The market introduction of generic versions will improve affordability of semaglutide.
- Lirgalutide is available at a lower cost as generic/biosimilar products are approved in the US and Europe.

- Current costs are also related to the injectable devices. With vial options (available without the injector pens) becoming available, costs will be reduced.
- In addition, the same mechanisms that are used in large scale medicine access programs may need to be adopted. These may include negotiation of more favorable access and pricing conditions, facilitation of competition, design and implementation of market shaping strategies, pooled procurement, tiered pricing, compulsory and voluntary licensing, innovative financing and strategic planning at expiration of pharmaceutical patents that hinder generic manufacturing limiting production and affordability.

Regulatory consideration
This medicine has been approved for treatment of obesity without diabetes 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).

Conclusion
The efficacy of GLP-1 RAs and dual GLP-1/GIP dual agonists in the treatment of obesity is moderate to high. Currently, this class of medicines represents the only efficacious pharmacotherapy available. They have a good safety profile apart from their known gastrointestinal side effects. However, the current evidence is very limited in LMICs.

The current cost of GLP-1 RAs and dual GLP-1/GIP dual agonists severely limits access in low-, middle- and high-income countries. However, with injectable semaglutide going off patent in 2026, generic and biosimilar products will be available at a lower price in the market. Availability of generic products and the possibility to operationalize other mechanisms to lower prices will expand the access ecosystem to the benefit of the population living with obesity.

WHO guidelines, to be published in August 2025, will include a recommendation (conditional) on the use of GLP-1 RAs and dual GLP-1/GIP dual agonists for the treatment of obesity in adults. This will reinforce the current efforts of countries that are in the process of mounting a health system response to ensures that health services to prevent, care and treat obesity and associated co-morbidities will be universally available, accessible, affordable, and sustainable.

Because of the current morbidity and mortality associated with obesity and its complications, GLP-1 RAs and dual GLP-1/GIP dual agonists being the only efficacious pharmacological intervention, and no other medicines for the treatment of obesity included in the Essential Medicines List, the technical unit recommends the addition of GLP-1 RAs and dual GLP-1/GIP dual agonists.

2. **The Essential Medicines List Application for Deletion to the EML and EMLc of Iodine, it is noted that:**

Iodine is listed under the category of Vitamins and minerals, specifying:
- Capsules, 190 mg
- Iodized oil, 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.

Guerbet, the product owner and marketing authorization holder of the human proprietary medicinal product Oriodol® (formerly Lipiodol® capsules), was granted the inclusion of Oriodol (iodine) in the WHO EML and the WHO EMLc, section 27. VITAMINS AND MINERALS, in 1994 (Who Drug Information, Vol.7, No.4, 1993).

The medical indication of Oriodol is the prevention of iodine deficiency but was never commercialized in France and was only commercialized in export countries outside Europe, in particular Africa and South-East Asia. Due to decrease medical needs over years and the absence of demands of Oriodol for the past 5 years, Guerbet has started withdrawing the marketing authorizations worldwide. Since 2022, all the marketing authorization in export countries was withdrawn and

Guerbet has applied the withdrawal of Oriodol last marketing authorization, in France. Therefore, Guerbet is applying for the deletion from the WHO EML and the WHO EMLc.

A 2007 joint statement by WHO and UNICEF (*Reaching optimal iodine nutrition in pregnant and lactating women and young children*) recommends iodine supplementation for increasing iodine intake if iodized salt is not accessible in specific situations. Iodine supplements could be administered on a daily or annual basis using an iodized oil preparation in doses ranging from 90 µg/d from children under 2 years to 250 µg/d for pregnant and lactating women and 200 mg/year for children under to 2 years to 400 mg for women of reproductive age, and pregnant and lactating women.

As described in the application, we are also not aware of any countries implementing iodine supplementation with iodized oil capsules. Outreach to partners did not also reveal any country implementing iodized oil capsules.

Iodine tablets are important for use as in iodine thyroid blocking in planning and responding to radiological and nuclear emergencies, however, these are generally provided as potassium iodide or potassium iodate. Potassium iodide is listed on the EML under Thyroid hormones and antithyroid medicines (60 mg tablets).

The Department of Nutrition and Food Safety is not opposed to removing iodine capsules from the EML and EMLc, but note that currently the EML does not specify the use of Oriodol® (only as general Iodine Capsules, 190 mg).

Thank you.

Luz De Regil