

ORIGINAL ARTICLE



Dupilumab in children with moderate-to-severe asthma: A cost utility analysis

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Abstract

Introduction: Dupilumab is an effective and safe medicine for the management of severe asthma. Due to its high cost, concerns are generated regarding its cost-effectiveness. This study aimed to estimate the cost-utility of dupilumab plus standard of care (SoC) versus SoC alone in children between 6 and 11 years old with severe asthma and eosinophilic phenotype.

Methods: A Markov-type model was developed to estimate costs and health outcomes of a simulated cohort of pediatric patients with persistent asthma treated over a 6-year period. To determine the robustness of the model deterministic and probabilistic sensitivity analyses were conducted.

Results: The quality-adjusted life-years (QALYs) per patient estimated were 0.85 with dupilumab and 0.84 with SoC. The total mean of discounted costs per patient per cycle were US\$ 379 for dupilumab and US\$ 19 for SoC. The incremental cost-effectiveness ratio estimated was \$24 660 US\$ per QALY

Conclusion: Dupilumab is not cost-effective in Colombia in children between 6 and 11 years old with severe asthma and eosinophilic phenotype. Our evidence should motivate regulatory agencies to improve negotiations for new drugs with better information and evidence.

KEYWORDS

health economics, healthcare, public health

1 | INTRODUCTION

Asthma is the most common chronic condition among children.¹ Trends suggest growing asthma prevalence globally predominantly in developing countries.² It is estimated that 3%–5% asthmatic patients may require intensive treatment with high doses of ICS-LABA and more than half of them persist with poor disease control despite such management.³ These patients, especially those with a type 2 inflammation phenotype, may benefit from the use of monoclonal antibodies that inhibit interleukin (IL)-4 and IL-13 signaling.⁴

Dupilumab has been approved and used in adolescents and adults for the management of severe asthma and severe atopic dermatitis for several years.⁵ A recent clinical trial conducted in 408 children between 6 and 11 years of age demonstrated its efficacy in this age group.⁶ Dupilumab reduced the risk of severe exacerbation by 59.9% (relative risk reduction in the dupilumab group, 59.3%; 95% CI, 39.5–72.6; $p < 0.001$) compared to standard management without this drug, in addition to achieving improvement in spirometry parameters (mean difference, 5.2 percentage points; 95% CI, 2.1–8.3; $p < 0.001$), symptom control ($p < 0.001$); without differences

Abbreviations: CHEERS, Consolidated Health Economic Evaluation Reporting Standards; EOS, blood eosinophil; FeNO, exhaled nitric oxide test; FEP, flows expiratory peak; FEV1, Forced expiratory volume in the first second; ICS plus LABA, Inhaled corticosteroids plus long-acting β_2 -agonists; OCS, oral corticosteroids; QALYs, quality-adjusted life-years; SoC, standard care; WTP, willingness-to-pay.

in the incidence of serious adverse events with respect to the control group.⁶

These results will encourage its approval and use in the pediatric population in the coming years given this evidence and the existing experience in adolescents and adults. However, given its high cost, concerns arise regarding the impact that this drug may have in middle or low-income countries. We recently demonstrated that with a 60% reduction in the cost of this drug, the estimated incremental cost-effectiveness ratio (ICER) in the adult and adolescent population would be below the WTP suggested for Colombia.⁷ It is precisely at this moment, with the current evidence and before approval in low- or middle-income countries, when providing economic evidence is useful for public health decision-makers. The objective of the present study is to determine the cost-utility of dupilumab in patients aged 6–11 years with severe asthma. This evidence will undoubtedly guide to the policymakers toward more efficient use of health resources.

2 | MATERIALS AND METHODS

A Markov state-transition model was used to estimate the cost-effectiveness of dupilumab plus SoC compared to SoC alone, using data from the NCT02948959 trial.⁶

According to patients included in NCT02948959 trial; our base case for the Markov model was defined as a “Children 6 to less than 12 years of age, with a physician diagnosis of persistent asthma for greater than or equal to higher than 12 months before screening, based on clinical history and examination, pulmonary function parameters according to global initiative for asthma (GINA) 2015 Guidelines and the following criteria: existing background therapy of medium-dose ICS with second controller medication or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months, prebronchodilator forced expiratory volume in 1 s (FEV1) $\leq$ 95 percentage of predicted normal or prebronchodilator FEV1/forced vital capacity ratio <0.85 , reversibility of at least 10% in FEV1 after the administration of 200–400 μ g albuterol/salbutamol, and must have experienced, within 1 year prior treatment with a systemic corticosteroid (oral or parenteral), as prescribed by a healthcare professional for worsening asthma at least once or, hospitalization or emergency visit for worsening asthma or evidence of uncontrolled asthma. In NCT02948959 trial was administered dupilumab (200 mg) for >30 kg or 100 for less than or equal to 30 kg) via SC injection q2w for 52 weeks in combination with stable-dose background therapy of medium-dose ICS with a second controller medication (i.e., LABA, LAMA, and LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication. The comparator was SOC which consisted of “medium-dose inhaled corticosteroids (ICS) with a second controller medication (i.e., long-acting β_2 agonist [LABA], long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist [LTRA], or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication.”

In our Markov model and according to the natural history, three health states were defined: “no symptoms or asthma controlled,” “sub-optimal control without exacerbation,” and “asthma exacerbation” with a

cycle length of 2 weeks; according to the average duration of an exacerbation and its recovery following models of natural history of the disease previously published in the Colombian population.^{7–13} The time horizon in this analysis was 5 years. Half-cycle correction with an annual discount rate of 5% were apply to both costs and benefits.¹⁴ Cost-effectiveness was evaluated at a willingness-to-pay (WTP) value of US \$5180.¹⁵ Dupilumab was considered cost-effective if the incremental cost-utility ratio was below \$ 5180 per quality-adjusted life-year (QALY) gained or if the net monetary benefit (NMB) of this strategy is higher than strategy SoC.

2.1 | Clinical data

Data on relative risk of asthma exacerbation with dupilumab were obtained from the NCT02948959 trial, while utilities and transition probabilities were obtained from a local study of pediatric asthma.¹⁶ Exacerbation rates associated with emergency room visits, hospitalization, and intensive care were extracted from previously published local data (Table 1).¹⁷

2.2 | Cost analysis

We did this analysis from a societal perspective (including direct and indirect costs). All direct costs for each health state defined in the model were extracted from a previously Colombian study in children with asthma.¹⁸ For the valuation of the indirect costs associated with parents' loss of productivity, the human capital method was used, assuming everyone receives an income of at least the legal minimum wage for formal or informal work. The cost-opportunity of the productivity loss at the workplace and the caregiver was assessed based on the minimum wage without including transportation assistance for 2021.¹⁹ Since all the patients with asthma included in this study were children, we assumed that at least one family member accompanied the patient permanently during hospitalization, since pediatric hospitals in the country usually only allow one companion per patient in the hospital. The cost associated with transportation and food (not including an overnight stay) was assumed to correspond to 50% of the minimum wage per day. Drug cost were taken from the National Drug Price Information System (SISMED).²⁰ Since most pediatric patients with severe allergic asthma are older than 6 years, a dose of 200 mg via SC injection q2w for 52 weeks was used to perform the costing in this study.²¹ We used US dollars (Currency rate: US\$ 1.00 = COP\$ 3000) to express all costs in the study.¹⁹ The ICER was calculated using the following formulae:

$$\text{ICER} = \frac{\text{Expected annual cost per patient with dupilumab} - \text{Expected annual cost per patient without dupilumab}}{\text{QALYperpatientwithdupilumabsupplementation} - \text{QALYperpatientwithoutdupilumab}}$$

Also, we estimated the NMB. NMB represents the value of an intervention in monetary terms.²² NMB is calculated as (incremental benefit $\times$ threshold)–incremental cost. Incremental NMB measures

TABLE 1 Base case

Variable	Base case	Valor high	Valor low	References
Cost US\$				
Dupilumab 200 mg every 2 weeks	\$ 392	\$ 490	\$ 294	[18]
Cost ED visit (per episode)	\$ 43	\$ 54	\$ 32	
Cost hospitalization (per episode)	\$ 639	\$ 799	\$ 479	
Utilities (annual)				
Utility no symptoms	0.99	1.0	0.74	
Utility suboptimal control	0.71	0.9	0.53	[16]
Utility asthma exacerbation	0.28	0.3	0.21	
Dupilumab effect				
Relative risk on exacerbation rate	0.41	0.27	0.61	[6]
Exacerbations				
Exacerbation annual rate	2	3	1	[17]
# Hospitalization annual	1	2	0	
Transition probabilities				
No symptoms to suboptimal control	0.097	0.1213	0.0728	
No symptoms to asthma exacerbation	0.004	0.0050	0.0030	[16]
Suboptimal control to asthma exacerbation	0.007	0.0088	0.0053	
Suboptimal control to no symptoms	0.817	1.0000	0.6128	
Asthma exacerbation to no symptoms	0.274	0.3425	0.2055	
Annual discount rate	5.00%	6%	0%	

the difference in NMB between alternative interventions, a positive incremental NMB indicating that the intervention is cost-effective compared with the alternative at the given WTP threshold

2.3 | Sensitivity analysis

Sensitivity analyses were made for relative risk, annual discount rate, exacerbation annual rate, utilities cost, utilities, and transition probabilities. Since relative risk does not come from the Colombian population, they were subjected to probabilistic sensitivity analysis (PSA) as detailed below as recommended by Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement. In the deterministic sensitivity analysis, we use the confidence interval of relative risk mentioned above. In the case of utilities, transition probabilities, and utilities the upper and lower ranges were estimated by adding or subtracting 25% of the value from the central value defined for the base case. We also perform a deterministic sensitivity analysis using one-way sensitivity analysis, threshold analysis, and tornado diagram. For PSA, random sampling was made from each of the parameter using pre-specified distributions for each variable in the model. Beta distribution was used for relative risk and

utilities; dirichlet distribution for transition probabilities, and gamma distribution for costs. For each treatment strategy and using a second-order Monte Carlo simulation with 10,000 replications of each parameter, we determined the expected costs and QALYs of each treatment strategy with their 95% CI. We plot the cost-effectiveness and acceptability frontiers to present the uncertainty of decision analysis. Microsoft Excel® was used in all analyses (Figure 1).

3 | RESULTS

The main results are presented in Table 2. The base-case analysis showed that dupilumab was associated with higher costs and QALYs than SoC in the base-case analysis. The median probability of surviving free of asthma exacerbation in the Markov cohort simulation was of 0.88 in SoC and 0.94 in add-on therapy with dupilumab. The QALYs per patient estimated were 0.85 with dupilumab and 0.84 with SoC. The total mean of discounted costs per patient per cycle were US\$ 379 for dupilumab and US\$ 19 for SoC. The ICER estimated was \$24 660 US\$ per QALY; value higher than WTP per QALY (US\$5180) accepted in Colombia.¹⁵

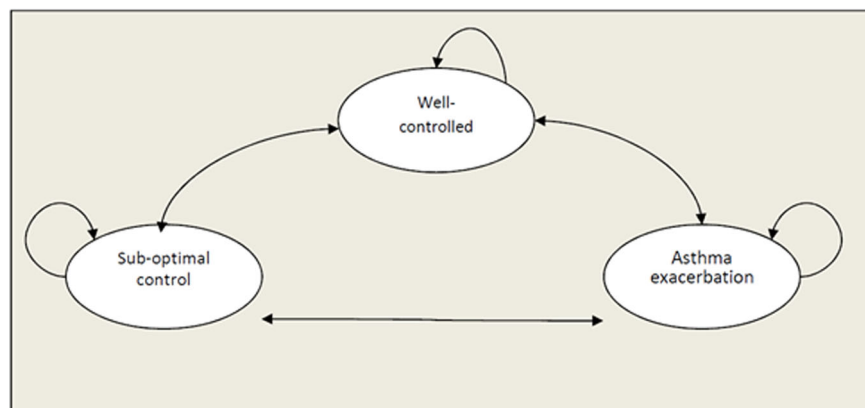
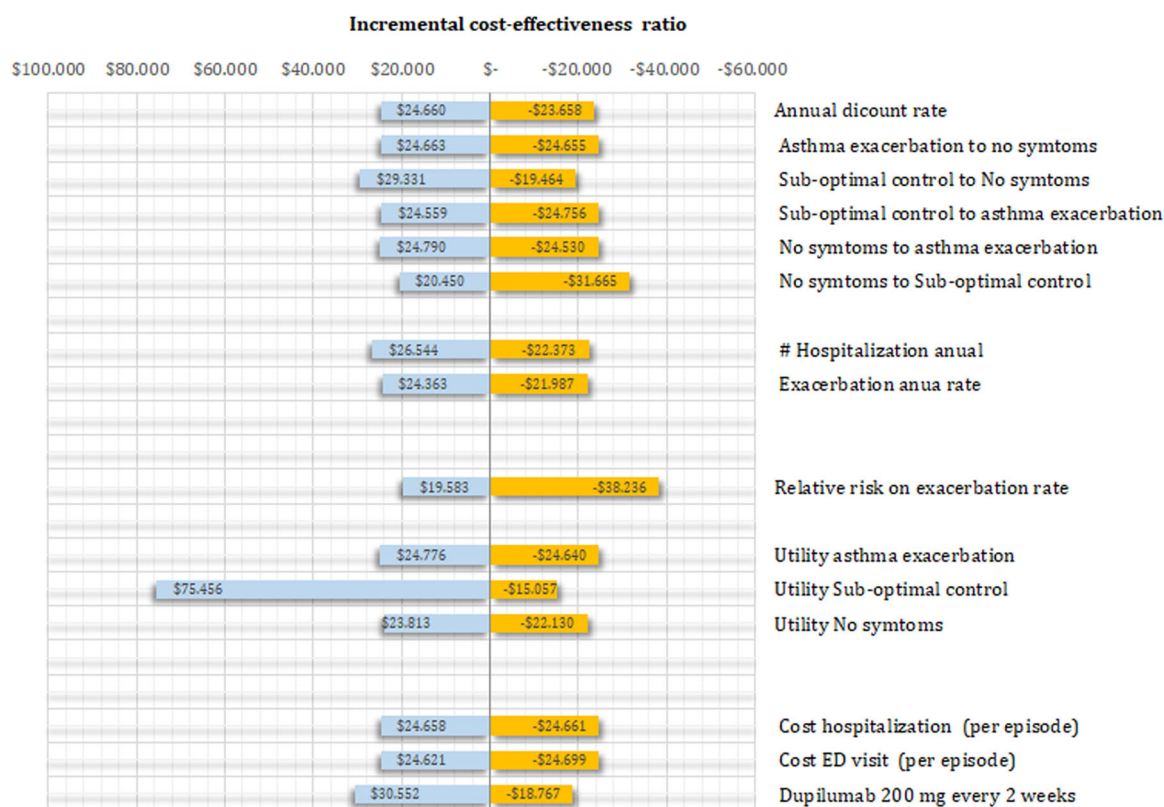


FIGURE 1 Markov model

Strategy	Cost (\$)	Difference (\$)	QALY	Difference	Cost/QALY	ICER (\$)
Dupilumab	379	-	0.85	-	444	24,660
SOC	19	360	0.84	0.015	23	-

TABLE 2 Cost-effectiveness of dupilumab versus SOC

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; SOC, standard of care.

FIGURE 2 Tornado diagram [Color figure can be viewed at wileyonlinelibrary.com]

3.1 | Sensitivity analysis

In the deterministic sensitivity analysis, our base-case results were robust to variations in all assumptions and parameters. For none of

the variables evaluated, variations within the established ranges led to the ICER being lower than the WTP as can see in the tornado diagram (Figure 2). The threshold analysis of the cost of dupilumab, shows that if the cost of injection of 200 mg will be equal to or less

than US\$ 68 (a reduction of 83% of their cost), the ICER will be less than WTP of US\$ 5180. The QALYs per patient estimated by the PSA were 0.24 (95% CI: 0.22–0.29) with dupilumab, and 0.28 (95% CI: 0.27–0.34) with SoC. The total mean of discounted costs per patient per cycle were US\$ 673 (95% CI: \$663–\$684) for dupilumab and US\$ 414 (95% CI: \$409–\$420) for SoC. The NMB was greater in SoC compared to dupilumab. The NMB for SoC was \$2051 (95% CI: \$2044–\$2058) while for dupilumab was \$1919 (95% CI: \$1912–\$1926). The results of the 10,000 monte carlo simulations in the PSA are graphically represented in the cost-effectiveness plane (Figure 3). After the 10,000 s-order Monte Carlo simulations performed, 95% of them were plotted in quadrant 1 (high cost, high QALY), of which only 8% presented an ICER below the WTP. The acceptability curve reveals that dupilumab becomes a cost-effective strategy with respect to SoC only if the WTP is greater than \$22,000 in Colombia, see Figure 4.

4 | DISCUSSION

Our economic evaluation shows that with the current costs of dupilumab, this drug is not cost-effective in our country. This information is highly relevant considering the growing incidence of asthma in our population, as well as the near entry of this drug to the market for use in the population between 6 and 11 years of age.

Our model yields similar results to other economic analysis. We recently demonstrated that Dupilumab, under the current costs of this drug, is not cost-effective in the adult and adolescent population in Colombia.⁷ The estimated ICER was US \$ 50,160 per QALY. As in the present work, a reduction in the cost of dupilumab in that case of 60% made this monoclonal antibody cost-effective. To our

knowledge, our work is the first that addresses cost-effectiveness in the pediatric population and generates evidence in accordance not only with the results in the adult population but also with what happens with other biological drugs in Colombia. Previously, we also evaluated benralizumab in severe asthma in the adult population in Colombia. Benralizumab is not cost-effective given that the cost per QALY is US \$ 42,760.²³ Only a 41% reduction in the cost of benralizumab allowed it to have an ICER below the WTP. In the same way, in patients with severe asthma and hyper-IgE, omalizumab, under the current costs of this drug, is not cost-effective, and only with a 41% reduction in its price, the estimated ICER could be lower than the WTP in Colombia.²⁴ The problem of high costs of biological drugs is not exclusive to developing countries; also, in the United States; despite the entry into the market of biosimilars, costs have not dropped significantly, generating a great economic burden for health systems.^{25–27} With the evidence presented here, the effectiveness and safety of biological drugs such as dupilumab is not in doubt. Furthermore, our mathematical simulation with local data shows a significant improvement in exacerbation-free time with said drug. Our study provides evidence aimed at establishing the efficiency of this drug, going beyond simply showing whether it is cost effective; and estimating the cost that dupilumab should have to be cost-effective with the current data. These estimates should motivate regulatory agencies to improve negotiations for new drug entry with better information and evidence such as the one provided here.

Even though not having local estimates of the relative risk of dupilumab, our model was robust to variations in all parameters. Availability of data about cost-effective treatments for severe asthma is without doubt beneficial to patients. Differences in drug prices are the key drivers of the ICER in asthma treatments.²⁸ This highlights the importance of economic evaluations in providing information on

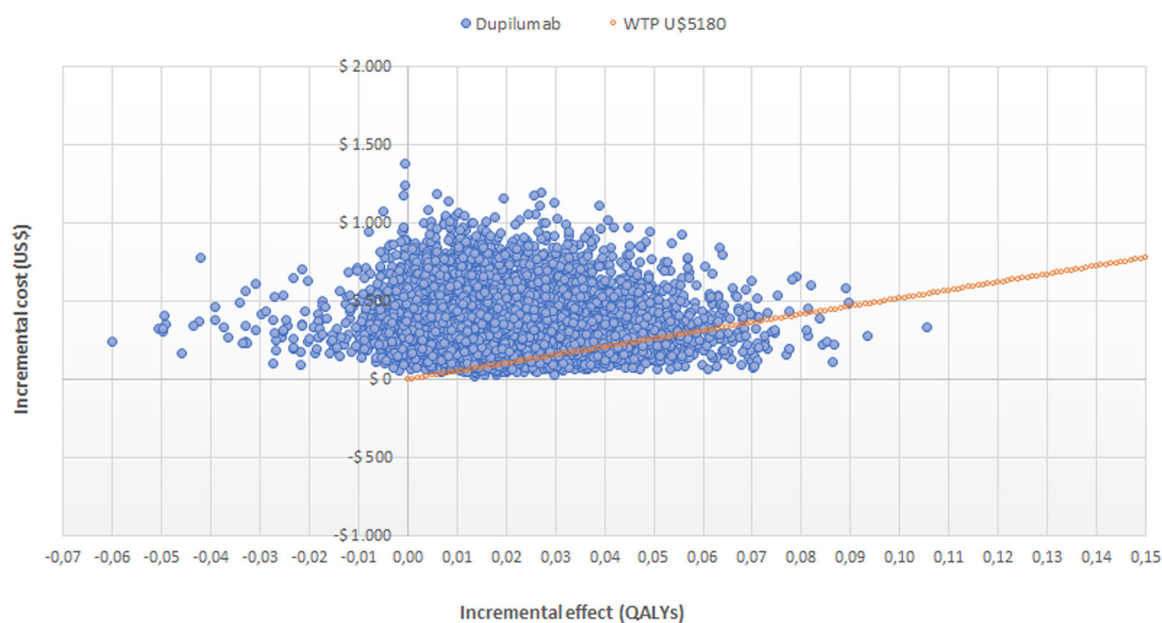


FIGURE 3 Cost effectiveness plane [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/terms-and-conditions)]

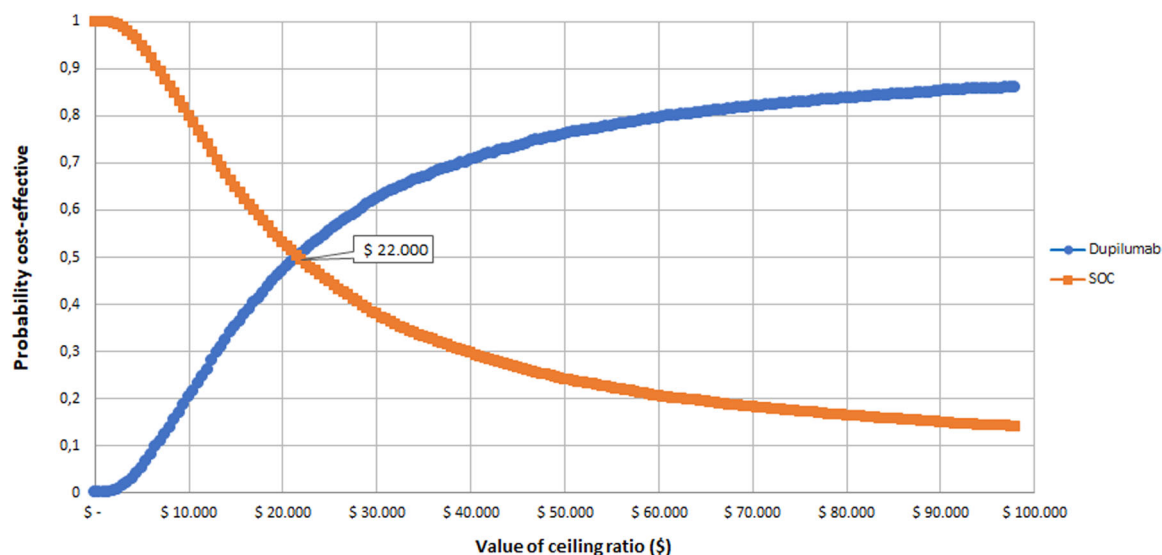


FIGURE 4 Acceptability curve [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ppul.26033)]

the efficiency of a new technology, complementing existing information on effectiveness and safety. Making decisions based only on effectiveness and safety, ignoring its efficiency, can lead to serious consequences in the financing of health systems that end up affecting the health of each patient.

Our study has some limitations. We use relative risk not estimated directly from Colombian children. However, the deterministic and PSA showed the robustness of our results following the international recommendations of CHEERS.²⁹ The results of this economic evaluation given the base case are only applicable to patients between 6 and 11 years old with severe asthma. Our result cannot be extrapolated to the patient with current use of oral corticosteroids and only have external validity on the patient with current treatment with medium-dosage to high-dosage inhaled corticosteroids

5 | CONCLUSION

Dupilumab is not cost-effective using WTP of US\$ 5180 per QALY threshold in Colombia. Our evidence should motivate regulatory agencies to improve negotiations for new drugs with better information and evidence.

AUTHOR CONTRIBUTIONS

Jefferson A. Buendia: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing—original draft; writing—review and editing. **Diana G. Patiño:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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