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Cost-effectiveness and budgetary impact of lipegfilgrastim for the reduction of chemotherapy-induced neutropenia in Brazil

Custo-benefício e impacto orçamentário do lipegfilgrastim para a redução de neutropenia induzida por quimioterapia no Brasil

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Keywords:
granulocyte colony-stimulating factor, cost-effectiveness, lipegfilgrastim, filgrastim, neutropenia

ABSTRACT

Background: Granulocyte-colony stimulating factors (G-CSFs) reduce the risk of chemotherapy-induced neutropenia. Lipegfilgrastim is a long-acting, once-per-cycle G-CSF, while Brazil's standard of care is short-acting filgrastim. A cost-effectiveness and budget impact analysis of lipegfilgrastim was conducted with filgrastim and once-per-cycle pegfilgrastim for adults at risk of neutropenia in Brazil. **Methods:** The decision model used national and clinical data to evaluate the costs and outcomes of each treatment. Costs included drug and medical expenses, outpatient and inpatient neutropenia treatments, and adverse events. Health outcomes included incidence of neutropenia-related events. For the budget impact analysis, health outcomes and costs for the pre/post-lipegfilgrastim scenarios were combined to identify expenditure with lipegfilgrastim's introduction. **Results:** Total cost per patient during a course of four chemotherapy cycles was estimated at R$12,920 for lipegfilgrastim, R$15,168 for filgrastim, and R$13,232 for pegfilgrastim. Based on better outcomes and lower total costs with lipegfilgrastim compared with filgrastim as well as pegfilgrastim, lipegfilgrastim was the dominant treatment strategy over both filgrastim and pegfilgrastim during the duration of chemotherapy treatment. Over 5 years, the uptake of lipegfilgrastim led to savings of R$61,532,403 in overall medical costs. Neutropenic events decreased by 17,141 and deaths linked to febrile neutropenia decreased by 239. **Conclusion:** Due to better outcomes and lower overall cost, lipegfilgrastim was a cost-saving strategy compared with filgrastim and pegfilgrastim in the Brazilian healthcare system. Furthermore, the budget impact analysis estimated a reduction in overall medical costs and improved health outcomes over 5 years following the introduction of lipegfilgrastim.

Palavras-chave:
fatores estimuladores de colônias de granulócitos, análise de custo, benefício e impacto orçamentário, lipegfilgrastim, filgrastim, neutropenia

RESUMO

Introdução: Fatores estimuladores de colônias de granulócitos (G-CSFs) reduzem risco de neutropenia induzida por quimioterapia. Lipegfilgrastim é um G-CSF de longa ação, de "um por ciclo", enquanto o padrão de cuidado no Brasil é filgrastim de curta ação. Realizou-se uma análise de custo/benefício e impacto orçamentário (IO) no Brasil do lipegfilgrastim um por ciclo com filgrastim e pegfilgrastim para adultos sob risco de neutropenia. **Métodos:** O modelo de decisão usou dados nacionais e clínicos para avaliar resultados e custos dos tratamentos que incluíam medicamentos, médicos, tratamentos ambulatoriais e hospitalares para a neutropenia, e eventos adversos. Resultados de saúde incluíam a incidência de eventos relacionados à neutropenia. Para a análise do IO, os custos e resultados de antes/depois do lipegfilgrastim foram combinados para identificar gastos com o lipegfilgrastim. **Resultados:** O custo total por paciente em quatro ciclos foi estimado em

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R$ 12.920 para lipegfilgrastim, R$ 15.168 para filgrastim e R$ 13.232 para pegfilgrastim. Com base em melhores resultados e custos totais menores, o lipegfilgrastim, comparado ao filgrastim e ao pegfilgrastim, representou a estratégia de tratamento predominante. Em 5 anos, o lipegfilgrastim gerou uma economia de R$ 61.532.403 em custos médicos gerais. Houve 17.141 menos eventos neutropênicos e as mortes relacionadas à neutropenia febril reduziram em 239. **Conclusão:** Devido a melhores resultados e menores custos, lipegfilgrastim, comparado ao filgrastim e ao pegfilgrastim, foi uma estratégia econômica no sistema brasileiro. A análise de IO estimou uma redução nos custos médicos e melhorou os resultados em 5 anos após a introdução do lipegfilgrastim.

Introduction

Neutropenia is one of the most frequent causes of chemotherapy dose reductions and delays. It is also associated with prolonged hospitalization, serious infections, the use of broad-spectrum antibiotics, decreased quality of life, and increased mortality. The prophylactic use of recombinant granulocyte colony-stimulating factor (G-CSF) is one of the primary methods of reducing the risk of chemotherapy-induced severe neutropenia (SN; absolute neutrophil count [ANC] of $<0.5 \times 10^9/1$) and febrile neutropenia (FN; severe neutropenia with fever), defined as an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 hours and an ANC of $<0.5 \times 10^9/1$ or expected to fall below $0.5 \times 10^9/1$ (Barnes *et al*., 2014; Klastersky *et al*., 2016). Treatment with G-CSFs is associated with a shorter duration of neutropenia, reduced risk of FN, shorter FN-related hospitalization, and lower mortality rate due to infection (Kuderer *et al*., 2007; Cooper *et al*., 2011; Lyman *et al*., 2013). In addition, G-CSFs are associated with an increased probability of receiving a full dose of chemotherapy (optimal relative dose intensity [RDI]) (Lyman *et al*., 2003; Shayne *et al*., 2006; Kuderer *et al*., 2007; Almenar Cubells *et al*., 2013), as well as with a greater possibility of the use of highly myelosuppressive dose-dense regimens at shorter intervals than without G-CSF support (Kuderer *et al*., 2007; Lyman *et al*., 2012). Practice guidelines in the United States (US) and Europe suggest that G-CSFs should be used as primary prophylaxis after chemotherapy when the risk of FN is >20% (Bennett *et al*., 1996; Smith *et al*., 2006; Aapro *et al*., 2011; Freifeld *et al*., 2011; Lyman *et al*., 2013).

In Brazil, the short-acting G-CSF filgrastim (Neupogen®; Amgen Inc., Thousand Oaks, CA, USA) is the standard of care for patients at risk of chemotherapy-induced neutropenia (CIN). Previous clinical trials (Crawford *et al*., 1991; Trillet-Lenoir *et al*., 1993; Holmes *et al*., 2002a; Holmes *et al*., 2002b; Green *et al*., 2003; Vose *et al*., 2003) have indicated that 7 to 14 days of filgrastim produce the most optimal results, with 11 injections as the average (Weycker *et al*., 2006; Cooper *et al*., 2011). However, in actual clinical practice, the average duration of filgrastim prophylaxis falls short of 11 days, with estimates from real-world observational studies ranging from 4.8 to 6.4 days (Morrison *et al*., 2007; Weycker *et al*., 2012; Naeim *et al*., 2013). Patients receiving less than 7 days of injections had a significantly higher risk of hospitalization than patients receiving 7 days or more (Weycker *et al*., 2012).

The long-acting G-CSF pegfilgrastim (Neulasta®; Amgen Inc., Thousand Oaks, CA, USA) is administered once per chemotherapy cycle; however, it is not currently reimbursed in Brazil. A number of meta-analytic studies using randomized comparative clinical trials have found that a single dose of pegfilgrastim is equivalent, and in some instances superior, to a 10- to 14-day course of filgrastim with respect to incidence of FN (Pinto *et al*., 2007; Cooper *et al*., 2011; Pfeil *et al*., 2015; Wang *et al*., 2015). Results from observational studies suggest that compared with filgrastim, patients treated with pegfilgrastim had a lower risk of developing neutropenia and neutropenia-related complications as well as a lower risk of hospitalization (Morrison *et al*., 2007; Almenar *et al*., 2009; Tan *et al*., 2011; Almenar Cubells *et al*., 2013). One possibility for the superiority of pegfilgrastim in observational studies is that, unlike in controlled clinical trials, patients in a clinical setting often receive less than 6 or 7 days of filgrastim or receive it later than 2–3 days after chemotherapy (Weycker *et al*., 2006; Almenar Cubells *et al*., 2013; Wright *et al*., 2013; Wang *et al*., 2015). Real-world studies suggest that such underutilization of filgrastim is associated with reduced efficacy and increased risk of FN and hospitalization (Scott *et al*., 2003; Weycker *et al*., 2006; Weycker *et al*., 2012).

Lipegfilgrastim (Lonquex®; Teva Pharmaceuticals Industries Ltd, Petach Tikva, Israel) is a long-acting, fixed-dose, recombinant human G-CSF that was approved by the European Medicines Agency (EMA) in 2013. A phase III trial of chemotherapy-naive patients with breast cancer reported that lipegfilgrastim was noninferior to pegfilgrastim with respect to duration of SN (Bondarenko *et al*., 2013). No differences between lipegfilgrastim and pegfilgrastim in the incidence and duration of FN-related dose reductions, hospitalizations, and antibiotic use were reported (Gladkov *et al*., 2016). However, statistically significant differences favoring lipegfilgrastim were found for secondary endpoints such as faster time of ANC recovery in cycles 1–3, incidence of SN in cycle 2, and depth of ANC nadir in cycles 2 and 3. A phase III trial of lipegfilgrastim was conducted in patients with advanced non-small cell lung cancer receiving cisplatin/etoposide. Pos-

t-hoc analyses suggested that in patients aged ≤65 years, FN incidence during cycle 1 was similar in the lipegfilgrastim and placebo groups. In elderly patients (>65 years), there was a reduction in FN incidence with lipegfilgrastim. Overall, lipegfilgrastim reduced the incidence and duration of SN, time of ANC recovery, and depth of ANC nadir (Volovat *et al.*, 2016). The safety profile of lipegfilgrastim is also similar to that of pegfilgrastim, and bone pain-related symptoms were similar in patients receiving lipegfilgrastim or pegfilgrastim (Bondarenko *et al.*, 2013; Volovat *et al.*, 2016).

To facilitate the health economic evaluation of the market entry of lipegfilgrastim for adult patients at risk of CIN, a model was developed to evaluate and compare health and economic outcomes associated with lipegfilgrastim versus the reimbursed standard of care in Brazil, short-acting filgrastim, as well as long-acting pegfilgrastim. This type of analysis is critical for payers to fully understand what the potential net impact associated with the introduction of a new health technology will be, including expenditures on drug, medical, and other related healthcare costs. The objectives of this model were two-fold, to estimate: 1) the cost-effectiveness and 2) the 5-year budget impact of lipegfilgrastim compared with filgrastim and pegfilgrastim when used for managing adult patients at risk of CIN from the perspective of the health care system in Brazil.

Methods

An interactive model was constructed to evaluate the cost--effectiveness of G-CSFs as well as the changes in drug and medical costs due to the introduction of lipegfilgrastim for managing adult patients at risk of CIN in Brazil. It was developed in accordance with the Economic Evaluation Guidelines in Brazil (Ministério da Saúde 2009). The model used a set of inputs based on data from a variety of sources, including national databases, clinical trial evidence, meta-analyses, and expert opinion; no patient-level identifiable data were used.

Model structure

The model included three G-CSFs: short-acting filgrastim as well as long-acting lipegfilgrastim and pegfilgrastim. Pegfilgrastim is not currently reimbursed in Brazil; however, as there were no direct randomized head-to-head trials that compared lipegfilgrastim and filgrastim, a meta-analysis was conducted to compare pegfilgrastim with lipegfilgrastim and filgrastim (Bond *et al.*, 2017). Based in part on the results of this meta-analysis, a decision analytic model was constructed using Microsoft Excel® 2010 to assess: 1) the cost-effectiveness of lipegfilgrastim compared with filgrastim (the primary comparator) as well as pegfilgrastim and 2) the budget impact associated with the introduction of lipegfilgrastim. According to the product label, filgrastim should be administered once daily until a patient's ANC has reached 10,000/mm^3, which takes an average of 11 injections (Weycker *et al.*, 2006; Cooper *et al.*, 2011). Interviews with three Brazilian payers and physicians were conducted to validate certain model inputs and assumptions.

An overview of the decision tree structure is shown in Figure 1. The model calculated and compared the expected costs and health outcomes associated with each treatment arm by scenario. Costs included direct drug and medical expenses, as well as outpatient and inpatient treatments of neutropenia and G-CSF treatment-related adverse events (AEs). Health outcomes included incidence of SN, incidence of FN, mortality due to FN, time at risk with neutropenia, and the likelihood of chemotherapy delay. Cost-effectiveness outcomes were estimated over a time horizon that included the initial four cycles of chemotherapy treatment; budget impact outcomes were estimated during a 5-year time horizon.

Target Population

The present model included adult patients (at least 18 years of age) who were treated with cytotoxic chemotherapy for malignancy in Brazil. For the budget impact analysis, it was estimated that 6% of these patients would receive G-CSF treatment for CIN (IMS 2012); all patients currently receiving filgrastim or pegfilgrastim were considered eligible to receive lipegfilgrastim. Population estimates are summarized in Table 1. Based on the clinical trial populations (Bondarenko et al., 2013; Buchner et al., 2014; Volovat et al., 2015), patients started in the model at a mean age of 45 years.

Clinical parameters and survival estimates

the key efficacy parameters included in the model were 1) incidence of SN, 2) incidence of FN, 3) mortality rate due to FN, 4) time at risk with neutropenia until ANC recovery, and 5) likelihood of chemotherapy treatment delay due to low neutrophil counts. Furthermore, patients experiencing AEs related to their G-CSF treatment (bone pain or nausea) were included as AEs in the model.

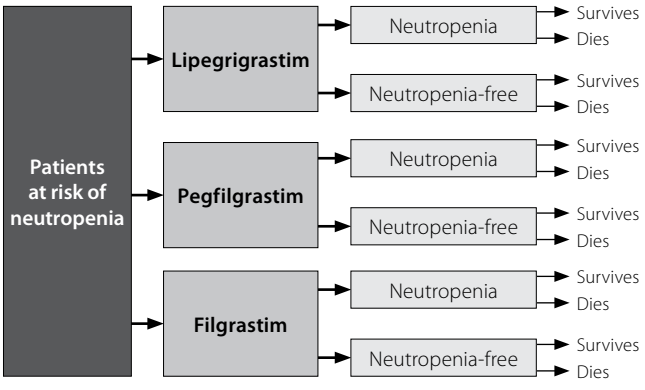


Figure 1. Decision tree structure

Table 1. Population estimates

Parameter	Estimated Value	Eligible Population (N)
Brazilian population (IBGE, 2017A)	203,981,756	203,981,756
Annual age-adjusted incidence of cancer treatment (IBGE, 2017B)	205.5 per 100,000	419,183
Proportion of cancer patients who receive chemotherapy (IMS, 2012)	54%	226,359
Proportion of chemotherapy-treated patients who receive granulocyte-colony stimulating factor (IMS, 2012)	6%	13,582

The clinical data were derived primarily from a recent meta-analysis (Bond *et al*., 2017) of three lipegfilgrastim clinical trials (Bondarenko *et al*., 2013; Buchner *et al*., 2014; Volovat *et al*., 2015), as well as studies identified from a literature review on the use of G-CSFs in the prevention and treatment of CIN and FN. The objectives of the meta-analysis were to produce a direct comparison of lipegfilgrastim and pegfilgrastim as well as an indirect comparison of lipegfilgrastim and filgrastim. Based on the literature search criteria, 91 records were screened, of which 56 were excluded. Thirty-five articles were assessed for eligibility, of which 24 were selected for inclusion in the meta-analysis. Study quality was assessed using guidelines established by the Centre for Reviews and Dissemination (National Collaborating Centre for Methods and Tools 2012). All the studied included utilized prospective, randomized designs and met the following criteria: specified eligibility criteria, adequate sample size, number of patients randomized reported, adequate details of treatment groups at baseline presented, treatment groups comparable at baseline, co-interventions that could affect results similar across groups, and adequate compliance with treatment assignment (Bond *et al*., 2017).

The clinical input parameters incorporated into the model are summarized in Table 2. Lipegfilgrastim inputs were based on the three lipegfilgrastim clinical trials (Bondarenko *et al*., 2013; Buchner *et al*., 2014; Volovat *et al*., 2015), whereas the relative risk (RR) ratios from the meta-analysis were used to calculate the filgrastim and pegfilgrastim inputs (Bond *et al*., 2017). FN was assumed to require hospitalization and the mortality rate due to FN was set to 9.5% across all G-CSF regimens based on prior literature linking mortality to FN (Kuderer *et al*., 2006). As there were no recent comparative data available, the chemotherapy delay rate for lipegfilgrastim was also applied to filgrastim and pegfilgrastim as a percentage of the SN rate

Table 2. Clinical parameters

Parameter	**Lipegfilgrastim** (Bondarenko et al., 2013; Buchner et al., 2014; Volovat et al., 2015)	**Pegfilgrastim** (Bondarenko et al., 2013; Volovat et al., 2015)	**Filgrastim** (Holmes et al., 2002a; Holmes et al., 2002b; Green et al., 2003; Grigg et al., 2003; Vose et al., 2003; Bondarenko et al., 2013; Park et al., 2013; Shi et al., 2013; Volovat et al., 2015)
Severe neutropenia (cycle 1 / cycles 2-4)			
Relative risk (lipegfilgrastim/pegfilgrastim and lipegfilgrastim/filgrastim)		0.80 / 0.53	0.79 / 0.45
Incidence	356.23 / 132.13 per 1000	445.29 / 249.31 per 1000	450.93 / 293.65 per 1000
Febrile neutropenia (all cycles)			
Relative risk (lipegfilgrastim/pegfilgrastim and lipegfilgrastim/filgrastim)		0.34	0.22
Incidence	27.43 per 1000	80.68 per 1000	124.12 per 1000
Mortality due to febrile neutropenia	2.61 per 1000	7.66 per 1000	11.79 per 1000
Time of absolute neutrophil count recovery Difference (lipegfilgrastim vs. pegfilgrastim and lipegfilgrastim vs. filgrastim)		1.75 days	1.88 days
Duration	6.35 days	8.10 days	8.23 days
Chemotherapy treatment delay (cycles 2–4)	11.10%	13.88%	14.05%
Bone pain (all cycles)	141 per 1000	126 per 1000	132 per 1000
Nausea (all cycles)	33 per 1000	58 per 1000	148 per 1000

Market share (Budget Impact Analysis only)

Marketplace dynamics are critical to budget impact models in terms of existing product utilization and the effect of the new treatment on this utilization, including the rate of adoption following introduction. The budget impact of including lipegfilgrastim on the Brazilian national formulary was estimated by comparing the pre-lipegfilgrastim reference scenario with the post-lipegfilgrastim new scenario. For a base-case model scenario, a conservative assumption was made on the rate at which patients would switch to lipegfilgrastim if it were approved and reimbursed in the new scenario. In the first year, the assumption was that 5% of patients would be treated with lipegfilgrastim, followed by 15% in the second year, 25% in the third year, 50% in the fourth year, and 85% in the fifth year. Meanwhile, pegfilgrastim's market share increased from 10% in the reference scenario to 15% for years 1 through 5 in the new scenario, and filgrastim's market share decreased proportionally from 90% in the reference scenario based on lipegfilgrastim and pegfilgrastim's annual market share.

Costs

The model used direct medical costs, such as drug-associated costs, medical visits, and hospitalizations; indirect costs, including those due to lost productivity, were not considered. Drug cost estimates were taken from the Agencia Nacional de Vigilancia Sanitaria / CMED: Lista De Precos De Medicamentos - Precos Fabrica E Maximos De Venda Ao Governo (Agencia Nacional de Vigilancia Sanitaria). Teva Pharmaceuticals supplied the price for lipegfilgrastim (IMS 2012), which was assumed to be the same as for pegfilgrastim. Lipegfilgrastim and pegfilgrastim require a single injection per chemotherapy cycle, whereas filgrastim requires 11 days of injections; a total of four cycles of chemotherapy were assumed based on the clinical trials of lipegfilgrastim (Bondarenko *et al*., 2013; Buchner *et al*., 2014; Volovat *et al*., 2015).

The model included management of SN with one course of ciproflaxin, plus amoxicillin and clavulanate potassium, as well as one follow-up medical visit. As it was assumed that FN required hospitalization, the Brazil national payer interview responses were used for inpatient costs (Data on File). Additionally, subsequent FN care (i.e., outpatient care or re-hospitalization) was assumed to be 22% of the initial hospitalization cost (Liu *et al*., 2009). Bone pain management costs assumed the maximum daily dose (4 g) of paracetamol. For nausea management, it was assumed that 0.15 mg/kg dose of ondansetron was administered intravenously 30 minutes before chemotherapy. Table 3 provides the unit cost estimates used in the model; all costs expressed are in 2015 Brazilian real (R$).

Model outcomes

For the cost-effectiveness analysis, the time horizon was based on the duration of chemotherapy treatment and included total economic costs per patient as well as treatment-associated health outcomes starting with each G-CSF regimen. Model outputs were used to estimate an incremental cost-effectiveness ratio (ICER) in terms of the incremental cost per outcome. If a more costly approach provided no additional benefit (i.e., both more costly and less effective) compared with an alternative one, it was said to be "dominated" by the alternative approach.

For the budget impact analysis, the health outcomes and costs for the pre-lipegfilgrastim and post-lipegfilgrastim scenarios were combined with population and market share information to calculate the expenditure and budget impact associated with the introduction of lipegfilgrastim and subsequent changing treatment patterns over 5 years.

Sensitivity analyses

A series of one-way sensitivity analyses were conducted to assess how changes in key input parameter values affected the results of the model. For the cost-effectiveness analysis, sensitivity analyses were performed only for the primary comparison of lipegfilgrastim and filgrastim. For population inputs (budget impact analysis only), the base-case values were varied by +/–20%, whereas for cost inputs, the lower

Table 3. Drug, medical and adverse event costs

Parameter	Unit Cost (R$)	Frequency of Cost
Lipegfilgrastim drug cost (IMS 2012)	3125.25	Per administration
Pegfilgrastim drug cost (Agencia Nacional de Vigilancia Sanitaria)	3125.25	Per administration
Filgrastim drug cost (Agencia Nacional de Vigilancia Sanitaria)	296.16	Per administration
Injection administration cost (Data on File)	30.00	Per administration
Severe neutropenia management cost (Agencia Nacional de Vigilancia Sanitaria; Data on File)	257.41	Per event
Febrile neutropenia hospitalization cost (Data on File)	3000.00	Per event
Bone pain management cost (Agencia Nacional de Vigilancia Sanitaria)	5.16	Per event
Nausea management cost (Agencia Nacional de Vigilancia Sanitaria)	130.58	Per event

and upper bounds were set to +/–10%. Regarding the clinical inputs for the duration of chemotherapy, the lower and upper bounds were based on the 95% confidence intervals of the meta-analysis (Bond *et al.*, 2017), except for mortality rate due to FN, which was set to +/–10%. Table 4 summarizes the model input parameter values and their ranges; scenarios with the largest (positive or negative) impact on results were displayed in the form of tornado diagrams.

Results

Using the base-case assumption that the cost of lipegfilgrastim was equivalent to pegfilgrastim, total G-CSF drug and administration costs per patient were R$12,621 for lipegfilgrastim and pegfilgrastim and R$14,351 for filgrastim. The SN management cost per patient for lipegfilgrastim was R$294, less than that of pegfilgrastim (R$602) or filgrastim (R$797), whereas AE treatment costs ranged from R$5.05 for lipegfilgrastim to R$8.23 for pegfilgrastim and R$20.06 for filgrastim. Overall, treating a patient with lipegfilgrastim over four chemotherapy cycles resulted in total savings of R$311 compared with pegfilgrastim, and R$2248 compared with filgrastim (Table 5).

Cost-effectiveness analysis

Based on better clinical outcomes and lower total costs with lipegfilgrastim compared with filgrastim as well as pegfilgrastim, lipegfilgrastim dominated both filgrastim and pegfilgrastim during the duration of the chemotherapy treatment (Table 6).

ICER = incremental cost-effectiveness ratio. *Cost (R$) per day.

Budget impact analysis

Total costs and health outcomes, estimated over the 5-year model time horizon, were reported for all three treatment regimens combined. The assumptions for market uptake of lipegfilgrastim in the base-case scenario led to savings of R$61,532,403 in overall medical costs over 5 years (Table 7). G-CSF treatment was the greatest overall contributor to costs, making up 97%, 94%, and 86% of costs for lipegfilgrastim, pegfilgrastim, and filgrastim, respectively. G-CSF administration costs resulted in the greatest budget impact savings associated with the introduction of lipegfilgrastim.

The total annual expenditure decreased every year due to savings related to lipegfilgrastim uptake, leading to budget impact savings of approximately R$2,842,000, R$5,895,000, R$8,948,000, R$16,581,000, and R$27,267,000 in years 1 through 5, respectively. The changes in health outcomes by year, given the assumed market uptake of lipegfilgrastim in the base-case scenario, are presented in Table 8. Overall health outcomes were estimated to improve following the introduction of lipegfilgrastim due to its better efficacy as compared with filgrastim. For example, the projected number of neutropenic events (SN and FN) decreased by 17,141 events and deaths linked to FN decreased by 239 deaths over 5 years.

Table 4. Sensitivity analyses parameters

Input Variables	Low Input Value	Base Case Value	High Input Value
Population inputs			
Incidence of cancer per year	164.4	205.5	246.6
Percent receiving chemotherapy	43%	54%	65%
Percent treated with G-CSF for neutropenia	5%	6%	7%
Cost (R$) inputs			
Cost of lipegfilgrastim injections (per administration)	2812.73	3125.25	3437.78
Cost of filgrastim injections (per administration)	266.54	296.16	325.78
Cost of SN management	231.67	257.41	283.15
Cost of FN hospitalization	2,700.00	3,000.00	3,300.00
Efficacy inputs			
RR of SN incidence (filgrastim) in cycle 1	61%	79%	103%
RR of SN incidence (filgrastim) in cycles 2–4	27%	45%	75%
RR of FN incidence (filgrastim) all cycles	3%	22%	151%
Mortality rate due to FN	8.6%	9.5%	10.5%
ANC time of recovery, filgrastim mean difference	0.95	1.88	2.82
Chemotherapy treatment delay (filgrastim) cycles 2–4	11.24%	14.05%	16.86%

G-CSF = granulocyte colony-stimulating factor; FN = febrile neutropenia; RR = relative risk; SN = severe neutropenia

Table 5. Per patient treatment costs

Parameter	Lipegfilgrastim	Pegfilgrastim	Filgrastim
G-CSF drug cost (R$)	12,501	12,501	13,031
Injection administration cost (R$)	120	120	1,320
Severe neutropenia management cost (R$)	294	602	797
Adverse event management cost (R$)	5.05	8.23	20.06
Total cost per patient (R$)	12,920	13,232	15,168

G-CSF = granulocyte colony-stimulating factor

Table 6. Cost-effectiveness results

	Regimen			ICER	
Outcome	Lipegfilgrastim	Pegfilgrastim	Filgrastim	Cost (R$) per Event: Lipegfilgrastim versus Pegfilgrastim	Cost (R$) per Event: Lipegfilgrastim versus Filgrastim
Total cost (R$)	12,920	13,232	15,168	—	—
Severe neutropenia risk	0.356	0.445	0.451	- 3503	- 23,738
Febrile neutropenia risk	0.027	0.081	0.124	- 5859	- 23,250
Mortality risk	0.003	0.008	0.012	- 61,782	- 244,880
Neutropenia duration (days)	6.35	8.10	8.23	- 178*	- 1196*
Chemotherapy delay risk	0.111	0.139	0.141	- 11,223	- 76,203

ICER = incremental cost-effectiveness ratio. *Cost (R$) per day.

Table 7. Total 5-year budget impact

Cost Component	Pre-lipegfilgrastim Scenario (R$)	Post-lipegfilgrastim Scenario (R$)	Budget Impact (R$)
G-CSF treatment	881,306,841	866,549,413	(14,757,428)
G-CSF administration	81,489,080	48,078,557	(33,410,523)
Adverse event management	1,282,156	874,971	(407,185)
Neutropenic event management	52,808,141	39,850,873	(12,957,268)
Total expenditure	1,016,886,218	955,353,814	- 61,532,403

G-CSF = granulocyte-colony stimulating factor.

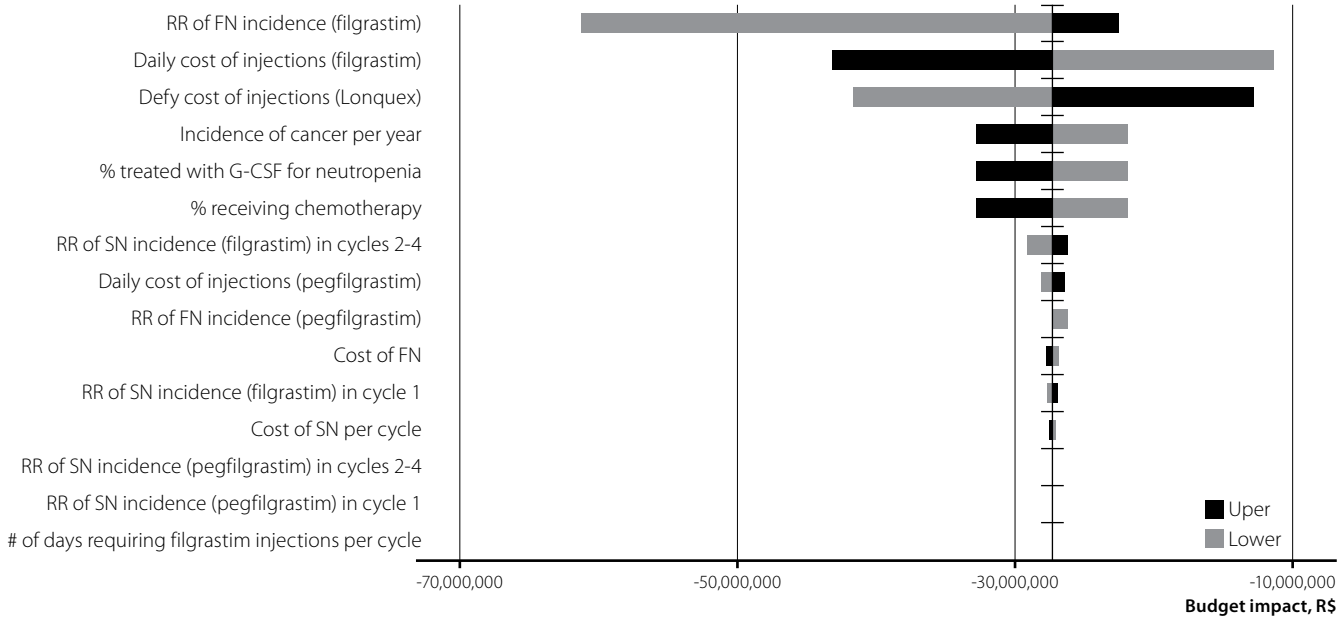
Table 8. Change in patient counts by health outcome and year following the introduction of lipegfilgrastim

Event	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Neutropenia	- 583	- 1501	- 2418	- 4713	- 7926	- 17,141
Chemotherapy delay	- 21	- 61	- 101	- 202	- 342	- 727
Death	- 9	- 22	- 34	- 65	- 109	- 239

Sensitivity analyses

One-way sensitivity analyses were performed based on the core cost-effectiveness analysis comparing lipegfilgrastim and filgrastim. In most scenarios tested, lipegfilgrastim remained dominant (more effective and lower in cost) over filgrastim. The model was most sensitive to the RR ratio of SN incidence (cycle 1) and FN incidence for filgrastim. When the upper limit of the SN incidence for cycle 1 was applied (a RR of 103%), filgrastim became more effective at a higher cost (with an associated ICER of R$237,175 per SN event); when the upper limit of the FN incidence was applied (a RR of 151%), filgrastim also became more effective at a higher cost (with an associated ICER of R$200,934 per FN event).

The results of the one-way sensitivity analyses performed on the budget impact analysis results are shown in Figure 2, which displays the 10 most sensitive parameters based on the overall budget impact in year 5. The variables that had the largest impact on the model results included the RR ratio



FN = febrile neutropenia; G-CSF = granulocyte-colony stimulating factor; RR = relative risk; SN = severe neutropenia

Figure 2. One-way sensitivity analysis based on year 5 budget impact

of FN incidence for filgrastim, the filgrastim drug cost, and the lipegfilgrastim drug cost. These results were similar for sensitivity analyses based on years 1 through 4.

Discussion

Lipegfilgrastim is a long-acting G-CSF that was compared with both long-acting pegfilgrastim and short-acting filgrastim in Brazil. As such, an appraisal of its likely cost-effectiveness and budget impact can inform healthcare payers as they make formulary decisions related to the access and affordability of new health technology. In the analysis described here, a cost-effectiveness model was developed from the perspective of the Brazilian healthcare system to estimate the costs and health outcomes of lipegfilgrastim versus short-acting filgrastim as well as pegfilgrastim, another long-acting, once-per cycle G-CSF. Additionally, a budget impact model was developed to estimate the 5-year net cost associated with the introduction of lipegfilgrastim versus filgrastim and pegfilgrastim. According to the base-case results of the model, reflecting data from the meta-analysis, the safety profiles of the three G-CSF treatments under evaluation were relatively similar. The SN incidence of lipegfilgrastim for the first chemotherapy cycle was 20% less than that of pegfilgrastim, and 21% less than that of filgrastim. Additionally, the FN incidence of lipegfilgrastim was about 66% less than that of pegfilgrastim, and about 78% less than that of filgrastim. Correspondingly, the risk of mortality was estimated to be lower with lipegfilgrastim (0.003) compared with pegfilgrastim (0.008) and filgrastim (0.012). Finally, the neutropenia duration for lipegfilgrastim was 1.75 days less than pegfilgrastim, and 1.88 days less than filgrastim (Volovat *et al.*, 2015).

The model also showed that lipegfilgrastim drug cost was lower than filgrastim, while additional savings occurred due to reduced administration requirements and reduced treatment costs associated with fewer neutropenia events. Over four chemotherapy cycles, lipegfilgrastim had a total per-patient saving of R$2248 compared with filgrastim. The SN management cost per patient for lipegfilgrastim was 49% less than that of pegfilgrastim and 37% less than that of filgrastim. The primary cost driver is the G-CSF drug acquisition cost, which makes up 97%, 94%, and 86% of the total cost per patient for lipegfilgrastim (R$12,501), pegfilgrastim (R$12,501), and filgrastim (R$13,031), respectively. There are R$1200 in cost savings due to administration with lipegfilgrastim or pegfilgrastim, compared with filgrastim, as filgrastim requires a higher number of injections during a chemotherapy cycle (11 injections, per drug label).

In the cost-effectiveness analysis, lipegfilgrastim dominated both filgrastim and pegfilgrastim during the duration of chemotherapy treatment. In the budget impact analysis, projected to the population of patients at risk of CIN, lipegfilgrastim could provide cost savings of R$61,532,403 if the lipegfilgrastim market uptake increases gradually from 5% in year 1 to 85% by year 5. Sensitivity analyses confirmed that these results were generally robust although they were sensitive to some variables including the cost of G-CSF treatments and the RR ratio of SN and FN incidence for filgrastim.

To our knowledge, this is one of the first health economic analyses conducted for the Latin-American region, looking at the cost-effectiveness and budget impact of lipegfilgrastim in Brazil. In the health economics literature, some health economic analyses were reported comparing pegfilgrastim and filgrastim. They generally focused on cost-effectiveness analyses and appeared to support improved health outcomes and cost-effectiveness with long-acting G-CSF, although many of these studies were either from Europe or North America (Danova *et al.*, 2009; Liu *et al.*, 2009; Lyman *et al.*, 2009; Whyte *et al.*, 2011; Sun *et al.*, 2015). As none of these analyses were from Latin America, direct comparisons were unavailable. Comparing direct medical costs with those reported internationally as its limitations, as healthcare costs are generally lower in Brazil than in North America or Europe.

There are several study limitations related to the availability of relevant input data used to populate the model. Due to a lack of randomized head-to-head trials comparing lipegfilgrastim with filgrastim, the efficacy and safety comparisons in the model were based on a recent meta-analysis that combined data from several multi-national clinical trials, with filgrastim studies tending to be older. The extent to which these values will translate to real-world practice in Brazil is unknown. For example, there is limited comparable clinical information on the efficacy of filgrastim when less than the label-defined administration number is applied in certain clinical practices. In addition, the literature contained limited comparable data on chemotherapy treatment delay and mortality; these outcomes had to be estimated based on neutropenia data using an observed link between neutropenia and these events. Likewise, some estimates of resource use during regular clinical treatment of neutropenia were based on expert opinion and could reasonably be expected to vary, with an associated impact on costs. For example, although FN was assumed to require hospitalization, some research has shown that home therapy may substantially decrease this cost (Innes *et al.*, 2003). The focus of the model was on direct medical costs, including those associated with drug acquisition and administration, medical visits, and hospitalizations; no indirect costs such as those due to lost productivity were included. Further analysis is warranted to identify additional savings in productivity costs due to reduced treatment requirements with lipegfilgrastim when considering a broader societal perspective. In addition, the model assessed cost from the public payer perspective in Brazil; however, there are private payers in Brazil whose costs may differ from the model's current assumptions. Finally, the model was based on 11 daily injections of filgrastim, and while previous clinical trials (Crawford *et al.*, 1991; Trillet-Lenoir *et al.*, 1993; Holmes *et al.*, 2002a; Holmes *et al.*, 2002b; Green *et al.*, 2003; Vose *et al.*, 2003) have indicated that 7 to 14 (11 injections being the average) produced the most optimal results, real-world observational studies suggest that filgrastim is only given 4.8 to 6.4 days (Morrison *et al.*, 2007; Weycker *et al.*, 2012; Naeim *et al.*, 2013). However, receiving less than 7 daily injections is associated with a significantly higher risk of hospitalization (Weycker *et al.*, 2012).

Conclusion

Due to better health outcomes and lower overall cost, lipegfilgrastim was a cost-saving strategy compared with filgrastim and pegfilgrastim from the perspective of the Brazilian healthcare system. Furthermore, the budget impact analysis estimated a reduction in overall medical costs along with improved health outcomes over 5 years following the introduction of lipegfilgrastim in Brazil. These findings appear to be robust as confirmed by sensitivity analyses across a wide range of input values.

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