Application to add GLP-1 Receptor Agonists to the WHO Essential Medicines List for Adults

Sanjana Garimella
Yale New Haven Health

Micah Johnson
Brigham and Women's Hospital

Alyssa Grimshaw
Yale School of Medicine

Sandeep P. Kishore
University of California, San Francisco

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1. Summary statement of the proposal for inclusion.

The purpose of this application is to add the incretin based therapy of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) to the core list of the WHO Model of Essential Medications (EML) under a novel section of obesity with the indication of weight loss. The significant of this proposal is outlined below:

A. At present, there are no medications included in the EML that specifically target weight loss for the ongoing global burden of obesity. In the United States, the U.S Preventative Services Task Force included the recommendation of screening for adult obesity in 2012[1]. The WHO has described the global burden of obesity and since 2016, 39% of adults over the age of 18 were overweight with 13% of adults considered to be obese[2]. At this time, the EML includes mineral supplements for nutritional deficiencies yet it is also described that most of the population live in "countries where overweight and obesity kills more people than underweight"[2]. The WHO even state that obesity is preventable however the discrepancy is certainly highlighted when the EML does not include any medications to treat this chronic condition.
B. The use of GLP-1 RAs in the treatment of obesity has been well studied and meta analyses of various GLP-1 RAs have demonstrated that this class of medications can lead to clinically significant weight loss. Compared to control groups, GLP-1 RAs were found to lead to more significant weight loss with a mean difference of approximately 7.1 kg as well as an improvement in glycemic control, with low concern for hypoglycemia[3].
C. Obesity in and of itself is a risk factor for many non-communicable diseases, including type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) thus the other effects of GLP-1 RAs, including inhibition of gastric mobility pathways, decreased cardiovascular risk factors, decreased endothelial dysfunction, and protection against ischemia and reperfusion injury further support the utility of this drug class[4]. It is worth mentioning that SGLT-1 inhibitors, which have been adopted into the EML for cardiovascular disease reduction, have separate, but certainly important mechanims of action that cannot be compared to GLP-1 RAs for weight loss purposes. SGLT2 inhibitors work to improve ventricular loading, reduce cardiac fibrosis and renal hypoxia, and improve cardiac energetics however do not play a role in gastric mobility[4].
D. At present, both the United States' Federal Drug Administration (FDA) and the European Medicines Agency (EDA) have approved liraglutide for long term chronic weight management [5, 6]. The FDA has approved liraglutide as one five medications for long term chronic weight management
E. At current prices, available cost-effectiveness studies on the use of GLP-1 RAs for obesity have yielded mixed results, with some analyses (notably NICE in the UK) finding these agents to be cost-effective and other analyses recommending price reductions to meet cost-effectiveness benchmarks [7]. Notably, drug compound patents on liraglutide have recently expired in China and Japan and are set to expire in 2023 in the US and Germany, indicating that lower-priced generics or biosimilars may soon become available to make these agents cost-effective in a wider set of contexts.

2. Relevant WHO technical department and focal point (if applicable).

- **Department of Non-Communicable Diseases**
  - https://www.who.int/health-topics/noncommunicable-diseases#tab=tab_1
- **Department of Nutrition and Food Safety**
  - https://www.who.int/teams/nutrition-and-food-safety/safe-healthy-and-sustainable-diets

3. Name of organization(s) consulted and/or supporting the application.

None

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

Category: A10B Blood Glucose Lowering Drugs, excluding insulin

https://www.whocc.no/atc_ddd_index/?code=A10BJ02
INN: Liraglutide
ATC code : A10BJ02
DDD 0.6
U mg
Adm.R P
DrugBank : https://go.drugbank.com/drugs/DB06655

5. Dose forms(s) and strength(s)proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

SC: 0.6-3.0 mg daily

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

We are requesting the addition of liraglutide as representative of the GLP-1 receptor agonist pharmacologic class to the EML.

7. Treatment details (requirements for diagnosis, treatment and monitoring).

Obesity, a preventable disease, is defined as excess body weight for height with the most commonly used classification method being body mass index (BMI) which is body weight in kilograms divided by height in meters, squared [8]. The threshold for obesity is that of a BMI >30 with further in class classes of class 1 obesity (BMI 30.00-34.99), class II obesity (BMI 35.00 – 39.99), and class III, or morbid, obesity (BMI >40.00) [8].

At present, there are two indications to start liraglutide, the representative medication being considered for this drug class, which include treatment for type 2 diabetes mellitus and chronic weight management [9]. When used in supplement to life style modifications, including a decrease in caloric intake and an increase in exercise, liraglutide is indicated for adults with obesity (BMI >30.00) or overweight (BMI >27.00) with a weight-related comorbidity. Weight related comorbidities include dyslipidemia, type 2 diabetes mellitus (T2DM), and hypertension. For weight loss, subcutaneous dosing initially begins at 0.6 mg once daily for one week, following the first week, dose is increased by 0.6 mg daily at weekly intervals for a goal of 3 mg once daily [9, 10]. Typically, the dose escalation is well tolerated however if a patient is unable to tolerate the ramp up, dose escalation can be deferred for one week. After twelve weeks at the maximum tolerated dose, or after sixteen weeks after initiating the medication, weight is re-evaluated; if there is not a decrease of at least 4-5% of baseline body weight, the medication can be discontinued [10, 11]

Side effects of liraglutide include hypoglycemia (in 2% of adults without T2DM and 13-28% in adults with other treatment for T2DM), increased heart rate of >10 beats per minute (34%), local injection site reactions (1-14%) and most commonly, GI disturbance. The most common side effect is nausea (39-42%) followed by diarrhea (21-22%)[9].

The only strict contraindications to liraglutide are prior serious hypersensitivity to liraglutide, a personal or family history of medullary thyroid cancer, a personal history of multiple endocrine neoplasia syndrome type 2 (MEN2), and pregnancy[9].

When a patient is initiated on liraglutide, heart rate, renal function, plasma glucose, a lipid panel, signs of pancreatitis and gall bladder disease, signs of worsening depression, and body weight should be checked [9]. Follow up body weight at the twelve and sixteen week mark should also be checked to determine continuity of the medication.

Table 1. Excerpts from national and international guidelines on the pharmacological treatment of obesity

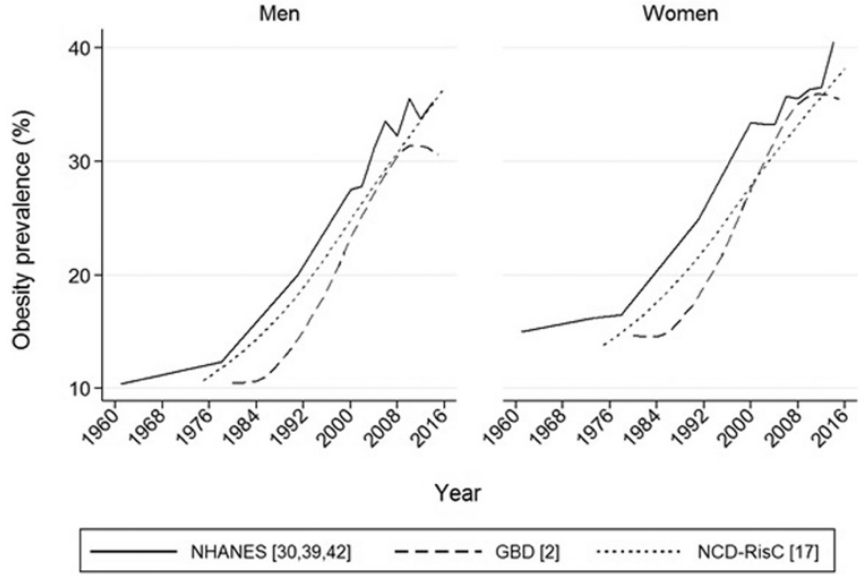
Source	Year	Excerpt
American College of Cardiology [12, 13]	2021	"..GLP-1 receptor agonists are used in patients with type 2 diabetes as glucose-lowering therapies, with additional benefits of weight loss and blood pressure reduction."
South Asian Task Force [14]	2019	"GLP-1 RAs are associated with weight loss benefits which might be due to suppressed appetite, reduced body fat or improved endothelial function (Grade A; EL 1)"
International Diabetes Federation[15]	2017	"A GLP1 receptor agonist may also be considered if there is a concern about an insufficient rate of weight loss.
National Institute for Health and Care Excellence (NICE)[16]	2022	"recommending semaglutide (also known as Wegovy and made by Novo Nordisk) to adults with at least one weight-related condition and a body mass index (BMI) of at least 35 kg/m2, and exceptionally, to people with a BMI of 30.0 kg/m2 to 34.9 kg/m2."
Position statement from the Brazilian Diabetes Society (SBD), the Brazilian Cardiology Society (SBC) and the Brazilian Endocrinology and Metabolism Society (SBEM) [17]	2017	"GLP-1 analogues were associated with a significant decrease in body weight compared with placebo"
Korean Society for the Study of Obesity Guidelines for the Management of Obesity in Korea [18]	2020	"…four types of obesity treatments have been approved for long-term administration in Korea: orlistat (Xenical), naltrexone-bupropion (Contrave), liraglutide (Saxenda), and phentermine-topiramate (Qsymia).31 These drugs have been approved for use in the treatment of obesity based on the results of clinical studies on long-term use"
European Medical Association [19]	2015	"The intended dose for its use in weight management is 3 mg to be administered as an injection once a day. Its active substance, liraglutide, is currently approved in the European Union (EU) under the trade name Victoza for the treatment of type 2 diabetes at lower doses up to 1.8 mg per day."
Australia: NPS Medicine Wise [20]	2022	"There are several drugs for weight loss available in Australia…Liraglutide is a glucagon-like peptide-1 (GLP-1) agonist with a hunger-suppressing action. It requires a daily

		injection with a starting dose of 0.6 mg…The dose can be slowly increased up to 3 mg daily, if required."
Singapore HPB-MOH Clinical Practice Guidelines [21]	2016	"Liraglutide may be used for weight management up to 2 years while orlistat may be used as an anti-obesity drug for long-term therapy (up to 4 years). Grade A, Level 1+"
Canadian Medical Association Journal-Obesity in adults: a clinical practice guideline [22]	2020	"Pharmacotherapy for weight loss can be used for persons with BMI ≥ 30 kg/m2 or BMI ≥ 27 kg/m2 with adiposity-related complications, in conjunction with medical nutrition therapy, physical activity and psychological interventions (liraglutide 3.0 mg...)"

8. Information supporting the public health relevance.

What was once thought to be a problem of high income countries, obesity has become a rising issue in low and middle income countries. Furthermore, not only is the prevalence of obesity increasing, but the number of global deaths attributed to BMI has substantially increased from 1990 to 2017 (Figure 1) [23]. The global burden of disease of obesity study also found that though the age-standardized rate of high BMI related disability adjusted life years (DALY) increased by 12.7% for females and 26.8% for males, the actual global number of high BMI DALYs has doubled, despite sex [23]. Obesity also plays a role in health care related costs; for patients and families, total healthcare costs for patients with obesity were higher than that of patients who are overweight [24].

Figure 1: Trends in US adult obesity prevalence based on data from the National Health and Nutrition Survey (NHANES), and US data included in the Global Burden of Disease (GBD), the NCD Risk Factor Collaborations (NCD-RisC). [23, 25]



The obesity pandemic is by no means a new problem. In fact, obesity was discussed during the 2004 World Health Assembly at which point stake holders were called upon in local and regional settings to improve exercise and nutrition in order to decrease obesity. The Sustainable Development Goals (SDG) include reducing preventable deaths; specifically, SDG 3.4 includes the goal of reducing by one-third premature mortality from noncommunicable diseases through prevention and treatment by 2030. Given the global burden of obesity and the goal of reducing preventable disease related deaths, it is evident that affordable and available pharmacotherapy for obesity is needed on a global level.

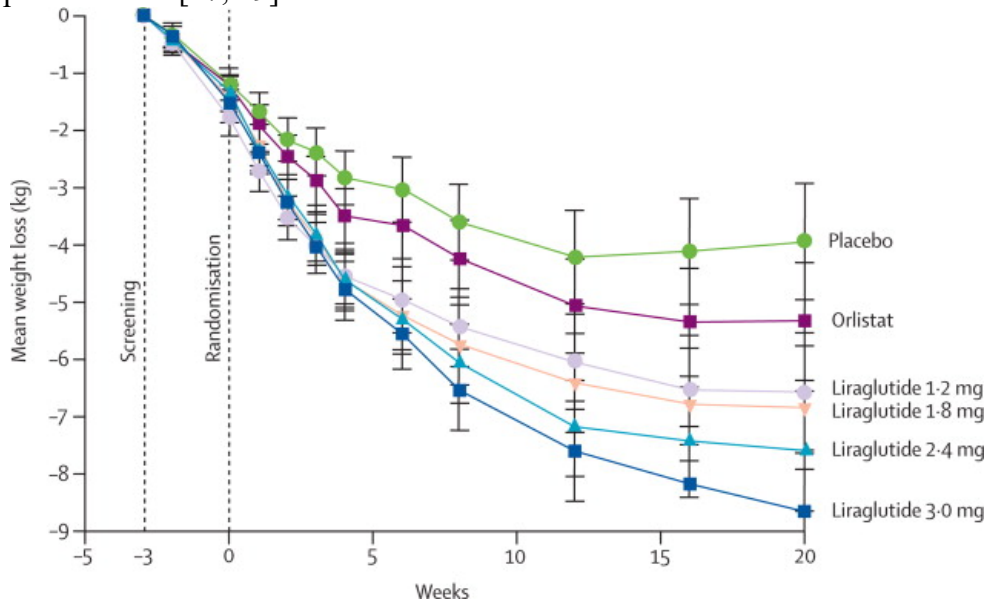
9. Review of harms and benefits

9.1 Summary of evidence of comparative effectiveness

Liraglutide was first approved as a medication for T2DM in 2009 in Europe and in 2010 in the USA[26]. Then, in 2014, the Food and Drug Administration (FDA) approved Liraglutide for the treatment of chronic weight management followed closely by approval from the European Medicines Agency (EMA) in 2015. Liraglutide, and all GLP-1 receptor agonists, cause a directly proportional increase in insulin secretion based on glucose increase, decreases glucagon secretion and inhibits appetite [26]. Liraglutide is a long acting human incretin hormone analog, specifically of glucagon-like peptide-1; thus, similar to other medications in the same class, liraglutide works by stimulating the secretion of insulin and decreasing glucagon secretion, all based on glucose levels [27]. Additionally, gastric motility is slowed and appetite is depressed via an anorectic effect in the arcuate nucleus of the brain [27]. The weight loss effects of liraglutide are thought to be due to decreases in diastolic blood pressure, waist circumference, and an increase in HDL[28].

The first study to assess the efficacy of Liraglutide in patients without T2DM was a randomized, double blind, placebo controlled study in which 19 separate sites in Europe were included[29]. In this study, all subjects had a 500 Calorie dietary deficit and an increase in physical activity. Overall, the group on liraglutide lost significantly significant ($p = 0.003$) more weight than their placebo counterparts, losing 2.1 kg (95% CI 0.6-3.6) to 4.4 kg (CI 6.9-6.0) greater than the placebo group. Furthermore, the weight loss experienced was found to be dose dependent (Figure 2).

Figure 2: Change in bodyweight with liraglutide 1 · 2–3 · 0 mg subcutaneously daily, orlistat 120 mg three times a day orally, or placebo, in addition to lifestyle intervention in obese individuals without type 2 diabetes.[27, 29]

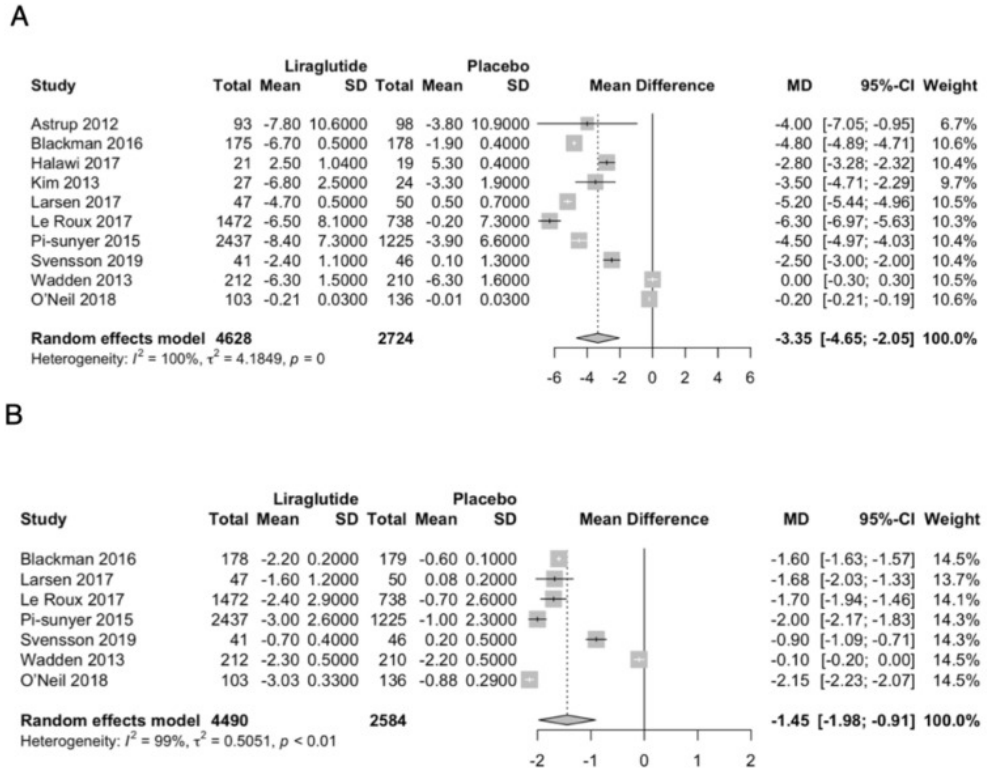


Prior to FDA approval, liraglutide was studied in the series six phase III LEAD studies [30-33]. In these studies, there was evidence of HbA1c reduction as well as reduction in body weight of 1-3 kg with the 1.2 mg daily dose and 2-3.4 kg weight loss in the 1.8 mg daily dose group[27].

Meta-Analysis and Systematic Review Findings

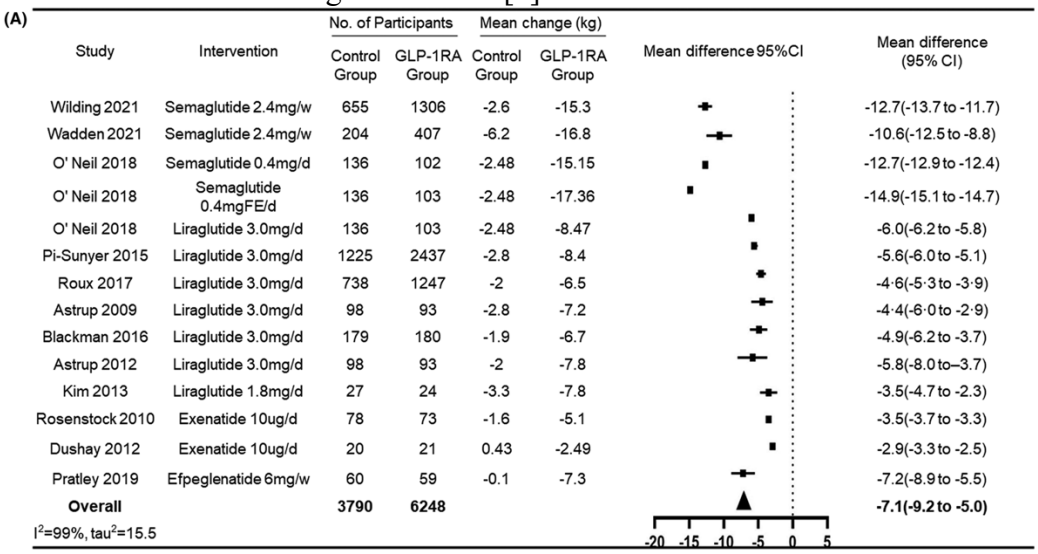
In continued assessment of the safety and efficacy of GLP-1 receptor agonists, a systematic review and meta-analysis was conducted in 2022, published in the Journal of Clinical Medicine[34]. In this study, six databases were reviewed and after review of inclusion criteria (including randomized controlled trial, adults without type 1 or type 2 diabetes, and liraglutide versus placebo) and exclusion criteria (observational studies, systematic reviews, case studies, and abstracts), twelve studies were assessed which was a total of 8,249 patients. The primary outcome that was assessed in this meta-analysis included a reduction in BMI and weight loss. Overall, liraglutide significantly reduced BMI by mean difference -1.45 (95% confidence interval (CI), -1.98 to -0.9, $p<0.0001$) and significantly reduced body weight by -3.35 kg (95% CI -4.65 to -2.05, $p<0.0001$) (Figure 3).

Figure 3: Forest Plot of Primary Outcomes in Journal of Clinical Medicine Meta- Analysis [34]



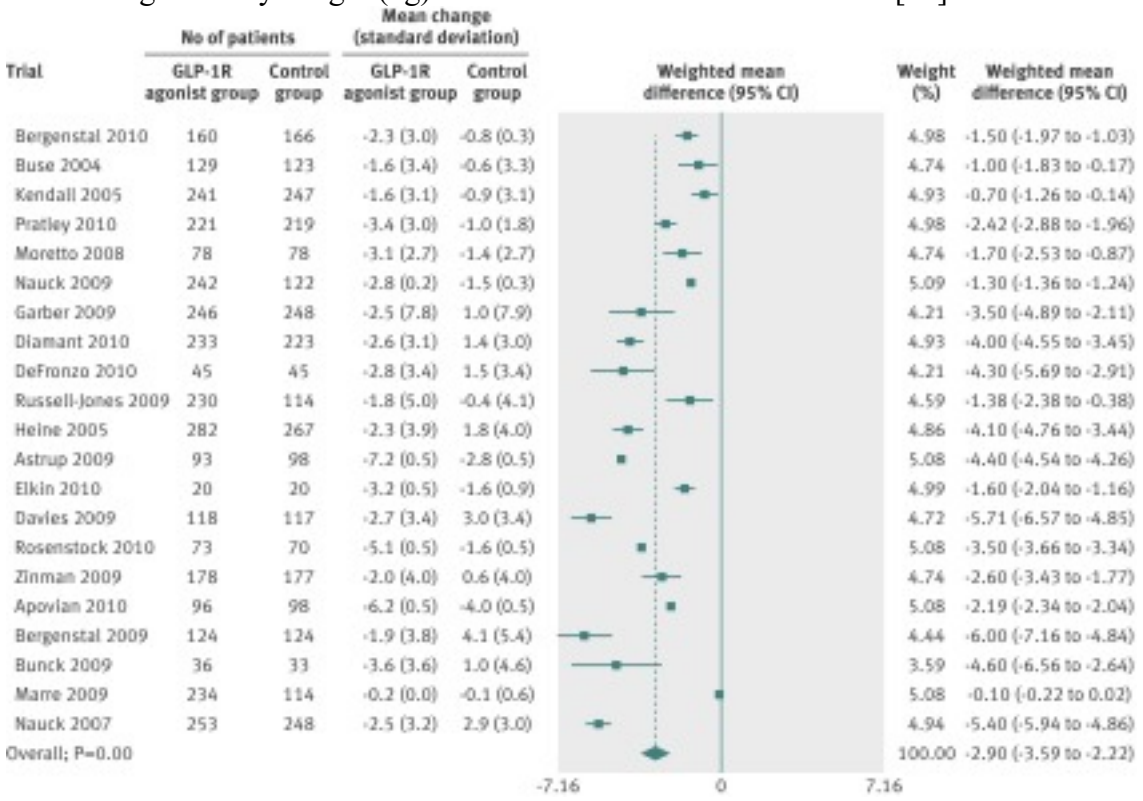
In another meta-analysis, this time with the research group based in Hunan, China, similar results were found [3]. In this study, PubMed and Embase were searched with the inclusion criteria being the following four restrictions: randomized controlled trials were the only study design included, the trial population was ≥ 18 years of age, BMI ≥30 or 27 with treated or untreated obesity related comorbidities, and studies investigating GLP-1 receptor agonist induced changes in body weight were excluded if the trial participants were diagnosed with type 1 or type 2 diabetes or participants who had drug induced obesity. Thus, after elimination, twelve studies were included which composed of 11,459 participants. Overall, compared to the control groups, there was a significant loss of weight in the groups with GLP-1 receptor agonists with a mean difference of -7.1 kg (95% CI, -9.2 to -5.0) (Figure 4). Secondary outcomes assessed in this study, which speak to the safety and efficacy of GLP-1 receptor agonists, demonstrated improved glycemic control without hypoglycemic events, and improved blood pressure, LDL, HDL, and triglycerides.

Figure 4: Mean Difference in weight reduction [3]



In another large scale systematic review and meta-analysis, published in the British Medical Journal, weight loss was assessed in overweight and obese patients [35]. In this meta-analysis, 25 trials were included, each trial including a mean number of 68 clinical trial sites. Similar to prior analysis, only randomized controlled trials were included but in this study, adults with a BMI greater than 25 were included, with or without type 2 diabetes. All trials resulted in weight loss however using a random effects meta-analysis with 3395 participants randomly assigned to GLP-1 receptor agonists and 3016 participants assigned to control groups, using 21 of the trials, the mean reduction of body weight for those on a GLP-1 receptor agonist ranged from -7.2 to -0.2 kg. Furthermore, the weight mean change in body weight was -2.9 kg (95% CI -3.6 to -2.2) compared to the control group (Figure 5). Subgroup analysis showed that there was greater weight loss when higher doses of GLP-1 receptor agonists were used and most importantly, weight loss was seen in patient both with diabetes (-2.8 kg, 95%CI -3.4 to -2.3) and without diabetes (-3.2 kg, 95% CI -4.3 to -2.1).

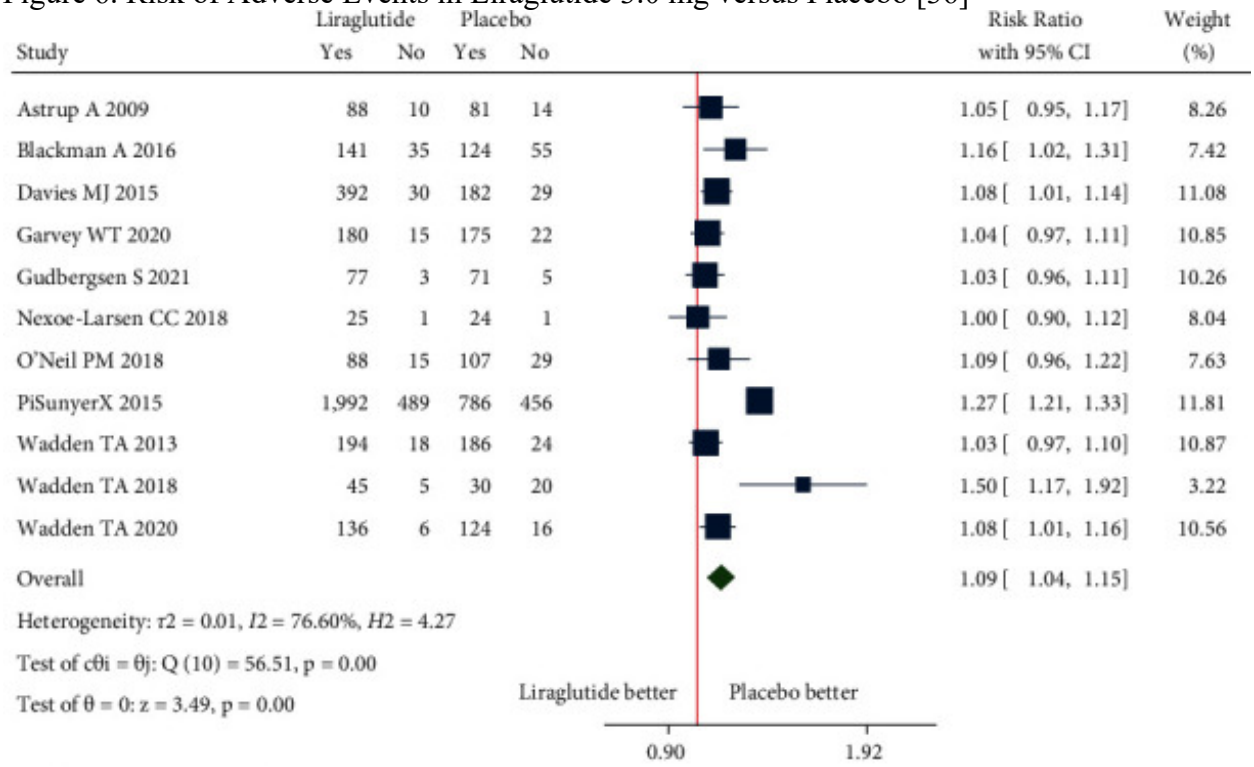
Figure 5: Change in body weight (kg) after at least 20 weeks of treatment [35]



9.2 Summary of evidence of safety and harms

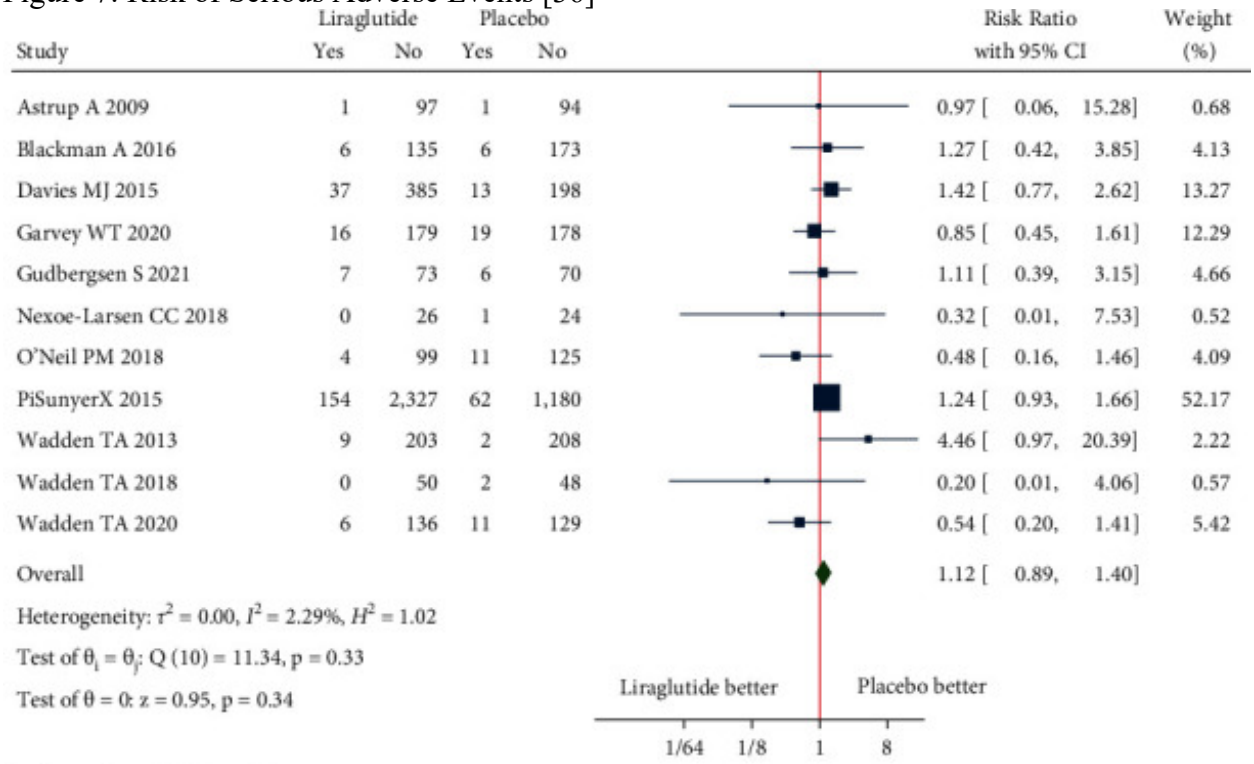
The safety profile of GLP-1 receptor agonists is also well studied. In 2022, the International Journal of Clinical Medicine published a systematic review and meta-analysis of the safety and efficacy of Liraglutide specifically [36]. After selecting for randomized controlled trials that evaluated 3.0 mg liraglutide against placebo in overweight (BMI ≥27 to 30) and obese (BMI ≥30) adults, 14 studies were included. Of these studies, twelve were specific to patients without type 2 diabetes. The safety outcome measures looked at the proportion of patients who experiences adverse events, serious adverse events, and treatment discontinuation due to adverse events (TDAEs). Of the 14 studies, 11 studies included the proportion of participants with adverse events or serious adverse events and five studies included TDAEs. In nondiabetic patients, the pooled estimate of nine studies revealed a significant proportion of patients experiencing adverse events in the liraglutide 3.0 mg group (RR = 1.11, 95% CI= 1.04 to 1.18, p=0.00) when compared to placebo, [Figure 6]. For serious adverse events, liraglutide 3.0 mg had a similar risk of compared to placebo (RR = 1.12, 95% CI = 0.89 to 1.40, p=0.33), [Figure 7]. And finally, of the five studies including TDAEs, there was a similar risk of TDAEs of liraglutide 3.0 to (RR = 1.14, 95% CI = 0.50 to2.60, p=0.01), (Figure 8).

Figure 6. Risk of Adverse Events in Liraglutide 3.0 mg versus Placebo [36]



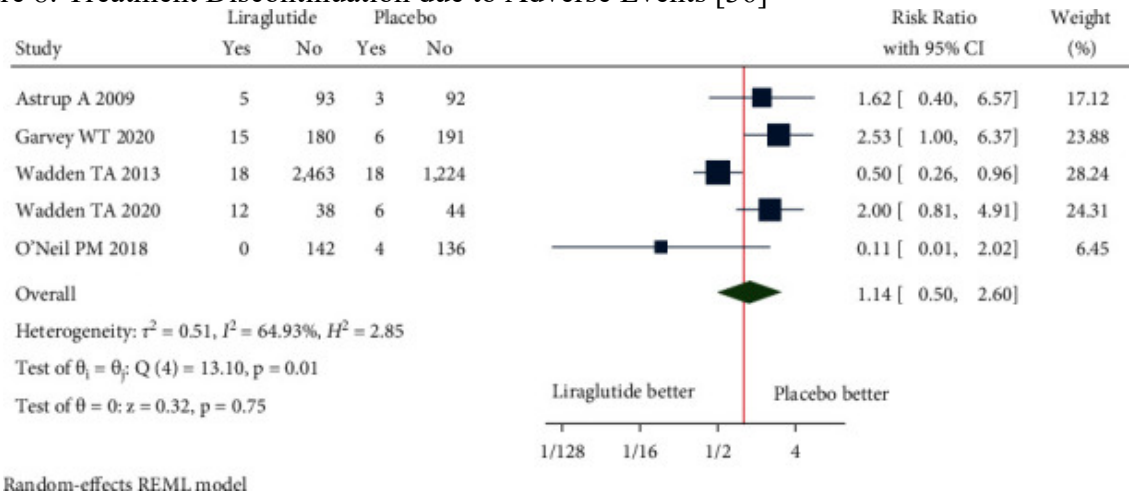
Random-effects REML model

Figure 7: Risk of Serious Adverse Events [36]



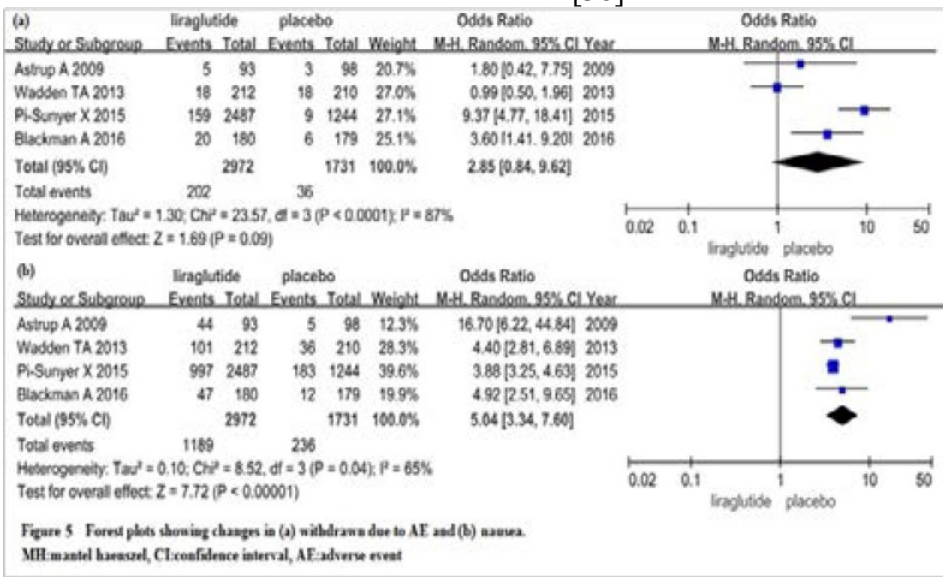
Random-effects REML model

Figure 8: Treatment Discontinuation due to Adverse Events [36]



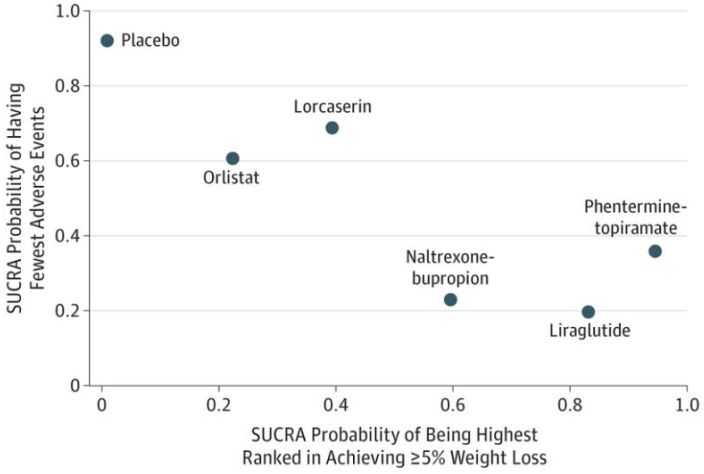
Another meta-analysis, this time published in the Journal of African Health Sciences, also investigated the safety of liraglutide [37]. In this analysis, a literature review looked for randomized controlled trials using liraglutide for treating obesity in non-diabetic patients. EMBASE, MEDLINE, and Cochrane were included and five publications, encompassing 4,754 patients, with sites including Europe, North America, South America, Asia, Africa, and Australia were reviewed. Four of the randomized controlled trials included the proportion of participants who had withdrawn due to adverse events, which is representative of 4.703 participants: 2,972 in the liraglutide group and 1,731 in the placebo group, (Figure 9). The random effects estimate of the odds ratio was 2.85 (95% CI= 0.84 to 9.62, p=0.09) thus suggesting that the incidence of withdrawing from the study due to adverse events was similar in the placebo and liraglutide groups. They further studied nausea specifically and found that in the four trials studies (accounting for 4,703 participants: 2,972 in the liraglutide group and 1,731 in the placebo group), nausea was more common in those being treated with liraglutide compared to placebo (OR 5.04, 95% CI =3.34 to 7.6, p<0.00001), (Figure 9).

Figure 9: Withdrawal due to adverse events and nausea. [38]



In another study, published in JAMA, a systematic review assessing multiple pharmacological treatments for obesity assessed for efficacy of weight loss and adverse events [39]. A systematic review and network meta-analysis was conducted which included randomized clinical trials in overweight and obese adults who were being treated for at least one year by one of the US Food and Drug Administration–approved long-term weight loss agents: orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, or liraglutide. Notably in this study, compared to placebo, liraglutide (OR 2.95, 95% CI= 2.11to 4.23) and naltrexone-bupropion (OR 2.64, 95% CI= 2.10 to 3.35) demonstrated higher odds of adverse event related discontinuation of treatment. A surface under the cumulative rankings score was done (with numbers between 0 to 1 representing the probability of being ranked the highest) and for adverse outcomes, the higher scores are represented by lower likelihood of TDAEs, once again showing liraglutide ranking higher for TDAEs (Figure 10) [39].

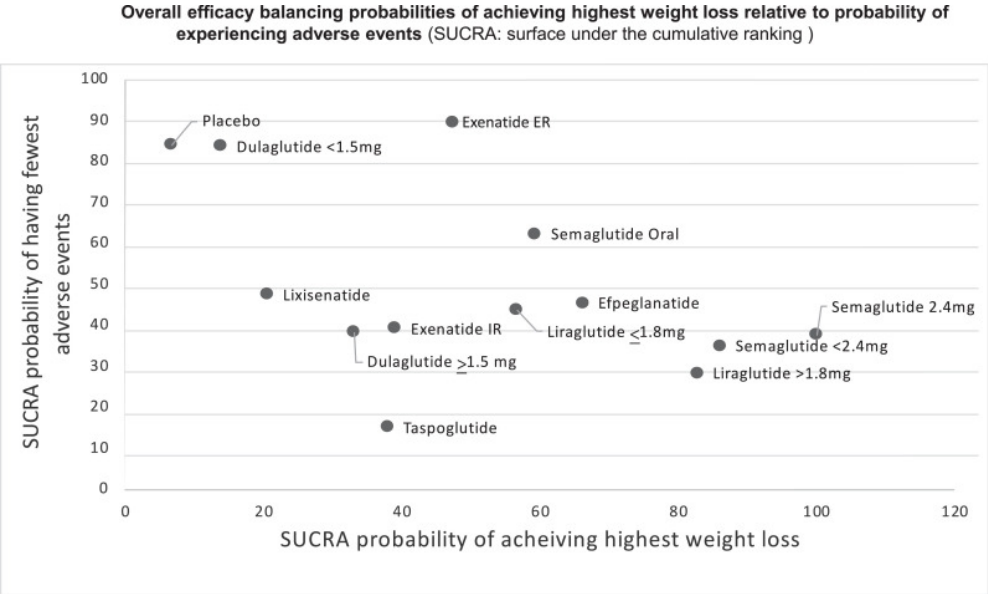
Figure 10: SUCRA for both Weight Loss and Adverse Outcomes in FDA approved pharmacotherapy [39]



	Placebo	Orlistat	Lorcaserin	Naltrexone-bupropion	Liraglutide	Phentermine-topiramate
Weight loss rank (95% CrI)	6 (6-6)	5 (4-5)	4 (3-5)	3 (2-4)	2 (2-3)	1 (1-1)
Adverse event rank (95% CrI)	1 (1-1)	3 (2-4)	2 (2-3)	5 (5-6)	6 (4-6)	4 (3-6)

Finally, as a part of the Lancet's Discovery Science journal, published last year was a systematic review and network meta-analysis investigating GLP-1 receptor agonists in obesity for use of weight loss and related adverse events [40]. 64 randomized controlled trials (from 2004 to 2021) encompassing 27,018 patients were included and weight loss efficacy as well as TDAEs were assessed. The network meta-analysis showed that there was a higher probability of TDAE in taspoglutide (SUCRA 15.1) and liraglutide (greater than 1.8 mg dosing) (SUCRA 28.3) (Figure 11) [40].

Figure 11. SUCRA for Weight Loss and Adverse Events in GLP-1 analogs and receptor agonists. [40]



9.3 Search strategy and identified studies

A literature review was performed for randomized controlled trials and meta-analyses on efficacy and safety, harms and toxicity, and cost of liraglutide for treatment of obesity through September 2022 in Ovid, Embase, and MEDLINE.

10. Comparative cost-effectiveness

Literature search identified several rigorous studies on the cost-effectiveness of liraglutide and semaglutide for the treatment of obesity. Of note, this literature is smaller than the analogous literature examining the cost-effectiveness of GLP-1 RAs for the treatment of diabetes, and the analyses have generally been performed only for high-income countries.

In the UK context, the National Institute for Health and Care Excellence (NICE) published a technology appraisal of liraglutide for managing obesity in December 2020, focusing on the subgroup of patients with BMI of 35 or higher, prediabetes (non-diabetic hyperglycemia), and a high risk of cardiovascular disease [16]. At the chosen threshold of £20,000 per quality-adjusted life year (QALY) gained, the report concluded that liraglutide is cost-effective for the management of obesity. Specifically, the ICER for liraglutide plus diet and exercise compared with diet and exercise alone was £11,293- £13,569 per QALY gained.

NICE also published a report on semaglutide for obesity treatment in June 2022 [41]. For the population of people with a BMI of 30 or higher with at least one weight-related comorbidity, semaglutide was cost-effective with an ICER estimated at £14,827- £16,337 per QALY gained.

A report by the Canadian Agency for Drugs and Technologies in Health (CADTH) found that compared to standard care, the ICER for liraglutide was $196,876 per QALY gained, and that the

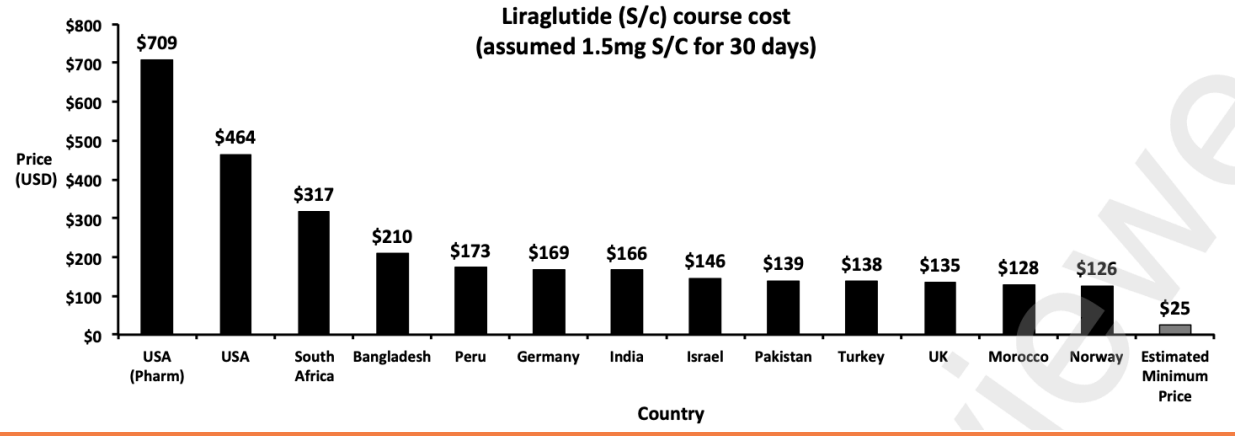
price of liraglutide would need to decrease by at least 62% to achieve cost-effectiveness at a $50,000 per QALY threshold [7].

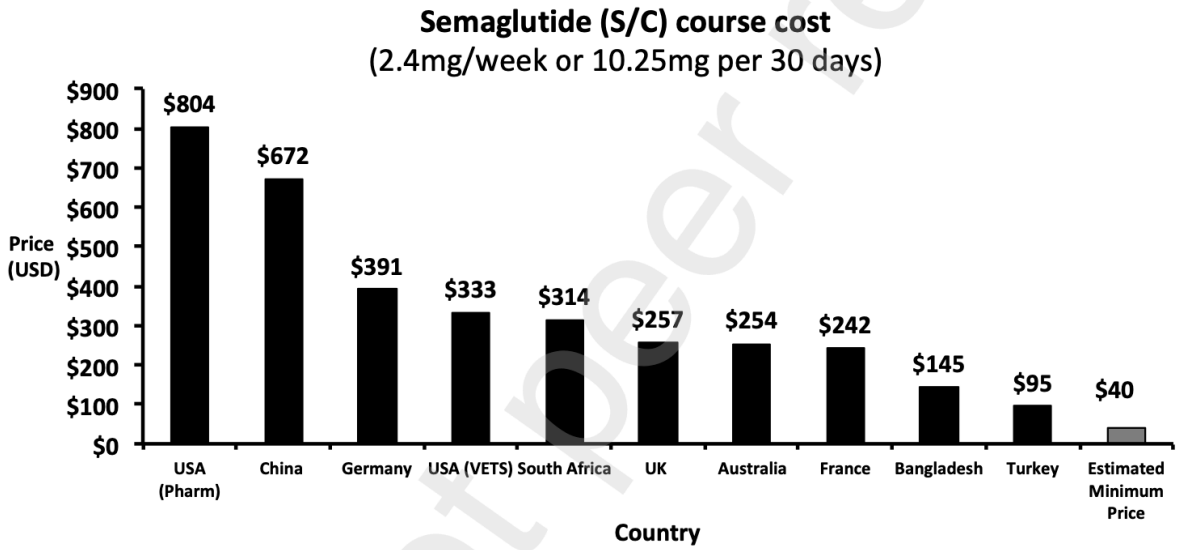
In the US context, the Institute for Clinical and Economic Review released a report on the effectiveness and value of medications for obesity management in October 2022 [42]. The report concluded that U.S. prices would need to decrease for semaglutide and liraglutide to meet cost-effectiveness benchmarks. Specifically, to achieve ICERs between $100,000 and $150,000 per QALY or evLY gained, the health-benefit price benchmark range for semaglutide was estimated as $7500 - $9800 per year, which would require a discount of 28-45% from the current US net price.

An independent analysis by Hu et al (2022) found that semaglutide was cost-effective in a US context, with an ICER of $135,467 per QALY gained [38]. A manufacturer-sponsored analysis (Kim, 2022) reported that semaglutide was cost-effective over a 30-year time horizon, with an ICER of $122,549 per QALY gained when compared to diet and exercise (and an ICER of $27,113 when compared to no treatment) [43].

10.1 Summary of costs

Figure 12: A preprint study from Levi at al (2022) used publicly available sources to estimate standardized 30-day treatment costs for liraglutide and semaglutide. [44]





Importantly, patents for liraglutide have begun to expire, as detailed in Section 11 below. Cost-effectiveness studies to date have been based on prices of the branded product without generic competition. Generic or biosimilar versions of liraglutide are expected to bring price reductions – for instance, Robinson and Jarrion (2021) studied three important biologic medications in the French national health system and found that biosimilar entry was associated with substantial price reductions. Lower prices for liraglutide will improve its cost-effectiveness for obesity treatment.

11. Summary of regulatory status and market availability of the medicine.

Regulatory status of subcutaneous Liraglutide daily injection

Liraglutide, currently sold under the brand name Victoza, has been approved by the United States FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. It has also been launched in Germany, Italy, Denmark, the Netherlands, Sweden, Japan, Canada, the United States, France, Indonesia, Malaysia and Singapore.

Patent and Exclusivity

According to a report released by the manufacturer, the drug compound patent for liraglutide has expired in China and Japan as of February 2022, and is set to expire in 2023 in the United States and Germany. The manufacturer reports that generic versions of liraglutide could be available in the United States from June 2024.[45]

12. Availability of pharmacopoeial standards

At present, liraglutide is not included in the United States Pharmacopoeia, the British Pharmacopoeia, nor the WHO's International Pharmacopoeia.

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