Cost-effectiveness analysis of liraglutide for obesity treatment in Colombia.

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ABSTRACT

Research question Is liraglutide treatment cost-effective for adult obese patients in Colombia?

Type of economic evaluation Cost-effectiveness study**.**

Alternatives and comparators For the present study, pharmacological treatment with orlistat, and changes in diet and exercise habits are determined.

Target population Adult patients between 18 and 64 years of age with overweight and obesity, defined as a body mass index equal to or greater than 25 kg / mt2.

Time horizon One year.

Design of the model Decision tree model.

Perspective General System of Social Security in Health (SGSSS).

Discount rate No discount rate is applied since the time horizon is one year.

Data sources of effectiveness and safety with Randomized clinical trials and systematic reviews of the literature.

Outcomes and assessment Decrease in BMI equal to or greater than 10% compared to the initial.

Complications from obesity, for this study, type 2 diabetes mellitus will be evaluated.

Costs included Medication costs, procedural costs.

Cost data sources SISMED, ISS Tariff Manual 2001.

Modeling Success outcomes 10% decrease in BMI and absence of complications from obesity.

Base case results The use of liraglutide treatment for the management of patients with obesity in Colombia is a more effective but more expensive strategy, with an Incremental Cost-Effectiveness Ratio (ICER) of $ 36,858,100, changes in habits associated with diet and exercise are less expensive but less effective.

Deterministic univariate sensitivity analysis The probability of a decrease in BMI with liraglutide impacts 71.09%, followed by a decrease in the risk factor associated with obesity DM2, which impacts 14.24%, and thirdly the cost of liraglutide treatment with 12.87%.

These three variables in a grouping are equal to 98.2% of the uncertainty of the ICER.

Discussion Liraglutide treatment is more effective and more expensive than the two comparators. It is possible to plan new economic evaluation studies that evaluate liraglutide's pharmacological scheme, taking into account adverse drug reactions and additional data.

KEYWORDS

Overweight, obesity, liraglutide, epidemiology, cost-effectiveness evaluation.

1. INTRODUCTION

Obesity is a public health problem, which has continued growing in Colombia and the world. It estimated that approximately a third of the world population is overweight and obese (1) (2). In Colombia, more than half of adults between 18 and 64 years old (56%) were overweight and obese in 2015, increasing more than 10 points compared to 2005 (45.9%) according to the National Survey on the Nutritional Situation (ENSIN) (3).

The gradual increase in the incidence and prevalence of obesity in the world context has brought multiple events, including its recognition as an independent nosological entity and its identification as a public health problem (4).

The World Health Organization (WHO) defines obesity and being overweight as an abnormal or excessive accumulation of fat that can be harmful to health. One way to measure obesity and the most widely used globally is the body mass index (BMI); BMI is the weight of a person in kilograms divided by the square of the height in meters (5). A person with a BMI equal to or less than 18.5 is considered underweight, BMI between 18.5-24.9 healthy weight, BMI between 25.0-29.9 overweight, BMI 30.0-34.9 degree obesity I, BMI 35.0-39.9 obesity grade II, BMI equal to or greater than 40 obesity grade III (6).

The progressive increase in the prevalence of overweight and obesity is associated with the increase in other chronic pathologies such as cardiovascular diseases, type 2 diabetes mellitus, osteoarticular, gastrointestinal diseases, metabolic syndrome, some types of cancer, and high blood pressure, among

which found the first causes of morbidity and general mortality. All diseases have an associated economic impact, some with more significant influence than others. In this case, obesity is related to lost productivity, decreased quality of life, absenteeism from work, shorter life expectancy, and increased expenses doctors secondary to the disease (7).

Several components influence the epidemiological behavior of overweight and obesity, such as genetic, metabolic, sociocultural, economic, political, and ethnic aspects.

Given the high prevalence of overweight and obesity, which in recent decades have considered as an independent pathology and not only as a risk of suffering from other pathologies, the therapeutic approach should be evaluated and, likewise, redirected, taking as one of the main pillars for the intervention are modifiable risk factors, as well as adequate healthy lifestyle practices, eating habits, physical activity, and in cases that require complementary pharmacological or surgical management.

There are several approved interventions for weight loss, including different medications, therapies, targeted programs for weight loss and optimizing healthy lifestyle habits focused on diet and exercise, invasive and surgical procedures, for which not only its effectiveness should consider, but if they are cost-effective for the study population (8).

Weight-loss interventions should aim to improve or decrease the risk of different obesity-related conditions, especially cardiovascular risk factors (8). Just as it is a

multifactorial and highly complex disease, the therapeutic approach should direct in a multidisciplinary way, knowing a priori that a single intervention for a short time is not enough, but, on the contrary, it must do once. The therapeutic choice is consistent and disciplined over time, and the multidisciplinary team chosen follows periodic controls for the required time, even more so if, in the first instance, the chosen treatment changes in diet and exercise habits, for which, without any doubt, the discipline and collaboration of the patient are decisive in the future results, as well as to ensure that the weight loss is permanent over time.

Liraglutide belongs to the group similar analogs to glucagon GLP-1. The mechanism of action is to stimulate insulin secretion, inhibit the release of glucagon, and produce a decrease in gastric emptying, which increases the feeling of satiety and decreases the perception of hunger.

Liraglutide initially was developed and approved for the treatment of patients with type 2 diabetes mellitus. However, it subsequently studied for the treatment of patients with obesity due to its effect on weight loss in addition to its effect on glycemic control (9).

The FDA approved liraglutide at a dose of 3 mg daily in 2014 for the management of obesity. This medicine should administer subcutaneously once a day, the recommended starting dose is 0.6 mg daily for the first week, and gradually increase 0.6 mg weekly until reaching the dose of 3 mg daily. Liraglutide should discontinue if a 5% decrease in total body weight has not achieved after 12 weeks of treatment at a dose of 3 mg daily (10).

The FDA approved Orlistat in 1999; it is indicated for the management of obesity in weight loss and its maintenance when used in conjunction with a low-calorie nutritional plan (10). The mechanism of action of Orlistat is associated with the inhibition of gastric and pancreatic lipases, preventing the formation of monoglyceride fatty acids, resulting in a reduction in the absorption of lipids from ingestion by up to 30% (11). Several studies have concluded that Orlistat is an effective treatment to reduce weight, improve the lipid profile, and achieve glycemic control (12).

The purpose of the study is to estimate the cost-effectiveness of liraglutide treatment, versus changes in habits associated with diet and exercise or pharmacological treatment with orlistat for obesity management in Colombia.

2. INVESTIGATION QUESTION

In the Gil-Rojas et al., in the year of the disease burden attributable to overweight and obesity in Colombia in 2019, it concluded that overweight and obesity are associated with more significant disability and mortality, defining that the main conditions with the most extended disability-adjusted life years (DALYs). Attributable to this condition is high blood pressure, type 2 diabetes mellitus, and ischemic heart disease, which with effective interventions focused on prevention, can have a high impact on the quality of life (13).

Lasalvia et al., in 2017, performed a cost-effectiveness analysis of dulaglutide compared to liraglutide and insulin glargine in type 2 diabetes mellitus in

Colombia. It determined that dulaglutide treatment is cost-effective compared to insulin glargine, as the population weight increases or insulin glargine consumption (14).

However, in Colombia, no evidence was found regarding cost-effectiveness evaluations of liraglutide for the management of overweight and obese patients.

The present study aims to estimate the cost-effectiveness of liraglutide treatment for obese patients in Colombia, compared to pharmacological treatment with orlistat or changes in habits given by diet and exercise. These two comparators were chosen, which are orlistat and changes in diet and exercise habits. Orlistat was chose since it is currently a recommendation in the Colombian clinical practice guidelines published in 2016, within the pharmacological recommendations for obesity in adult patients. Changes in diet and exercise habits were selected as comparators since they are considered one of the most critical pillars in the multidisciplinary treatment of obesity, as well as being adjuvants in the other pharmacological and surgical therapies involved in the management of obesity.

For the above, the following research question asked, is treatment with liraglutide cost-effective for adult patients with obesity in Colombia? Table 1 shows the PICOT question of the research problem.

Table 1. PICOT question

Population	Adults between 18 and 64 years of age with obesity, which is defined as a BMI higher than or equal to 25 kg / m2.
Intervention	Liraglutide 3 mg / day.
Comparators	Changes in diet and exercise habits. Orlistat 360 mg / day.
Outcomes	Decrease by 10% BMI.
Time	One year.

3. Methodology

This study carried out according to the methodological guide for conducting economic evaluations within the framework of clinical practice guides of the Institute of Technological Evaluation in Health (IETS) of the year 2014 for Colombia (15).

3.1 Perspective

The analysis was performed from the perspective of a third-party payer, for this case, Colombian system health care. This perspective implies only direct medical costs considered.

3.2 Discount rate

For the present analysis, no discount rate applied since the time horizon is one year.

3.3 Outcomes and assessment

The clinical outcome defined as a decrease in the minimum BMI of 10% compared to the initial one.

- Body mass index (BMI): it is the most frequently used measure to determine patients' nutritional status. It is a measure of association between weight and height. People with a BMI higher than or equal to 25 kg/m2 is considered overweight and over 30 kg/m2 with obesity (6). The loss of 10% of BMI determined for the present study as a favorable clinical outcome.
- Complications associated with obesity extensively described in the literature; however, for the study analysis, only diabetes mellitus type 2 will evaluate since it considered one of the complications most frequently associated with obesity globally and with the most significant socioeconomic impact (16).
- Decreased risk factor: the decrease in the risk factor associated with obesity evaluated for this type 2 diabetes mellitus study. In the study by Fruh 2017, it concluded that with moderate weight losses associated with changes in lifestyle or interventions pharmacological, the risk of developing type 2 diabetes mellitus in patients with obesity and prediabetes could reduce from 31% to 58% (17).

3.4. Synthesis of clinical evidence

The subsequent controlled clinical trials found within the literature review carried out:

Astrup, et al. 2009: Randomized, double-blind clinical trial to evaluate liraglutide effects in the treatment of obesity versus placebo. Five hundred sixty-four people

between 18 and 65 years with BMI 30-40 kg/mts2 randomly assigned to one of the four intervention groups, liraglutide 1.2 mg/day, 1.8 mg/day, 2.4 mg/day, 3 mg/day, or to the placebo or orlistat group 3 times a day orally. All groups had associated diet and exercise during the study. The results found were greater weight loss in the liraglutide groups compared with the placebo and orlistat. The mean weight loss in the 1.2 mg/day liraglutide group was 4.8 kg, for 1.8 mg/day 5.5 kg, 2.4 mg/day 6.3 kg, 3 mg/day 7.2 kg, compared to 2.8 kg in the placebo group and 4.1 kg orlistat (18).

Wadden, et al. 2013: maintenance in weight loss and additional weight loss with liraglutide, followed up overweight and obese patients (422) with a BMI equal to or higher than 27 kg/m2, who in a previous SCALE clinical trial had lost 5% of the weight body weight during the study, randomized to liraglutide 3 mg/day or placebo for 56 weeks. During the follow-up, they provided with a diet and exercise guide. Among the results they obtained, they found that the majority of patients who received liraglutide (81.4%) maintained a weight loss of 5% at baseline compared to placebo (48.9%). Additionally, they estimated that liraglutide produces small but significant cardiometabolic risks compared to placebo (19).

Davies, et al. 2015: conducted a controlled clinical trial evaluating the efficacy of liraglutide versus placebo for weight loss in patients with type 2 diabetes mellitus. The interventions were randomized in 3 arms, the first received liraglutide 3 mg/day (n = 423), the second liraglutide 1.8 mg/day (n = 211), and the third placebo group (n = 212), all groups along with diet and increased physical

activity. Weight loss of more than 10% occurred in 25.2% liraglutide 3 mg/day, 15.9% in liraglutide 1.8 mg/day, and 6.7% in the placebo group. They showed greater gastrointestinal disorders as an adverse effect on the drug in the liraglutide 3 mg/day group (20).

Pi-Sunyer, et al. 2015: double-blind, randomized controlled clinical trial, follow-up for 56 weeks, with a total of 3,731 patients with a BMI of at least 27 kg/m2, allocation in two groups, liraglutide 3 mg/day subcutaneously and placebo. Both groups received habit change counseling. They found that 63.2% of the patients in the liraglutide arm decreased 5% of their initial weight and in the placebo group, 27.1%. 33.1% of the liraglutide group and 10.6% of the placebo group lost more than 10% of body weight (21).

3.4 Costs

Drug costs taken from the database of the Drug Price Information System (SISMED) reported in April 2020 (22).

The costs associated with the treatment of the complication due to obesity, for this type 2 diabetes mellitus analysis, were obtained from the ISS 2001 rate manual (23).

All costs for medications and procedures given in Colombian pesos.

3.4.1 Identification and measurement of resources

For the preparation and measurement of costs, the guidelines suggested in the methodological guide for conducting economic evaluations in the framework of

IETS Clinical Practice Guidelines were followed (15). The liraglutide dose of 3 mg/day defined according to the SCALE, and SCALE Maintenance controlled clinical trials (21) (24).

The orlistat dose of 120 mg 3 times a day, 360 mg/day, was determined according to the Clinical Practice Guideline's recommendation for the prevention, diagnosis, and treatment of overweight and obesity in adults for Colombia in 2016 (25).

For the identification and measurement of resources associated with changes in diet and exercise habits, it was carried out based on the Clinical Practice Guide for the prevention, diagnosis, and treatment of overweight and obesity in adults for Colombia 2016. Together with a study carried out in Colombia by Montenegro in 2007, where an analysis of the results of the overweight management in adults through exercise carried out, where an exercise program directed three times a week for four weeks implemented, achieving reductions in BMI by 8, 76% (26).

Table 2 shows the identification and measurement of the drugs that are the subject of this cost-effectiveness analysis of liraglutide for the management of patients with obesity in Colombia.

Table 2. Identification and measurement of resources

Medicines				**Posology**		
Name	**Concentration and dosage form**	**CUM**	**% of use**	**Dose (mg daily)**	**Anual amount miligrams**	**Total mg per presentation**
Liraglutida	C/Injectable solution	20028798	100%	3	1068	18
Orlistat	A/Capsule	230167	100%	360	131400	120

3.4.2 Valuation of resources

The minimum value per milligram for liraglutide is $ 8,450, and the maximum value per milligram is $9,041. The minimum value per milligram of orlistat is $25, and the maximum value per milligram is $27.14, which is shown below in table 3. For the assessment of resources related to changes in diet and exercise habits, based on the costs secondary to nutritional assessment and physical therapy for the prescription of directed exercise in said programs.

Table 3. Assessment of drug resources

Medicines				**Posology**				
Name	**Concentration and dosage form**	**CUM**	**% of use**	**Dose (mg daily)**	**Annual amount miligrams**	**Total mg presentation**	**Weighted minimum value mg**	**Weighted average value mg**
Liraglutida	C/Injectable solution	20028798	100%	3	1068	18	$8.450	$8.746
Orlistat	A/Capsule	230167	100%	360	131400	120	$25	$26

Medicines								
Name	**Maximum weighted value mg**	**Circular**	**Minimum dose value**	**Average dose value**	**Maximum dose value**	**Annual minimum value**	**Annual average value**	**Annual maximum value**
Liraglutide	$9.041,34	Circular ten de 2020	$25.350	$26.237	$27.124	$9.024.440	$9.462.354	$9.900.267
Orlistat	$27,14	Circular ten de 2020	$9.130	$9.450	$9.770	$3.332,304	$3.449.250	$3.566.196

Table 4. Assessment of resources, diet, and exercise procedures.

Procedures					
CUPS	**Procedures**	**Total amount**	**% of use**	**Unit value**	**Total value**
890306	Control and monitoring consultation for nutrition and dietetics	4	100%	$5.480	$21.920
931000	Integral physical therapy SOD	12	100%	$7.785	$93.420

The total annual cost of the diet and exercise comparator is $115.340.

Table 5. Assessment of resources procedures cost complication obesity –DM2

Procedures					
CUPS	**Procedure**	**Total amount**	**% of use**	**Unit value**	**Total value**
902210	Blood count	4	100%	$11,015	$44,060
903825	Creatinine in serum, urine and others	4	100%	$3,095	$12,380
903856	Ureic nitrogen	4	100%	$3,665	$14,660

907107	Urinalysis with sediment and urinary density	4	100%	$3,785	$15,140
903818	Total cholesterol	4	100%	$4,415	$17,660
903816	Low-density enzyme cholesterol (LDL)	4	100%	$5,515	$22,060
903815	Hogh density cholesterol (HDL)	4	100%	$5,515	$22,060
903868	Triglycerides	4	100%	$5,170	$20,680
903027	Nephelometry microalbuminuria	4	100%	$13,675	$54,700
903426	Glycosylated hemoglobin by monoclonal antibodies	4	100%	$19,545	$78,180
890301	Control or follow-up consultation for general medicine	12	100%	$8,755	$105,060
890306	Control and monitoring consultation for nutrition and dietetics	4	100%	$5,480	$21,920
890402	Interconsultation for specialized medicine (Internal	6	100%	$12,510	$75,060

890402	Interconsultation for specialized medicine (Internal medicine, family medicine or endocrinology)	6	100%	$12,510	$75,060
890202	Interconsultation fos specialized	1	100%	$12,510	$12,510

Table 6. Assessment of resources inputs cost complication obesity-DM2

Supplies					
Medicine name	**Indication of use**	**Amount**	**% of use**	**Unit value**	**Total value**
Metformina tab 850 mg	Treatment DM2	365	100%	$299.74	$109,403.64
Insulina glargina 1000 UI/10ml (1000UI/ml)	Tratamiento DM2	4	100%	$104,331.86	$417,327.44

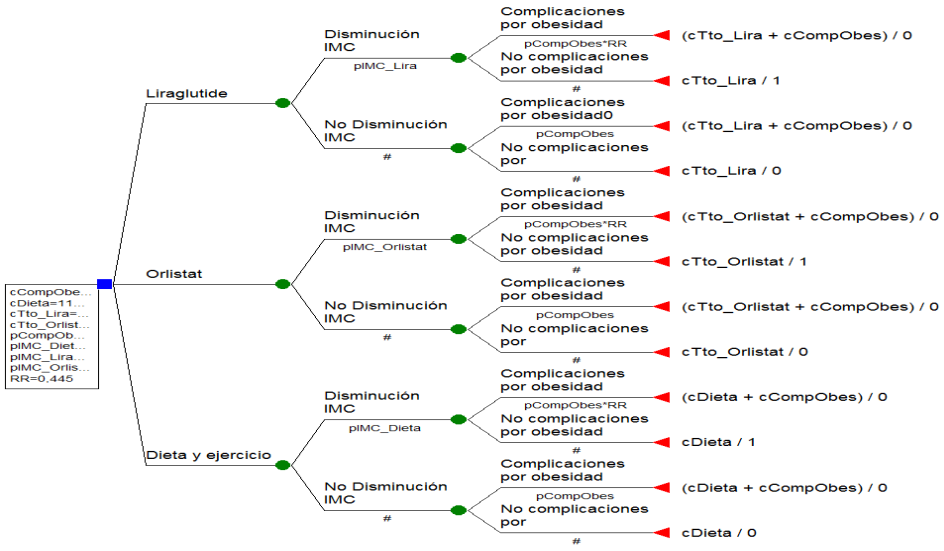
The total annual cost of the complication of obesity, diabetes mellitus 2, including procedures and supplies, is $ 526,731.

3.6 Mathematical model

3.6.1 Model design

A decision tree model carried out in the TreeAge Pro 2009 program, which included both the intervention with liraglutide and the two chosen comparators, orlistat and changes in diet and exercise habits, which were evaluated by a decrease in BMI and presence or not of complications from obesity (Figure 1).

Figure 1 Decision tree



3.6.2 Modeling

The model considers the loss of 10% of BMI and the absence of obesity complications as positive, in this case, type 2 diabetes mellitus.

The proposed model based on the following assumptions:

- It is considered an adult population over 18 years of age.
- Adverse drug reactions were not taken into account, since sufficient data from reports in Colombia and the probability of their presentation not found in the literature, possibly due to the short time of use of the drug in the country.

3.6.3 Parameters included in the model

Table 7 shows the parameters included in the decision tree model.

Table 7. Model parameters

Parameter	Base case	Minimun	Maximum	Source
Probability of decrease BMI liraglutida	0,283	0,254	0,311	Astrup et al.
Probability of decrease BMI orlistat	0,095	0,085	0,104	Astrup et al.
Probability of decrease BMI diet and exercise	0,02	0,018	0,022	Astrup et al.
Probability of complicación obesity	0,308	0,277	0,338	Gil-Rojas
Decrease risk factor - DM2	0,445	0,58	0,31	Fruh
Treatment cost liraglutida	$9.462.354	$9.024.440	$9.900.267	SISMED
Treatment cost orlistat	$3.449.250	$3.332.304	$3.566.196	SISMED
Cost diet and exercise	$115.340	$80.738	$149.942	Manual tarifario ISS 2001
Cost complication obesity – DM2	$1.042.861,08	$730.002,76	$1.355.718,40	ISS tariff manual 2001, SISMED

4. RESULTS

4.1 Base case results

The base case results show that the average annual costs for diet and exercise were $432,976: for orlistat $3,753,515 and liraglutide $9,733,106. On the other hand, the average annual cost per successful case, or average cost-effectiveness for diet and exercise of $25,508,251 for orlistat of $45,786,142 and

liraglutide of $39,855,146.

Regarding effectiveness, changes in habits associated with diet and exercise presented 1.7% of cases with decreased BMI and no complications due to obesity, orlistat 8.2%, and liraglutide 24.4%, which show in Figure 2. The incremental cost-effectiveness ratio between diet and exercise and Orlistat is $51,305,846, and between orlistat and liraglutide is $36,858,100.

Figure 2. Cost-effectiveness plan

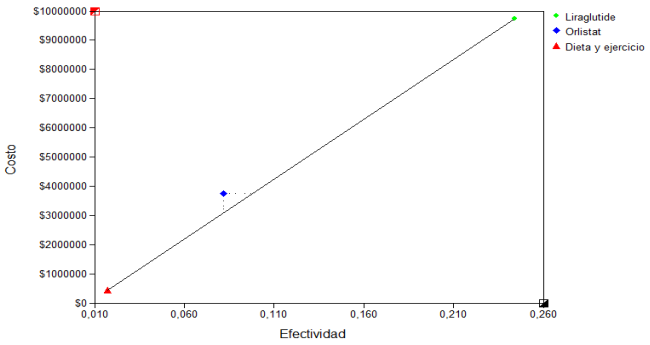


Table 8. Base case results

Alternatives	Cost	Incremental cost	Effectiveness	Incremental effectiveness	Incremental cost effectiveness ratio ICER
Diet and exercise	$432.976		0,017		
Orlistat	$3.753.516	$3.320.540	0,082	0,065	$51.305.846
Liraglutida	$9.733.106	$5.979.590	0,244	0,162	$36.858.100

4.2 Results of the discounted scenarios

In the present economic evaluation, since the time horizon is equal to one year,

no discount rates were used.

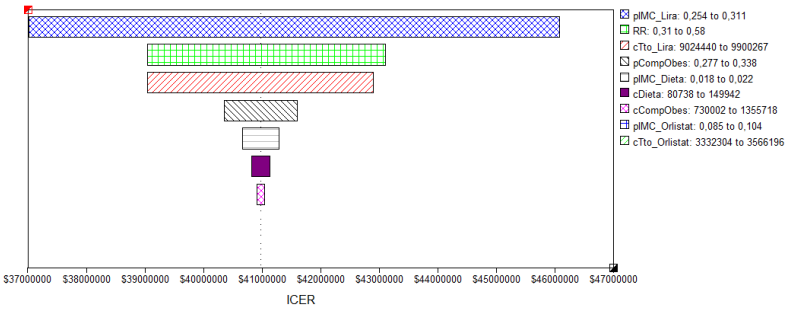
5. UNCERTAINTY ANALYSIS

5.1 Deterministic sensitivity analysis

For this evaluation, a univariate sensitivity analysis developed for the parameters used in the model using a tornado diagram (Figure 3), through which it can see to what extent the variables affect the incremental cost-effectiveness ratio.

Regarding the analysis of the variables responsible for the uncertainty of the incremental cost-effectiveness ratio, it found that the probability of decreasing BMI with liraglutide impacts 71.09%, followed by the decrease in the risk factor associated with obesity. DM2, which impacts 14.24%, and thirdly the cost of liraglutide treatment with 12.87%. These three variables in a grouping are equal to 98.2% of the uncertainty of the RCEI.

Figure 3. Tornado Analysis



6. DISCUSSION

Performing treatment with liraglutide for obesity control showed differences in the pharmacological treatment with orlistat and changes in habits given by diet and

exercise. However, treatment with liraglutide showed to be the most expensive from the perspective of the third payer. Each person who has a 10% decrease in BMI has to pay more than $36,858,100 if they want to treated with liraglutide. If the willingness to pay off the Colombian health system for this outcome is higher than the ICER, it is possible to conclude that liraglutide treatment is cost-effective for the management of obesity.

Among the limitations of the study that must be consider is the one associated with the generalization of the results. The perspective was from the third payer and not from society's perspective, which excludes indirect costs and direct out-of-pocket costs that patients must bear. Additionally, it considers as a limitation that the data obtained for the performance of the analysis are data of efficacy and not of effectiveness, and are not from Colombia.

The cost-effectiveness estimated in this analysis is similar to that found in the literature in similar economic evaluations, which are in favor of the inclusion of liraglutide as part of the multidisciplinary management of obesity. However, the performance not found at the moment of the present analysis, a model of obesity in Colombia.

Another aspect to consider is the inclusion of programs to change diet and exercise habits in patients who give pharmacological treatment with liraglutide and orlistat in the reported clinical trials, tha could positively affect weight loss, due to which when more information is available, it is possible to redo the model and the respective analysis, since the option of changes in diet and exercise habits can improve the results as a non-pharmacological treatment.

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