

Semaglutide

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 18. Medicines for endocrine disorders > 18.5. Medicines for diabetes > 18.5.2. Hypoglycaemic agents

ATC codes: A10BJ06

Indication	Obesity ICD11 code: 5B81.Z
INN	Semaglutide
Medicine type	Biological agent
List type	Core
Formulations	Parenteral > General injections > SC: 0.25 mg in pre-filled pen injection solution ; 0.5 mg in pre-filled pen injection solution ; 1 mg in pre-filled pen injection solution ; 2 mg in pre-filled pen injection solution ; 4 mg in pre-filled pen injection solution Oral > Solid > tablet: 3 mg
EML status history	Application rejected in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Weight restriction	BMI \geq 30 kg/m ²
Therapeutic alternatives	beinaglutide (ATC codes: A10BJ07) dulaglutide (ATC codes: A10BJ05) exenatide (ATC codes: A10BJ01) liraglutide (ATC codes: A10BJ02) tirzepatide (ATC codes: A10BX16)
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org  Read more about patents. 
Wikipedia	Semaglutide 
DrugBank	Semaglutide 

Expert Committee recommendation

The Expert Committee recognized that diabetes and obesity currently represent two major global health challenges, with both conditions reaching epidemic proportions in different populations and regions. According to a study by the NCD Risk Factor Collaboration, in 2022, there were an estimated 828 million adults globally living with diabetes. At the same time, the prevalence of obesity has increased globally – more than doubling in adults since 1990 – and now affecting more than 1 billion people. Growth in the prevalence of obesity is most rapid in low- and middle-income countries. Both diabetes and obesity are major contributors to mortality and morbidity, are responsible for substantial disability-adjusted life years and strain health systems worldwide. Notably, the relationship between obesity and diabetes is both causal and cyclical; excess adiposity significantly increases the risk of type 2 diabetes through mechanisms involving insulin resistance and chronic inflammation. Furthermore, diabetes and obesity together exacerbate the risk of cardiovascular diseases, forming a triad of interlinked conditions that influence each other and jointly account for a substantial proportion of preventable deaths. The Committee noted that 30% to 50% of people with type 2 diabetes have established cardiovascular disease and obesity, representing a large global cohort with this triad of comorbidities. The Committee also noted that for people with all three of these conditions, the risk of death is much higher than in people with either diabetes or obesity alone. The Committee noted the evidence from the large systematic review that demonstrated the efficacy of glucagon-like-peptide-1 (GLP-1) receptor agonists (particularly subcutaneous semaglutide for which more data have been

cumulated) and tirzepatide in people with obesity for achieving clinically meaningful weight loss and improving quality of life, compared with lifestyle modification alone. However, the Committee agreed that evidence of benefits in cardiovascular outcomes and mortality in people with obesity without diabetes was currently limited to a single, large, randomized controlled trial of semaglutide versus placebo. While the outcomes of this trial for cardiovascular outcomes were positive, there were more discontinuations due to adverse events in people receiving semaglutide. The Committee noted that the trial reported outcomes after almost 40 months of follow-up and considered that the available evidence on mortality outcomes was still at an early stage and limited. The Committee noted the evidence from multiple large-scale randomized controlled trials and systematic reviews that demonstrated the efficacy of GLP-1 receptor agonists and the GLP-1/GIP dual agonist tirzepatide in people with diabetes in improving glycaemic control, reducing the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), reducing the risk of end-stage kidney disease, reducing all-cause mortality, improving health-related quality of life and promoting weight loss, compared with placebo. The Committee noted the consistency of benefits across studies. The Committee also acknowledged that, while some degree of benefit was possible in all patients irrespective of risk of cardiovascular diseases, patients with type 2 diabetes with known cardiovascular or chronic kidney disease are a high-risk subgroup that is likely to experience the most relevant benefit, with a 10-fold decreased risk of premature death compared with the cohort of patients at low risk. The large difference in benefit between those at low risk and those at high risk for premature mortality is an important factor that could be used to identify those patients to be prioritized in the introduction of these medicines at the country level. Overall, the Committee considered that the magnitude of benefits and certainty of evidence for GLP-1 receptor agonists and tirzepatide were greater for people with diabetes than for people with obesity, particularly for important outcomes of cardiovascular events and mortality, upon which the Committee places greater value than outcomes of glycaemic control and weight loss. The Expert Committee therefore did not recommend the inclusion of GLP-1 receptor agonists and tirzepatide on the EML for the treatment of people with obesity without type 2 diabetes and established cardiovascular disease or chronic kidney disease, because of less relevant and mature evidence of benefit for cardiovascular outcomes and mortality in this population, and a lack of data about long-term net benefit to harm balance. However, in consideration of the application for GLP-1 receptor agonists for the treatment of adults with type 2 diabetes and established or at high-risk of cardiovascular disease, the Expert Committee recommended the inclusion of semaglutide, dulaglutide, liraglutide and tirzepatide on the core list of the EML as add-on glucose-lowering therapy for adults with type 2 diabetes and with (i) established cardiovascular disease or chronic kidney disease; and (ii) obesity ($BMI \geq 30 \text{ kg/m}^2$) having a significant impact on their physical health and/or quality of life. This recommendation is made based on evidence of a meaningful and favourable balance of benefits to harms in this patient population. Refer to the summary for the addition of GLP-1 receptor agonists for use in adults with type 2 diabetes for full details of the Expert Committee's recommendation for this indication.

Background

An application for the inclusion of GLP-1 receptor agonists, represented by liraglutide, on the EML for the treatment of obesity in adults was considered by the Expert Committee in 2023 (1). The Committee noted that GLP-1 receptor agonists have been shown to reduce weight and BMI in the short term compared with placebo. However, evidence about the efficacy in different populations was lacking. The optimal duration of treatment had also not been defined since maintenance of weight reduction once therapy is stopped seems to be rare. Furthermore, it was unclear whether treatment of overweight and obesity with GLP-1 receptor agonists affects long-term clinically important outcomes such as hypertension, hyperglycaemia, osteoarthritis and mortality. The Committee also noted that the use of GLP-1 receptor agonists was associated with an increased frequency of adverse events such as nausea, vomiting, constipation and diarrhoea compared with placebo, although these were usually manageable and self-limiting. The Committee stressed the importance of long-term safety data, which were currently lacking, given the potential need for long-term administration of these medicines to maintain weight loss. The Committee noted that the prices of the medicines were currently high, and treatments were unlikely to be cost-effective in several regions. The Expert Committee therefore did not recommend the inclusion of GLP-1 receptor agonists on the EML for weight loss in people with obesity because of uncertain long-term clinical benefit and safety in this population.

Public health relevance

Obesity is an important public health challenge with many implications for health systems and society. According to WHO, in 2022, one in eight people globally was living with obesity, marking a dramatic rise in prevalence since 1990. Adult obesity has more than

doubled and adolescent obesity has quadrupled during this period. In 2022, 2.5 billion adults were overweight, of whom 890 million were living with obesity, representing 43% and 16% of the global adult population, respectively. Among 390 million overweight children and adolescents aged 5–19 years, 160 million were living with obesity (2). The health risks caused by overweight and obesity are well known. According to the Global Burden of Disease Study, in 2021, about 3.7 million deaths from noncommunicable diseases (e.g. cancer, cardiovascular diseases, chronic respiratory diseases, diabetes, digestive disorders and neurological disorders) were attributable to a higher-than-optimal BMI (3). The economic impact of obesity is substantial. In 2014, the global cost of obesity was estimated to be 2 trillion United States dollars (US\$), or nearly 3% of the global gross domestic product. Costs include both direct health-care costs (e.g. treatment of obesity-related conditions) and indirect costs (e.g. productivity losses and premature death) (4, 5). If current trends continue, the global economic costs of obesity and overweight are predicted to exceed US\$ 3 trillion by 2030 and reach US\$ 18 trillion by 2060 (6).

Benefits

The application presented the results of an unpublished systematic review and network meta-analysis conducted for the purpose of the application. The review updates a previously published systematic review and meta-analysis of pharmacotherapy for adults with overweight and obesity (7). The review included 184 randomized controlled trials (80 155 participants) of adults with overweight or obesity, with or without cardiovascular or metabolic comorbidities. It compared weight-lowering pharmacotherapy with lifestyle modification alone or alternative weight-lowering pharmacotherapy. Median treatment duration was 24 weeks, and median length of follow-up was 26 weeks. Important outcomes included: percentage bodyweight change; bodyweight reduction of $\geq 5\%$, 10%, 15% or 20%; quality-of-life scores; all-cause death; non-fatal myocardial infarction; and non-fatal stroke. There were 78 trials (22 031 participants) involving GLP-1 receptor agonists or GLP-1/GIP dual agonists and these were the only results reported in the application. All medicines were associated with reductions in bodyweight from baseline compared with lifestyle modification alone: tirzepatide (mean difference (MD) of percentage bodyweight change -15.15 , 95% confidence interval (CI) -16.28 to -14.03 ; eight randomized controlled trials, 3396 participants); semaglutide (oral) (MD -12.70 , 95% CI -15.89 to -9.51 ; one randomized controlled trial, 667 participants); semaglutide (subcutaneous) (MD -9.48 , 95% CI -10.24 to -8.72 , 18 randomized controlled trials, 24021 participants); liraglutide (MD -4.96% , 95% CI -5.64 to -4.28 ; 26 one randomized controlled trials, 7756 participants); exenatide (MD -3.58% , 95% CI -4.78 to -2.37 ; three randomized controlled trials, 320 participants); beinaglutide (MD -3.27 , 95% CI -5.67 to -0.87 ; two randomized controlled trials, 484 participants); and dulaglutide (MD -1.38 , 95% CI -3.81 to 1.06 ; one randomized controlled trial, 91 participants). The certainty of evidence was high for tirzepatide, oral and subcutaneous semaglutide, and moderate for the remaining medicines. Compared with lifestyle modification alone, beinaglutide, liraglutide, oral and subcutaneous semaglutide and tirzepatide increased the proportions of participants who achieved body weight reduction of at least 5%, 10%, 15% and 20%. The certainty of evidence was very low to high for beinaglutide, high for oral semaglutide, moderate to high for subcutaneous semaglutide, and moderate for liraglutide and tirzepatide. Dulaglutide was not associated with an important increase in the proportion of individuals achieving these outcomes (refer to Table 11, TRS 1064). For the outcome of all-cause death, there was high-certainty evidence that liraglutide (risk ratio (RR) 0.44, 95% CI 0.08 to 2.25; three randomized controlled trials, 4332 participants), subcutaneous semaglutide (RR 0.81, 95% CI 0.71 to 0.93; six randomized controlled trials, 21 413 participants) and tirzepatide (RR 0.79, 95% CI 0.23 to 2.75; three randomized controlled trials, 2088 participants) reduced the risk of death. There was moderate-certainty evidence that beinaglutide reduced risk of death (RR 0.49, 95% CI 0.01 to 24.58; one randomized controlled trial, 240 participants). In each case, the treatment effect in absolute terms was considered trivial because of the low baseline risk across comparisons. There was high-certainty evidence that subcutaneous semaglutide reduced the risk of non-fatal myocardial infarction (RR 0.73, 95% CI 0.62 to 0.86; two randomized controlled trials, 17 908 participants). There was moderate-certainty evidence that liraglutide (RR 0.83, 95% CI 0.16 to 4.32; three randomized controlled trials, 4269 participants) and tirzepatide (RR 0.96, 95% CI 0.17 to 5.35; two randomized controlled trials, 652 participants) reduced the risk of non-fatal myocardial infarction. There was high-certainty evidence that subcutaneous semaglutide reduced the risk of non-fatal stroke (RR 0.93, 95% CI 0.75 to 1.16; one randomized controlled trial, 17 604 participants). In each case, the treatment effects in absolute terms were considered trivial because of the low baseline risk across comparisons and short median follow-up of the trials. Notably, the trials included did not provide sufficient information to stratify populations by risk of cardiovascular or chronic kidney disease. However, the SELECT trial was a multicentre, double-blind randomized, placebo-controlled trial that investigated the effect of semaglutide on cardiovascular outcomes in 17 604 patients with $\text{BMI} \geq 27$ and preexisting cardiovascular diseases but without diabetes (8). The primary endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. This trial provided moderate-certainty evidence that semaglutide

reduced the risk of all-cause mortality (RR 0.81, 95% CI 0.71 to 0.93; in absolute terms, 10 fewer deaths per 1000 people treated). There was also high-certainty evidence that semaglutide reduced the risk of non-fatal myocardial infarction (RR 0.72, 95% CI 0.61 to 0.85; in absolute terms, 10 fewer events per 1000 people treated). There was moderate-certainty evidence of no significant effect of semaglutide on non-fatal stroke (RR 0.93, 95% CI 0.74 to 1.15). For the effects of the treatment on quality of life, the review found moderate-certainty evidence that tirzepatide and oral semaglutide were associated with medium improvements in quality-of-life scores, and high-certainty evidence that liraglutide and subcutaneous semaglutide were associated with small improvements in quality-of-life scores. There was high-certainty evidence that subcutaneous semaglutide and tirzepatide were effective in reducing fat mass with MD from baseline of -18.63% (95% CI -24.21 to -13.05 ; one randomized controlled trial, 1961 participants) and -25.70% (95% CI -31.53 to -19.87 ; one randomized controlled trial, 1273 participants), respectively. There was moderate-certainty evidence for liraglutide (MD -7.99% , 95% CI -11.30 to -4.67 ; three randomized controlled trials, 354 participants) and very-low-certainty evidence for exenatide (MD -4.19% , 95% CI -11.07 to 2.69 ; indirect evidence only) for this outcome. There was high-certainty evidence that subcutaneous semaglutide (MD -7.57% , 95% CI -11.57 to -3.57 ; one randomized controlled trial, 1961 participants) and tirzepatide (MD -8.30% , 95% CI -12.45 to -4.15 ; one randomized controlled trial, 1273 participants) were associated with reductions in lean mass from baseline.

Harms

Results of the systematic review and meta-analysis found that all GLP-1 receptor agonists and GLP-1/GIP dual agonists were associated with increased risk of discontinuation of treatment due to adverse events compared with lifestyle modification alone: beinaglutide RR 5.32, 95% CI 0.87 to 32.41 (two randomized controlled trials, 484 participants, very-low-certainty evidence); dulaglutide RR 1.02, 95% CI 0.44 to 2.40 (one randomized controlled trial, 91 participants, very-low-certainty evidence); exenatide RR 1.28, 95% CI 0.57 to 2.87 (three randomized controlled trials, 320 participants, low-certainty evidence); liraglutide RR 2.43, 95% CI 1.91 to 3.08 (24 randomized controlled trials, 7604 participants, high-certainty evidence); oral semaglutide RR 1.63, 95% CI 0.72 to 3.70 (one randomized controlled trial, 667 participants, moderate-certainty evidence); subcutaneous semaglutide RR 1.88, 95% CI 1.51 to 2.33 (18 randomized controlled trials, 24 021 participants, high-certainty evidence) and tirzepatide RR 1.91, 95% CI 1.41 to 2.58 (nine randomized controlled trials, 3492 participants, moderate-certainty evidence). For gastrointestinal events, the most harmful medicines were tirzepatide (RR 3.08, 95% CI 2.49 to 3.81; eight randomized controlled trials, 2913 participants, moderate-certainty evidence), oral semaglutide (RR 2.96, 95% CI 1.65 to 5.32; one randomized controlled trial, 667 participants, high-certainty evidence), liraglutide (RR 2.82, 95% CI 2.45 to 3.25; 25 randomized controlled trials, 7654 participants, moderate-certainty evidence) and subcutaneous semaglutide (RR 2.78, 95% CI 2.35 to 3.29; 14 randomized controlled trials, 5446 participants, moderate-certainty evidence). There was low-certainty evidence of increased risk of gastrointestinal events for beinaglutide, dulaglutide and exenatide compared with lifestyle modification alone. For the outcome of gall bladder-related disorders, GLP-1 receptor agonists and tirzepatide were no more harmful than lifestyle modification alone. The certainty of evidence was high for subcutaneous semaglutide and tirzepatide, moderate for liraglutide and oral semaglutide and low for dulaglutide. Similarly, for the outcome of fatigue, GLP-1 receptor agonists and tirzepatide were no more harmful than lifestyle modification alone. The certainty of evidence was high for subcutaneous semaglutide, moderate for liraglutide, oral semaglutide and tirzepatide, low for beinaglutide and dulaglutide, and very low for exenatide. Subcutaneous semaglutide had an RR of 0.78 (95% CI 0.46 to 1.33, high-certainty evidence) for pancreatitis. Liraglutide had an RR of 1.34 (95% CI 0.40 to 4.49, high-certainty evidence) and tirzepatide had an RR of 0.96 (95% CI 0.34 to 2.71, high-certainty evidence). Dulaglutide had an RR of 0.32 (95% CI 0.01 to 9.25, moderate-certainty evidence). In the SELECT trial of semaglutide in obesity without diabetes (8), serious adverse events were reported more frequently in the placebo group than the semaglutide group. Adverse events (any grade) leading to treatment discontinuation occurred more frequently in the semaglutide group than the placebo group (16.6% versus 8.2%). The most frequently reported adverse events leading to treatment discontinuation were gastrointestinal disorders.

Cost / cost effectiveness

The application identified two systematic reviews that evaluated the cost-effectiveness of liraglutide, semaglutide and other weight-loss interventions for obesity management in adults and adolescents (9, 10). Additionally, the application includes a summary of the United Kingdom's National Institute for Health and Care Excellence technology appraisal of tirzepatide (11). One review found that semaglutide offered more quality-adjusted life years and was associated with more costs compared with phentermine plus topiramate, phentermine monotherapy, and naltrexone plus bupropion. Incremental cost-effectiveness ratios exceeded willingness-to-pay thresholds. Semaglutide appeared to be cost-effective compared with diet and exercise and

liraglutide, but was not cost-effective compared with surgical interventions (sleeve gastrectomy, endoscopic sleeve gastroplasty and gastric bypass). The total cost of semaglutide in patients with class III obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) was reported as 409 571 United States dollars (US\$), while costs for endoscopic sleeve gastroplasty and sleeve gastrectomy were US\$ 183 355 and US\$ 188 844 respectively (9). A 2024 economic analysis found that semaglutide would need to have a three-fold reduction in its annual cost to not be dominated by endoscopic sleeve gastroplasty for patients with stage II obesity ($\text{BMI} 35\text{--}39.9 \text{ kg/m}^2$) (12). A 2025 Canadian study evaluated the cost-effectiveness of semaglutide in overweight or obese patients with pre-existing cardiovascular disease and without diabetes (13). In the base case, semaglutide had an incremental cost-effectiveness ratio of 72 962 Canadian dollars (Can\$) per quality-adjusted life year (QALY) gained compared with standard care. There was a 14% probability of semaglutide being cost-effective at a willingness-to-pay threshold of Can\$ 50 000. The incremental cost-effectiveness ratio was sensitive to the mortality benefit and medication cost. With a 50% price reduction, the resultant incremental cost-effectiveness ratio was Can\$ 37 724 per QALY gained, for which there was a 75% probability of being cost-effective at a willingness-to-pay threshold of Can\$ 50 000. The NICE appraisal found tirzepatide to have an acceptable incremental cost-effectiveness ratio as an option for managing overweight and obesity in adults, along with a reduced calorie diet and increased physical activity, only in the subgroup of patients with an initial BMI of $\geq 35 \text{ kg/m}^2$ and at least one weight-related comorbidity (11). A 2023 modelling study evaluated the cost-effectiveness of liraglutide, semaglutide, tirzepatide, naltrexone plus bupropion, and phentermine plus topiramate as treatments for obesity from a United States payer perspective (14). Over a lifetime horizon, all treatments had similar QALYs although it was slightly greater for tirzepatide. The medicines differed in cost from US\$ 118 900 for phentermine plus topiramate to US\$ 308 767 for semaglutide. The lifetime cost for tirzepatide was US\$ 234 084. The incremental cost-effectiveness ratio for tirzepatide relative to phentermine plus topiramate was US\$ 355 616 per QALY, exceeding the willingness-to-pay threshold of US\$ 150 000 per QALY. Sensitivity analyses indicated that the price of tirzepatide would need to be reduced by almost 40% to be cost-effective at this willingness-to-pay threshold. The application noted potential limitations of the cost-effectiveness studies including: short follow-up periods that limit insight into the sustainability of weight loss; predominance of studies in high-income countries, with limited representation of low- and middle-income settings; effect of high cost and adverse events on adherence and real-world outcomes; and underreporting of non-monetary benefits such as improved productivity and quality of life in the economic evaluations. The application reported monthly prices of semaglutide and tirzepatide in different countries ranging from US\$ 83 in France to US\$ 936 in the United States of America for semaglutide, and from US\$ 150 in the United Kingdom of Great Britain and Northern Ireland to US\$ 1 023 in the United States for tirzepatide.

WHO guidelines

As of May 2025, WHO guidelines on the use of and indications for GLP-1 RA and GLP-1 /GIP dual agonists in the treatment of adults with obesity were being developed. WHO convened the guideline development group on 7–9 April 2025, to be able to inform the Expert Committee. This group made a conditional recommendation for the use of GLP-1 and GLP-1/GIP dual agonists in the treatment of adults with obesity. The critical outcomes that informed this decision were weight, quality of life, adverse events, major adverse cardiovascular events and mortality. Publication of the guidelines is expected in the fourth quarter of 2025.

Availability

Subcutaneous semaglutide has regulatory and marketing approval for use in the treatment of obesity in many high-income countries, but regulatory approval and market availability in low- and middle-income countries is more limited and variable. Basic patent expiry is reported for March 2026. Biosimilars are not currently available, although they are in development in some countries (e.g. India). Liraglutide has regulatory and marketing approval for use in the treatment of obesity in many countries globally. Key patents are expected to expire in 2026. Some companies are already marketing biosimilar liraglutide in China, India and the United Kingdom (15). Tirzepatide has regulatory and marketing approval for use in the treatment of obesity in several high-income countries. Its availability is expected to expand globally as regulatory applications are approved in other settings. It remains under patent protection until at least 2030 and biosimilar competition is unlikely in the near future. Information on the availability of other GLP-1 receptor agonists was not provided in the application.

Other considerations

The Department of Nutrition and Food Safety reviewed and provided comments on the application. The technical unit supported the inclusion of GLP-1 receptor agonists and GLP-1/GIP dual agonists on the EML for the treatment of adults ≥ 19 years with obesity

when body mass index (BMI) is ≥ 30 kg/m². The Expert Committee considered two separate applications for GLP-1 receptor agonists: one for the treatment of adults with type 2 diabetes and established or at high-risk of cardiovascular disease, and one for the treatment of adults with obesity. While keeping the recommendations for the diabetes and obesity applications separate, the Expert Committee evaluated the applications together to better contrast possible differences between benefits and harms across the two conditions and to understand the implications of coverage for the two cohorts of patients at global, regional and national levels. The Committee also recalled that previous applications (in 2017, 2021 and 2023) for inclusion of GLP-1 receptor agonists for use in the treatment of diabetes had been evaluated and not recommended.

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