



Common Drug Review

Pharmacoeconomic Review Report

July 2015

Drug	macitentan (Opsumit) (10 mg film-coated tablet)
Indication	<p>Indicated for long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce morbidity in patients of WHO Functional Class II or III whose PAH is either idiopathic or heritable, or associated with connective tissue disease or congenital heart disease.</p> <p>Macitentan is effective when used as monotherapy or in combination with PDE-5 inhibitors.</p>
Listing request	List in the same manner as Tracleer (bosentan)
Manufacturer	Actelion Pharmaceuticals Canada Inc.

Macitentan (Opsumit) Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in respirology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with [CDR Update — Issue 87](#), manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
ERA	endothelin receptor antagonist
FC	functional class
LFT	liver function test
NIHB	Non-Insured Health Benefits
PAH	pulmonary arterial hypertension
PDE-5	phosphodiesterase-5
SERAPHIN	Study With an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome
WHO	World Health Organization

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Macitentan (Opsumit) is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) to reduce morbidity in patients of World Health Organization (WHO) Functional Class (FC) II or III whose PAH is either idiopathic or heritable, or associated with connective tissue disease or congenital heart disease. It is effective when used as monotherapy or in combination with phosphodiesterase-5 (PDE-5) inhibitors. It is available as 10 mg tablets at a price of \$128.33 per tablet (\$128.33 per day).

The manufacturer submitted a cost-minimization analysis comparing macitentan with brand-name bosentan (Tracleer).¹ A time horizon of 365 days was used. The manufacturer concluded that macitentan is cost saving, driven by lower non-drug costs for macitentan compared with Tracleer, although the differences in cost are very small (< 0.1% of annual cost). The manufacturer reported that macitentan is more costly when compared with ambrisentan (by \$3,873 annually) or “multi-sourced” generic bosentan (by \$25,878 annually).

The manufacturer provided no direct or indirect evidence comparing macitentan with other drugs indicated for the treatment of PAH. Consequently, the comparative effectiveness of macitentan is uncertain. Furthermore, in the base-case analysis, the manufacturer did not account for patients receiving generic bosentan. CADTH Common Drug Review (CDR) reanalysis using the generic bosentan price of \$45 per day in 100% of patients demonstrated that macitentan costs \$30,441 more per patient per year. Utilization data obtained by the manufacturer and CDR (PharmaStat data from IMS Health Canada Inc., 2013), and validated by the clinical expert, indicate that generic bosentan use overall in Canada for this patient population is approximately 17% (83% brand-name bosentan), with wide variation among provinces. Using this estimated proportion of generic (17%) versus brand-name (83%) bosentan, macitentan costs \$5,166 more per patient per year. This incremental cost will increase if the proportion of patients receiving generic bosentan is greater.

At the submitted price of \$128.33 per tablet (\$128.33 per day), macitentan is more expensive than ambrisentan (\$122.52 per day), generic and brand-name sildenafil (\$18.76 to \$33.36 per day, based on the recommended dose of 20 mg three times daily), and tadalafil (\$26.72 per day).

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Macitentan (Opsumit) is an orally active, non-peptide, potent dual endothelin (ET_A and ET_B) receptor antagonist indicated for the long-term treatment of pulmonary arterial hypertension (PAH) to reduce morbidity in patients of World Health Organization (WHO) Functional Class (FC) II or III whose PAH is either idiopathic or heritable, or associated with connective tissue disease or congenital heart disease. It is effective when used as monotherapy or in combination with phosphodiesterase-5 (PDE-5) inhibitors. The recommended dose is 10 mg daily. Macitentan is available as 10 mg film-coated tablets, with a price of \$128.33 per tablet.²

1.1 Cost comparison table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 1: COST COMPARISON TABLE FOR DRUGS USED FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Drug/ Comparator	Strength	Dosage Form	Price (\$)	Average Daily Use	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Macitentan (Opsumit)	10 mg	tablet	128.3333^a	10 mg daily	128	46,840
Other ERAs						
Ambrisentan (Volibris)	5 mg 10 mg	tablet	122.5200	5 mg daily	123	44,719
Bosentan (Tracleer)	62.5 mg 125 mg	tablet	64.1786	125 mg, twice daily	128	46,850
Bosentan (generics)	62.5 mg 125 mg	tablet	22.4625		45	16,398
PDE-5 Inhibitors						
Tadalafil (Adcirca)	20 mg	tablet	13.3633	40 mg, once daily	27	9,755
Sildenafil (Revatio)	20 mg	tablet	11.1219	20 mg, 3 times daily	33	12,178
Sildenafil (generics)	20 mg	tablet	6.2520 ^b	20 mg 3 times daily	18.76	6,847
Parenteral Prostanoids^c						
Epoprostenol (Flolan)	0.5 mg 1.5 mg	vial	18.6400 37.2800	15 ng/kg/min to 30 ng/kg/min	77.22 to 114.50 Up to 170.42	28,185.to 41,793 Up to 62,203
	50 mL diluent ^d		10.6500			
Epoprostenol (Caripul)	0.5 mg/vial 1.5 mg/vial	vial	17.1800 34.4500	15 ng/kg/min to 30 ng/kg/min	57.93 to 92.38 Up to 144.01	21,144 to 33,718 Up to 52,564
	50 mL diluent ^d		3.1500			
Treprostinil sodium (Remodulin)	1 mg/mL 2.5 mg/mL 5 mg/mL 10 mg/mL	20 mL multi-use vial ^e	45.0000 114.2500 225.0000 450.0000	30 ng/kg/min ^f to 60 ng/kg/min ^e Up to 100 ng/kg/min has been reported	142.81 to 281.25 Up to 473.68	52,126 to 102,656 Up to 172,893

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Drug/ Comparator	Strength	Dosage Form	Price (\$)	Average Daily Use	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Stimulators of sGC						
Riociguat (Adempas)	0.5 mg 1.0 mg 1.5 mg 2.0 mg 2.5 mg	tablet	42.7500 ^g	1.0 mg to 2.5 mg, three times daily	128.25	46,811

ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase.

^a Manufacturer's submitted price.

^b Nova Scotia Formulary (January 2015)

^c Costs for infused products are based on a 70 kg patient and do not include administration or drug delivery system costs. The Saskatchewan formulary allows \$46.00 per diem for supplies.

^d Two vials of diluent for epoprostenol are assumed to be used each 24-hour period, as per product monograph, and are included in the average daily and annual drug cost.

^e Stable for 30 days after the initial puncture of the rubber stopper.

^f Clinical expert indicated that treprostinil average doses and ceilings are about twice that of epoprostenol.

^g Quebec formulary list price (exceptional access for chronic thromboembolic pulmonary hypertension).

Sources: Saskatchewan Drug Formulary (January 2015), unless otherwise stated.

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-minimization analysis comparing macitentan to brand-name bosentan (Tracleer) for treatment of PAH in Canada.¹ The manufacturer contends that a comparison of its effectiveness to that of other agents is not possible given differences in trial design (duration and outcomes assessed). Both public payer and societal perspectives were presented. Drug costs, physician visits, and monitoring costs were derived from Canadian sources. Drug costs were obtained from the Ontario Drug Benefit Formulary (Tracleer) and Quebec Formulary (Volibris).

Monitoring for PAH assumed three physician visits, six liver function tests (LFTs), and one additional full blood count regardless of drug treatment. The monitoring costs were obtained from the Ontario Schedule of Benefits for Physician Services and Ontario Schedule of Laboratory Services.

The placebo-corrected rates of edema and hepatotoxicity adverse events (AEs) were also included in the analysis. The resource utilization attributed to the AEs includes three extra liver function tests and physician visits for elevated LFT and one extra physician visit for edema.

The manufacturer used a time horizon of 365 days and performed sensitivity analyses on the following parameters: 1) Non-drug specific therapy costs: a) removing costs associated with physician and nurse visits, monitoring, and AEs, and b) a decrease in the number of LFTs attributed to macitentan. 2) Comparators: a) ambrisentan and b) multi-sourced generic bosentan.

In the base-case analysis (Table 2), the manufacturer reported that macitentan would save \$9.42 in annual drug costs (\$50,695.74 versus \$50,686.32) and \$23.84 in annual non-drug costs (\$633.38 versus \$657.22) when compared with Tracleer, with a total annual saving of \$33.26.

TABLE 2: MANUFACTURER'S BASE-CASE ANALYSES

Drug	Drug Cost	Incremental Drug Cost (Savings)	Non-drug Cost	Incremental Non-drug Cost (Savings)	Incremental Total Cost (Savings)
Macitentan	\$50,686.32	(\$9.42)	\$633.38	(\$23.84)	(\$33.26)
Tracleer	\$50,695.74		\$657.22		

Source: Adapted from Manufacturer's Pharmacoeconomic Submission,¹ page 18, Table 7.

The manufacturer also submitted a series of sensitivity analyses (Table 3). When non-drug costs were removed from the analyses, the cost saving of macitentan persisted but was reduced (−\$9.42). When the number of liver tests was reduced for macitentan, the cost saving increased (−\$78.75). When compared with ambrisentan and generic bosentan, the incremental costs for macitentan increased to \$3,873 and \$25,878, respectively.

TABLE 3: MANUFACTURER’S SENSITIVITY ANALYSES (INCREMENTAL TOTAL COST)

Scenario	Incremental Cost (Savings)
Base case	(\$33.26)
Removing non-drug costs	(\$9.42)
Reduced number of LFTs for macitentan (from 6 per year to 4 per year)	(\$78.75)
Ambrisentan as comparator	\$3,873
Multi-sourced bosentan as comparator	\$25,878

LFT = liver function test.

Source: Adapted from Manufacturer’s Pharmacoeconomic Submission,¹ page 18, Table 8.

3. KEY LIMITATIONS

Uncertain relative efficacy and safety versus bosentan and other PAH drugs

The manufacturer’s rationale for not conducting a cost-utility analysis is differences in the design of SERAPHIN³ (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) study compared with those of other PAH drugs’ clinical trials (outcome measure, longer duration), but no evidence supporting equivalent efficacy and safety with bosentan is provided, such as network meta-analysis on outcomes common to trials; for example, WHO FC status. The relative efficacy of macitentan with ambrisentan — another slightly less expensive, although less commonly used endothelin receptor antagonist (ERA) — as well as other, less expensive PAH drugs, such as tadalafil and sildenafil, is also unknown.

Brand-name versus generic bosentan

The manufacturer provided data indicating that public claims (excluding Quebec) for Tracleer comprised 83% of all bosentan claims in 2013, and that there was no clear trend toward a decreasing proportion of claims (data June 2012 to October 2013). CADTH Common Drug Review (CDR) analysis of utilization data (not available for Quebec) indicates claims for Tracleer ranging from 0% to 96% by province (Appendix 1, Table 4);

The base-case analysis does not incorporate the current utilization of brand-name versus generic bosentan across Canada, variability by jurisdiction (although “multi-sourced” generic bosentan is assessed in sensitivity analysis), or how reimbursement policies on generic versus brand-name bosentan might affect future incremental costs.

Source for drug costs and calculation of annual costs

Drug acquisition costs are the key drivers of total costs in this analysis. Several reanalyses have been conducted to explore this, as CDR noted variations in the drug costs of bosentan and macitentan.

Inclusion of mark-up and dispensing fees: Removing mark-up and dispensing fees leads to an annual cost of \$46,851 (versus \$50,696) for Tracleer and \$46,840 (versus \$50,686) for macitentan. This does not alter incremental drug costs (macitentan is approximately \$10 less costly per year).

Generic versus “multi-sourced” bosentan: The manufacturer indicated “multi-sourced” bosentan was derived from the Ontario Drug Benefit Formulary, but no other details were provided. The manufacturer’s price per day is \$64, which differs from the Saskatchewan Drug Formulary cost for generic bosentan of \$45 per day. When the Saskatchewan Drug Formulary cost is used, the incremental annual drug cost of macitentan versus generic bosentan increases to \$30,441 (versus \$23,426).

Current Canadian and provincial utilization of generic versus brand-name bosentan: assuming current use of brand-name bosentan (Tracleer) is 83%, and using CDR-sourced generic cost, the incremental annual cost of macitentan is \$5,166.

4. ISSUES FOR CONSIDERATION

- While it is appropriate to consider bosentan as a comparator given that it is the most commonly used ERA, the cost-effectiveness of bosentan versus non-drug therapy, or other PAH drug therapy, is not clear (and has not been reviewed by CDR in previous submissions).
- According to the clinical expert, current prescribing of brand-name versus generic bosentan is driven by 1) prescriber uncertainty regarding the relative efficacy and side effect profile of brand versus generic; 2) reluctance to switch “stable” patients from brand to generic bosentan; and 3) patient support programs that provide assistance to both providers and patients, including assistance with navigation of drug approval and coverage, or delivery of drugs to patients’ homes. According to the clinical expert, both patients and providers find the patient support programs beneficial, and in the context where neither the provider nor the patient are exposed to incremental drug costs, both are likely to choose brand versus generic to receive the support.

Issues 1) and 2) are purely speculative; there are no data indicating clinically important differences, which exist according to the clinical expert.

5. CONCLUSIONS

The manufacturer provided no direct or indirect evidence comparing macitentan with other drugs indicated for the treatment of PAH. Consequently, the comparative effectiveness of macitentan is uncertain. A network meta-analysis on outcomes that are common to clinical trials, such as WHO FC status, would have been useful, although there are limitations to this approach. Macitentan’s drug acquisition costs are similar to those of Tracleer, but macitentan is \$30,441 more costly than generic bosentan per patient annually. Using the estimated current proportion of brand-name (83%) versus generic (17%) bosentan use for PAH in Canada suggests that macitentan is \$5,166 more costly per patient annually. This incremental cost will increase if the proportion of patients receiving generic bosentan is greater. At the submitted price of \$128.33 per tablet (\$128.33 per day), macitentan is also more expensive than ambrisentan (\$122.52 per day), generic and brand-name sildenafil (\$18.76 to \$33.36 per day, based on the recommended dose of 20 mg three times daily), and tadalafil (\$26.72 per day).

APPENDIX 1: PROPORTION OF GENERIC VERSUS BRAND-NAME BOSENTAN AND PRICE REDUCTION SCENARIOS FOR MACITENTAN

There is variation in the proportion of generic versus brand-name bosentan among jurisdictions in Canada, and some jurisdictions may be imposing restrictions on brand-name bosentan use.

A CADTH Common Drug Review (CDR) analysis of utilization data from public plans (except Quebec) showed that the proportion of claims for bosentan that consisted of Tracleer varied widely among provinces, ranging from 0% to 96% of claims (PharmaStat data from IMS Health Canada Inc., 2013; see Table 4). There were no data available for Alberta and Manitoba. According to the clinical expert, in Alberta and Manitoba, approximately 100% and 80% of patients, respectively, are on Tracleer; further, the clinical expert noted that in some provinces (British Columbia), Tracleer is funded for existing patients, but only generic bosentan is funded for patients new to the drug.

TABLE 4: PROPORTION OF CLAIMS FOR BRAND-NAME BOSENTAN (TRACLEER) ACROSS PUBLIC PLANS

Province/Drug Plan	Proportion of Claims of Tracleer in Quartile 3, 2013	Proportion of Claims of Tracleer in Quartile 4, 2013
British Columbia	321/390 (82%)	252/317 (80%)
New Brunswick	0/22 (0%)	0/21 (0%)
Newfoundland	8/23 (35%)	8/22 (36%)
NIHB	10/82 (12%)	NA
Nova Scotia	10/21 (48%)	7/20 (35%)
Ontario	656/684 (96%)	674/700 (96%)
Saskatchewan	0/25 (0%)	0/17 (0%)
Overall (for provinces for which data were available, and excluding Quebec)	1,005/1,247 (81%)	941/1,097 (86%)

NIHB = Non-Insured Health Benefits.

Source: PharmaStat data from IMS Health Canada Inc., 2013.

Table 5 demonstrates the incremental costs of macitentan compared with varying proportions of brand-name versus generic bosentan. The price reduction required to achieve similar costs with bosentan is also shown.

TABLE 5: PROPORTION OF GENERIC BOSENTAN AND PRICE REDUCTION OF MACITENTAN

Proportion of Generic Bosentan	Annual Bosentan Cost (\$)	Annual Macitentan Cost (\$)	Incremental Annual Cost of Macitentan (\$)	Price Reduction of Macitentan for Equivalent Annual Cost
0%	46,851	46,840	-11	-
17%	41,675	46,840	5,166	11%
25%	39,238	46,840	7,602	16%
50%	31,625	46,840	15,215	32%
75%	24,012	46,840	22,828	49%
100%	16,399	46,840	30,441	65%

Note: The overall proportion of generic bosentan in Canada in 2013 was estimated to be 17%.

REFERENCES

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3. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani AH. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med.* 2013;369(9):809-18.