Common Drug Review
Pharmacoeconomic Review Report

December 2015

Drug	Riociguat (Adempas)
Indication	Treatment of pulmonary arterial hypertension (PAH, WHO Group 1), as monotherapy or in combination with endothelin receptor antagonists in adult patients (≥ 18 years of age) with Functional Class II or III pulmonary hypertension.
Listing request	Treatment of pulmonary arterial hypertension (PAH, WHO Group 1), as monotherapy or in combination with endothelin receptor antagonists in adult patients (≥ 18 years of age) with Functional Class II or III pulmonary hypertension *who are unable to achieve disease control with another PAH therapy.*
Dosage form(s)	0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets for oral administration
NOC date	March 2014
Manufacturer	Bayer HealthCare Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

6MWD	6-minute walk distance
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
ERA	endothelin receptor antagonist
ITC	indirect treatment comparison
NMA	network meta-analysis
PAH	pulmonary arterial hypertension
PC	prostacyclin
PDE5	phosphodiesterase type 5
PVR	pulmonary vascular resistance
sGC	soluble guanylate cyclase
WHO	World Health Organization

SUMMARY

Background

Riociguat (Adempas) is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1), as monotherapy or in combination with endothelin receptor antagonists (ERAs) in adult patients (≥ 18 years of age) with WHO functional class II or III pulmonary hypertension.[1] It is available in 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg oral tablets, with a recommended dose of 1 to 2.5 mg three times daily, based on a 0.5 mg incremental titration phase. The manufacturer submitted a price of $42.75 per tablet for all dosage strengths based on its current list price, which corresponds to a cost of $128.25 daily per patient or $46,811 annually per patient. The manufacturer is requesting riociguat to be listed for patients who are unable to achieve disease control with another PAH therapy.[2]

Riociguat is also indicated for the treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4) and persistent or recurrent CTEPH after surgical treatment in adult patients (≥ 18 years of age) with WHO functional class II or III pulmonary hypertension.[1] Riociguat was previously reviewed for this indication (at the same submitted price) and received a "list with conditions" recommendation by the CADTH Canadian Drug Expert Committee (CDEC) in July 2014,[3] one of which was the requirement of a substantial reduction in price.

Summary of the economic analysis submitted by the manufacturer

The manufacturer submitted a cost-minimization analysis comparing riociguat (1 mg to 2.5 mg three times daily) with phosphodiesterase type 5 (PDE5) inhibitors sildenafil (20 mg three times daily) and tadalafil (20 mg twice daily); ERAs bosentan (62.5 mg twice daily for four weeks followed by 125 mg twice daily) and ambrisentan (10 mg once daily); and prostacyclins (PCs) epoprostenol (22 to 50 ng/kg/min) and treprostinil (35 to 90 ng/kg/min).[4] The manufacturer conducted two comparisons as part of its base-case analysis: monotherapy for patients unable to achieve disease control on existing therapy, where riociguat was compared with other PAH drugs used as monotherapy; and as combination therapy for patients unable to achieve disease control with monotherapy, where the combination of riociguat and an ERA was compared with other PAH combination therapies, which included ERA + PDE5 inhibitor, PDE5 inhibitor + PC, or an ERA + PC.

The manufacturer conducted the analysis on a drug class level rather than on an individual drug level; this was done by applying the relative usage of each drug within a given class (derived from IMS Brogan PharmaStat claims data and by making assumptions), in order to calculate a representative weighted average drug class cost.[4] The perspective was that of a publicly funded health care system with a time horizon of four months.[4]

In the absence of head-to-head trials, the assumption of similar efficacy was based on a manufacturer-submitted indirect treatment comparison (ITC)[2]. [redacted]

[redacted] Findings of the manufacturer-submitted ITC were generally consistent with the network meta-analysis (NMA) conducted by CADTH for the therapeutic review on PAH drugs.[5]

The manufacturer's analysis included drug costs and other direct health care resource use , such as time spent with a nurse, visits to a physician specialist, liver function tests, and hemoglobin blood tests.[4] Unit drug prices for all comparators were obtained from the Saskatchewan drug benefit formulary (cited April 2014). All prices excluded mark-up and dispensing fees. The unit cost for the various resources were obtained primarily from the Ontario Schedule of Benefits (cited May 2015) and the British Columbia Medical Services Commission Payment Schedule (based on August 2013 update, cited May 2015).[4]

Key limitations

- **Variability in the pricing of comparator drugs across public drug plans:** The manufacturer used the Saskatchewan drug benefit formulary to obtain prices for the comparator drugs in its base-case analysis. The manufacturer did not consider the variation in pricing across CADTH Common Drug Review (CDR)-participating drug plans. Many brand name drugs (e.g., brand name bosentan and brand name sildenafil) are now listed at the same price as their respective generics on some drug formularies such as those for Nova Scotia, New Brunswick, and Prince Edward Island.[6-8] Additionally, the manufacturer did not use the most commonly reimbursed price for generic bosentan and generic sildenafil, which would have been a more appropriate approach. The use of brand pricing or higher prices for generics for the comparator drugs underestimates the incremental cost of riociguat compared with other oral PAH drugs.
- **Underestimation of resource utilization:** The manufacturer included costs based on resource utilization estimates for riociguat and the comparator drugs, which in turn were based on input from various sources including the opinions of Canadian clinical experts. The clinical expert involved in this CDR review indicated that several of these estimates may have underestimated the costs associated with treatment with riociguat or overestimated the costs associated with the comparator drugs. See Appendix 2, Table 6 , for further details.
- **Unclear place in therapy of riociguat as a first-line treatment:** In 2014, based on a CADTH Therapeutic Review on drugs for PAH[5], which included a cost-utility analysis based on efficacy estimates derived from an NMA, CDEC recommended that sildenafil or tadalafil be the preferred initial therapy for adult patients with functional class II and III PAH (i.e., first-line drugs).[9] In a situation where sildenafil or tadalafil are not used as first-line therapy (due to an intolerance or a contraindication), ERAs would represent the best alternative option. This is because, based on the CDR analysis using revised drug costs and resource utilization, riociguat appears more expensive over a one-year time frame than all ERAs, including macitentan, which was not included in the manufacturer's analysis and which received a CDEC recommendation of "list with clinical criterion and condition"[10] in January 2015 (Table 7).
- **Limited evidence on the effectiveness and cost-effectiveness of riociguat as second-line treatment:** Riociguat is contraindicated for use with PDE5 inhibitors,[1] thus it cannot be added on as second-line therapy to sildenafil or tadalafil. Riociguat may be used in patients who are non-responsive to monotherapy with an ERA. Appropriate comparators to the ERA + riociguat combination would be switching therapy to another ERA, or using ERA + PC in patients with functional class III PAH only (see Figure 1 and Figure 2). In regards to the first comparison, as presented in Table 8 and Table 9, adding riociguat to an ERA is more costly than switching to

another ERA (assuming generic bosentan, the lowest priced ERA, is used initially), with a total incremental cost ranging from $13,815 to $16,012 per patient annually. However, for this scenario, a cost-utility analysis is needed to fully assess the comparative cost-effectiveness. For the second comparison, [redacted] As shown in Table 9, the combination of generic bosentan + riociguat would be more costly than generic bosentan + epoprostenol (total incremental cost ranging from $180 to $8,600 per patient annually), but less costly then generic bosentan + treprostinil (savings of $44,249 per patient annually). However, as noted in the CDR clinical review report, although the PATENT-1 trial[11] included patients who were on a previous therapy (ERA or prostanoids), these were likely stable, prevalent cases. Therefore, the comparative efficacy of riociguat used as add-on therapy in patients non-responsive to monotherapy remains unknown.

Issues for consideration

- The clinical expert noted that the most frequent contraindication to PDE5 inhibitors is concurrent nitrate use. Concomitant use of nitrates is also contraindicated with riociguat,[1] making its place in therapy more limited.
- Several public drug plans reimburse only up to the generic price of bosentan and sildenafil. If a public drug plan does reimburse a higher branded price, riociguat could be less costly (smaller incremental costs) or result in cost savings versus the comparators.
- Sildenafil may be used at doses higher than 20 mg three times daily in clinical practice.[12] Although the comparative efficacy of sildenafil at doses higher than 20 mg three times daily versus riociguat is unknown, when only drug costs are considered, even at a dose of 80 mg three times daily, sildenafil ($75.02 daily) remains less costly than riociguat ($128.25 daily).
- The patent for brand name ambrisentan is expected to expire in October 2015. Should generics become available in a near future, riociguat would result in greater incremental costs.

Results and conclusions

When riociguat is used as first-line monotherapy, CDR reanalyses showed that it is more costly than all other oral PAH drugs, including ERAs and PDE5 inhibitors, with total incremental costs (drug costs plus resource use costs) ranging from $1,873 to $39,987 per patient annually. When only drug costs are considered, a price reduction of 75% to 85% would be required for riociguat to equal the daily cost of the lowest priced ERA (generic bosentan) and PDE5 inhibitor (generic sildenafil, at the recommended dose of 20 mg three times daily), respectively.

When used as second-line therapy, either as monotherapy after switching from another oral PAH drug or as add-on combination therapy, riociguat's place in therapy is unclear, and there is limited clinical evidence supporting its efficacy and cost-effectiveness versus other comparators. A cost-utility analysis is required to assess the comparative cost-effectiveness of adding riociguat to an ERA versus switching to another ERA. Compared with other combination therapies, since riociguat is contraindicated for use with PDE5 inhibitors, the only relevant comparator is a combination ERA + PC, although this combination would be used only in patients with more advanced PAH (e.g., WHO functional class III). CDR reanalyses showed that the combination of generic bosentan + riociguat is more costly than generic bosentan + epoprostenol (total incremental costs ranging from $180 to $8,600 per patient annually), but less costly then generic bosentan + treprostinil (savings of $44,249 per patient annually).

APPENDIX 1: COST COMPARISON

The comparators presented in Table 1 have been deemed to be appropriate by clinical experts. 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. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

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

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Stimulators of soluble guanylate cyclase (sGC)						
Riociguat (Adempas)	0.5 mg 1.0 mg 1.5 mg 2.0 mg 2.5 mg	tablet	42.7500	1 to 2.5 mg three times daily	128.25	46,811
Endothelin Receptor Antagonists (ERAs)						
Ambrisentan (Volibris)	5 mg 10 mg	tablet	122.5200	5 to 10 mg once daily	122.52	44,720
Bosentan (Tracleer, generics)	62.5 mg 125 mg	tablet	16.0447[a]	62.5 mg twice daily for four weeks then 125 mg twice daily	32.09	11,713
Macitentan (Opsumit)	10 mg	tablet	116.5000[b]	10 mg once daily	116.50	42,523
Phosphodiesterase Type 5 (PDE5) Inhibitors						
Sildenafil (Revatio, generics)	20 mg 25 mg	tablet	6.2520[a] 6.6254[c]	20 mg three times daily[d]	18.76	6,846
Tadalafil (Adcirca)	20 mg	tablet	13.4970	40 mg once daily	26.99	9,853
Parenteral Prostanoids (prostacyclins, prostacyclin analogues)[e]						
Epoprostenol (Caripul)	0.5 mg/vial 1.5 mg/vial 50 mL diluent[f]	10 mL vial	17.1800 34.4500 3.1500	35 to 50 ng/kg/min[g]	104.69 to 153.50[h]	38,212- 56,027-
Epoprostenol (Flolan)	0.5 mg/vial 1.5 mg/vial 50 mL diluent[f]	10 mL vial	18.6400 37.2700 10.6500	35 to 50 ng/kg/min[g]	127.76 to 181.01[h]	46,631-66,068
Treprostinil (Remodulin)	1 mg/mL 2.5 mg/mL	20 mL multi-use vial[i]	45.0000 114.2500	50 to 60 ng/kg/min[g]	249.48[j]	91,060

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
	5 mg/mL 10 mg/mL		225.0000 450.0000			

CDR = CADTH Common Drug Review; PAH = pulmonary arterial hypertension.
[a] Nova Scotia drug benefit formulary (accessed October 2015).[6] CDR noted variability in the pricing of brand name bosentan and sildenafil across participating drug plans (ranging from $16.0447 to $64.1786 for bosentan and $6.2520 to $11.1219 for bosentan).
[b] Quebec drug benefit formulary (accessed October 2015).[14]
[c] British Columbia drug benefit formulary (accessed October 2015).[15] Note that only the 20 mg dosage strength is indicated for PAH.
[d] Higher doses may be administered in clinical practice (up to 80 mg three times daily).[12]
[e] Daily and annual drug costs for infused products do not include administration or drug delivery system costs. The Saskatchewan drug benefit formulary allows $46.00 per diem for supplies.
[f] 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.
[g] Recommended dose based on feedback from clinical expert.
[h] Based on average dose of 4.284 mg for a 70 kg patient over 24 hours (average between 35 to 50 ng/kg/min). Range of costs based on using 1.5 mg vial-0.5 mg vial, in addition to the 2x the cost of the diluent. No wastage assumed.
[i] Stable 30 days after the initial puncture of the rubber stopper.
[j] Based on average dose of 5.544 mg for a 70 kg patient over 24 hours (average between 50 to 60 ng/kg/min). No wastage assumed.
Note: All prices are from the Saskatchewan drug benefit formulary (accessed October 2015),[13] unless otherwise indicated, and do not include dispensing fees.

APPENDIX 1: PRICE REDUCTION ANALYSIS

As shown in Table 2, when only drug costs are considered, the price of riociguat would need to be reduced by 75% to be equivalent to the lowest priced endothelin receptor antagonist (ERA) (generic bosentan) and by 85% to be equivalent to the lowest priced phosphodiesterase type 5 (PDE5) inhibitor (sildenafil, at the recommended dose of 20 mg three times daily).

TABLE 2: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

Current Riociguat Unit Price[a]	Scenario	Reduced Unit Price for Riociguat	% Price Reduction
$42.7500[a] ($128.25 daily)	**Endothelin Receptor Antagonists (ERAs)**		
	Price reduction needed to equal the daily drug cost of ambrisentan ($122.52)[b]	$40.8400	4.47%
	Price reduction needed to equal the daily drug cost of macitentan ($116.50)[c]	$38.8333	9.16%
	Price reduction needed to equal the daily drug cost of generic bosentan ($32.09)[d]	$10.6966	74.98%
	Phosphodiesterase Type 5 (PDE5) Inhibitors		
	Price reduction needed to equal the daily drug cost of tadalafil ($26.99)[b]	$8.9967	78.96%
	Price reduction needed to equal the daily drug cost of generic sildenafil ($18.76)[d]	$6.2533	85.37%

[a] Manufacturer's submitted price for the 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg tablets. Equal to a daily drug cost of $128.25, as per cost comparison table.
[b] Based on the price obtained from the Saskatchewan drug benefit formulary (October 2015),[13] as per the cost comparison table.
[c] Based on the price obtained from the Quebec drug benefit formulary (October 2015),[14] as per the cost comparison table.
[d] Based on the price obtained from the Nova Scotia drug benefit formulary (October 2015),[6] as per the cost comparison table.

APPENDIX 2: REVIEWER WORKSHEETS

TABLE 3: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	Riociguat (Adempas) 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg oral tablets
Treatment	1 mg to 2.5 mg three times daily
Comparators	PDE5 inhibitors: • sildenafil (brand and generic) (20 mg t.i.d.) • tadalafil (20 mg b.i.d.) ERAs: • bosentan (brand and generic) (62.5 mg b.i.d. for 4 weeks and then 125 mg b.i.d.) • ambrisentan (10 mg q.d.) PCs: • epoprostenol (Caripul and Flolan) (22 to 50 ng/kg/min) • treprostinil (35 to 90 ng/kg/min)
Study Question	What is the incremental cost-effectiveness of: 1) riociguat compared with other PAH drugs used as monotherapy (PDE5 inhibitors, ERAs, or PCs); and 2) riociguat + ERA combination therapy compared with other PAH drugs used as part of combination therapy (ERA + PDE5 inhibitor, PDE5 inhibitor + PC, or ERA + PC) for the treatment of PAH from the perspective of a publically funded health care system over a four-month time horizon?
Type of Economic Evaluation	Cost-minimization analysis
Target Population	PAH patients unable to achieve disease control with existing therapy who require PAH monotherapy or PAH combination therapy
Perspective	Publically funded health care system
Outcomes Considered	6MWD, Borg dyspnea index score, PVR, WHO functional class and clinical worsening events
Key Data Sources	
Cost	• Cost of riociguat based on manufacturer's list price • Cost of other PAH drugs determined from the Saskatchewan provincial drug formulary • Cost of resources obtained primarily from the Ontario Schedule of Benefits and the British Columbia Medical Services Commission Payment Schedule
Clinical Efficacy	Based on a manufacturer-submitted indirect/mixed treatment comparison
Harms	Not considered
Market Share Data	IMS Brogan PharmaStat, using national public claims data from the time period of 2012-2014
Time Horizon	Four months
Results for Base Case	The manufacturer compared total costs of PAH drugs on a drug class level, rather than by individual drugs. **Comparison 1 (monotherapy)**, total cost per patient over 4 months — riociguat is more expensive in all comparisons: • riociguat: $15,586 • PDE5 inhibitors: $3,587 ($11,999 less costly then riociguat) • ERAs: $14,390 ($1,196 less costly than riociguat) • PCs: $19,662 ($4,076 more costly than riociguat)

Drug Product	Riociguat (Adempas) 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg oral tablets
	Comparison 2 (combination therapy), total cost per patient over 4 months — riociguat is more expensive compared with ERA + PDE5 inhibitor and ERA + PC: • riociguat + ERA: $29,782 • ERA + PDE5 inhibitor: $17,784 ($11,999 less costly than riociguat) • PDE5 inhibitor + PC: $23,053 ($6,729 less costly than riociguat) • ERA + PC: $33,858 ($4,076 more costly than riociguat)

6MWD = six-minute walk distance; b.i.d. = twice daily; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PC = prostacyclin; PDE5 = phosphodiesterase type 5; PVR = pulmonary vascular resistance; q.d. = once daily; t.i.d. = three times daily; WHO = World Health Organization.

Manufacturer's results

As part of the base-case analysis, the manufacturer conducted two comparisons, where riociguat may be used as monotherapy or as part of combination therapy. As mentioned, the results of the analysis were presented by pulmonary arterial hypertension (PAH) drug class. The manufacturer conducted this by using the relative usage of each drug within a given class in order to calculate a representative weighted average drug class cost.

As seen in Table 4, the total cost of monotherapy treatment with riociguat over a four- and 12-month time horizon was calculated to be $15,586 and $46,655, respectively, which was more costly than the weighted average drug class cost for phosphodiesterase type 5 (PDE5) inhibitors and endothelin receptor antagonists (ERAs); however, it was cost-saving versus the weighted average drug class cost for prostacyclins (PCs).

TABLE 4: MANUFACTURER'S RESULTS FOR PATIENTS RECEIVING MONOTHERAPY (COMPARISON 1)

PAH Drug (Monotherapy)	Time Horizon of 4 Months		Time Horizon of 12 Months[d]	
	Total cost of treatment per patient	Incremental cost vs. riociguat (savings)	Total cost of treatment per patient	Incremental cost vs. riociguat (savings)
Riociguat	$15,586	Reference	$46,655	Reference
PDE5 inhibitors[a]	$3,587	($11,999)	$10,658	($35,997)
ERAs[b]	$14,390	($1,196)	$43,028	($3,627)
PCs[c]	$19,662	$4,076	$58,726	$12,071

ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PC = prostacyclin; PDE5 = phosphodiesterase type 5; vs. = versus.
[a] Includes brand sildenafil (Revatio), generic sildenafil, and brand tadalafil (Adcirca).
[b] Includes brand bosentan (Tracleer), generic bosentan, and brand ambrisentan (Volibris).
[c] Includes brand treprostinil (Remodulin), and brand epoprostenol (Caripul and Flolan).
[d] Not part of manufacturer's base-case analysis. Time horizon of 12 months was part of the manufacturer's sensitivity analysis.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[4]

As seen in Table 5, the total cost of combination therapy with riociguat + ERA over a four- and 12-month time horizon was calculated to be $29,782 and $89,200, respectively, which was more costly than ERA + PDE5 inhibitor and PDE5 inhibitor + PC; however, was cost-saving versus ERA + PC.

TABLE 5: MANUFACTURER'S RESULTS FOR PATIENTS RECEIVING COMBINATION THERAPY (COMPARISON 2)

PAH Drug (Combination Therapy)	Time Horizon of 4 Months		Time Horizon of 12 Months[a]	
	Total cost of treatment per patient, over 4 months	Incremental cost vs. riociguat (savings)	Total cost of treatment per patient	Incremental cost vs. riociguat (savings)
Riociguat + ERA	$29,782	Reference	$89,200	Reference
ERA + PDE5 inhibitor	$17,784	($11,999)	$53,203	($35,997)
PDE5 inhibitor + PC	$23,053	($6,729)	$68,899	($20,301)
ERA + PC	$33,858	$4,076	$101,271	$12,071

ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PC = prostacyclin; PDE5= phosphodiesterase type 5; vs. = versus.

[a] Not part of manufacturer's base-case analysis. Time horizon of 12 months was part of the manufacturer's sensitivity analysis.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[4]

CADTH Common Drug Review results

CADTH Common Drug Review (CDR) conducted reanalyses based on several key parameters. These included:

- updated prices for several of the comparator drugs based on the cost comparison table (i.e., use of lowest publicly available generic price as of October 2015, see Table 1)
- updated resource use probabilities based on feedback from the clinical expert (as reported in Table 6)
- updated cost associated with several resources (i.e., hourly salary of a registered nurse, liver function test, and hematology blood test), based on the same sources used by the manufacturer
- updated recommended dosages for the PCs, based on feedback from the clinical expert (also seen in the cost comparison table).

Costs were calculated based on a 12-month (one-year) time horizon, assuming 365 days in this time frame (different from the manufacturer's sensitivity analysis, which assumed only 360 days over 12 months). CDR reanalyses also included the comparator macitentan.

TABLE 6: RESOURCE UTILIZATION FOR THE FIRST FOUR MONTHS – MANUFACTURER AND CADTH COMMON DRUG REVIEW ESTIMATES

Drugs	Hours With Nurse		Number of Visits to Physician Specialists		Number of Liver Function Tests		Number of Hemoglobin Tests	
	MFR	CDR	MFR	CDR	MFR	CDR	MFR	CDR
sGC stimulators								
Riociguat	1	Same	1	2	0	1	0	1
PDE5 inhibitors								
Revatio (sildenafil)	1	NA[a]	1	NA[a]	0	NA[a]	0	NA[a]
Generic sildenafil	1	Same	1	2	0	1	0	1
Adcirca (tadalafil)	1	Same	1	2	0	1	0	1
ERAs								
Tracleer (bosentan)	1	NA[a]	1	NA[a]	4	NA[a]	3	NA[a]
Generic bosentan	1	Same	1	2	4	Same	3	Same
Volibris (ambrisentan)	1	Same	1	2	4	Same	2	Same
PCs								
Remodulin (treprostinil)	3	Same	1	3	0	1	0	1
Flolan (epoprostenol)	3	Same	1	3	0	1	0	1
Caripul (epoprostenol)	3	Same	1	3	0	1	0	1

CDR = CADTH Common Drug Review; ERA = endothelin receptor antagonist; MFR = manufacturer; NA = not applicable; PC = prostacyclin; PDE5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase.
[a] CDR did not consider this drug in the reanalysis, as the brand was priced the same as the generic.

In general, the manufacturer's resource utilization estimates for subsequent four-month periods were consistent with those indicated by the clinical expert involved in the CDR review. The only difference was that patients on riociguat and PCs would receive a hemoglobin test once every four months.

Note that macitentan was assumed to have the same resource utilization as ambrisentan.

CDR reanalysis considered three different scenarios:

- Scenario 1 assesses treatment with riociguat as a first line of therapy. When similar efficacy among drugs is assumed (as per the CADTH network meta-analysis [NMA] and the manufacturer's indirect treatment comparison [ITC]),[2,5], the incremental cost of treatment with riociguat monotherapy was compared with monotherapy treatment with other PAH drugs in treatment-naive patients. As seen in Table 7 , riociguat is more expensive than all ERAs and PDE5 inhibitors, with total incremental costs ranging from $1,873 to $39,987 per patient annually. Riociguat may be cost-saving versus select PCs; however, these do not represent valid comparator drugs.

TABLE 7: SCENARIO 1 — CADTH COMMON DRUG REVIEW REANALYSIS IN TREATMENT-NAIVE PATIENTS (MONOTHERAPY)

PAH Drug (Monotherapy)	Costs per Patient, Over 12 Months			Incremental Cost (Savings) With Comparators
	Drug costs	Resource use costs	Total cost	
sGC stimulators				
Riociguat	$46,811	$641	$47,452	Reference
ERAs				
Ambrisentan	$44,720	$859	$45,578	($1,873)
Generic bosentan	$11,713	$870	$12,582	($34,870)
Macitentan	$42,523	$859	$43,381	($4,071)
PDE5 inhibitors				
Generic sildenafil	$6,846	$619	$7,465	($39,987)
Tadalafil	$9,853	$619	$10,472	($36,980)
PCs[b]				
Epoprostenol (Caripul)	$38,212	$823	$39,035	($8,417)
Epoprostenol (Flolan)	$46,631	$823	$47,455	$3
Treprostinil (Remodulin)	$91,060	$823	$91,884	$44,432

ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PC = prostacyclin; PDE5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase.
[a] A higher dose of sildenafil may be used in clinical practice (20 mg 4 times daily instead of 3 times daily).
[b] Note that these drugs are not real comparators.

The manufacturer is requesting riociguat be listed as a second line of therapy for patients who are unable to achieve disease control with other PAH drugs. However, as mentioned, riociguat likely has a very limited place in therapy as a second-line drug. As noted by the clinical expert, riociguat would likely be used only in treatment-experienced patients who are intolerant to a PDE5 inhibitor (due to a side effect) and who are on monotherapy with an ERA and are non-responsive. In this scenario, patients would likely start on the ERA bosentan, as it is the cheapest and most widely prescribed by physicians.

From this, as described by the clinical expert, there are two treatment pathways:
Scenario 2 applies to patients with functional class II PAH. Upon failing to respond to monotherapy on bosentan, these patients would either be switched to another drug within the same drug class of ERAs (i.e., ambrisentan or macitentan) or riociguat would be added on to bosentan (i.e., combination therapy) (see Figure 1, Appendix 4). As such, CDR compared the difference in total costs. As seen in Table 8, adding riociguat to generic bosentan is more costly than switching therapies within the drug class, with total incremental costs ranging from $13,815 to $16,012 per patient annually. However, as noted in the limitations, a cost-utility analysis is needed to assess this comparison, as the comparative clinical efficacy is unknown.

TABLE 8: SCENARIO 2 — CADTH COMMON DRUG REVIEW REANALYSIS IN PATIENTS WITH FUNCTIONAL CLASS II PULMONARY HYPERTENSION

PAH Drug	Costs per Patient, Over 12 Months			Incremental Cost (Savings) With Comparators
	Drug costs	Resource use costs	Total cost	
1) Combination therapy				
Add riociguat to generic bosentan	$58,524[a]	$870[b]	$59,393	Reference
2) Switch within drug class (ERAs)				
Ambrisentan monotherapy	$44,720	$859	$45,578	($13,815)
Macitentan monotherapy	$42,523	$859	$43,381	($16,012)

ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension.
[a] Drug costs based on adding the drug cost of riociguat to the drug cost of generic bosentan (per patient annually).
[b] Assumed that resources would be combined if on combination therapy. Thus, CADTH Common Drug Review reanalysis assumed resource utilization estimate that was the most conservative (in this case, bosentan was more resource-intensive).

- Scenario 3 applies to patients with functional class III PAH. Upon failing to respond to monotherapy on bosentan, these patients would either be switched to ambrisentan or macitentan, or either riociguat or a PC would be added on to bosentan (combination therapy). As noted by the clinical expert, PCs are given to more severe patients, and thus may be applicable in this scenario. As seen in Table 9, treatment with generic bosentan + riociguat combination therapy is more costly than treatment with generic bosentan + epoprostenol (total incremental costs ranging from $180 to $8,600 per patient annually, depending on which epoprostenol brand is used), but less expensive than treatment with generic bosentan + treprostinil (cost savings of $44,249 per patient annually). It should be noted that it is difficult to completely assess the overall costs incurred with treatment with a PC, as there are substantial administration costs and resources that need to be considered.

TABLE 9: SCENARIO 3 — CADTH COMMON DRUG REVIEW REANALYSIS IN PATIENTS WITH FUNCTIONAL CLASS III PULMONARY HYPERTENSION

PAH Drug	Costs per Patient, Over 12 Months			Incremental Cost (Savings) With Comparators
	Drug costs	Resource use costs	Total cost	
1) Combination therapy				
Add riociguat to generic bosentan	$58,524[a]	$870[b]	$59,393	Reference
Add a PC to generic bosentan:[c]				
Epoprostenol (Caripul)	$49,924	$870[b]	$50,794	($8,600)
Epoprostenol (Flolan)	$58,344	$870[b]	$59,214	($180)
Treprostinil (Remodulin)	$102,773	$870[b]	$103,642	$44,249
2) Switch within drug class (ERAs)				
Ambrisentan	$44,720	$859	$45,578	($13,815)
Macitentan	$42,523	$859	$43,381	($16,012)

ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PC = prostacyclin.
[a] Drug costs based on adding the drug cost of riociguat to the drug cost generic bosentan (per patient annually), as calculated in Table 8.
[b] Assumed that resources would be combined if on combination therapy. Thus, CADTH Common Drug Review reanalysis assumed resource utilization estimate that was the most conservative (in this case, bosentan was more resource-intensive).
[C] Drug costs based on adding the drug cost of the prostacyclin to the drug cost of generic bosentan (per patient annually), as calculated in Table 8.

TABLE 10: KEY LIMITATIONS

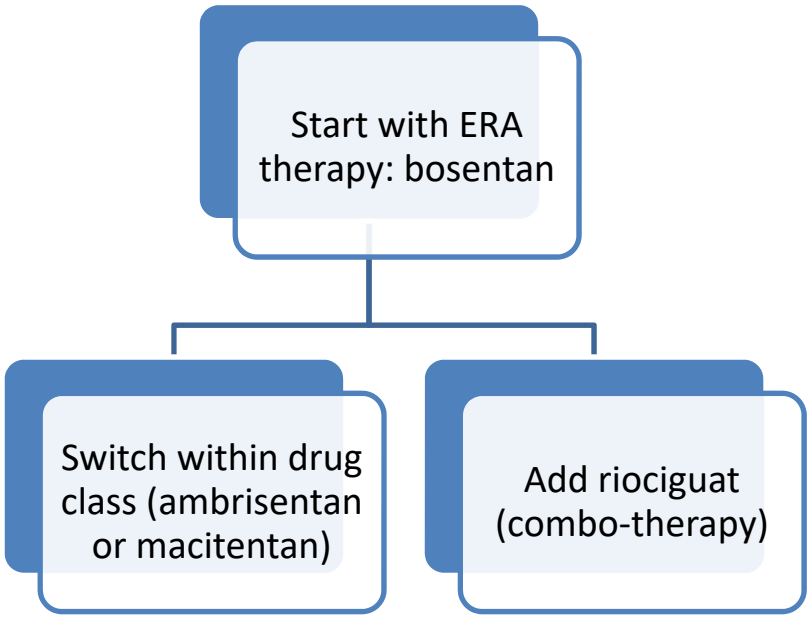
Identified Limitation	Description	Implication
Variability in the pricing of comparator drugs across public drug plans	The manufacturer used the Saskatchewan drug benefit formulary to obtain prices for the comparator drugs in its base-case analysis, while lower prices are available on other CDR-participating drug plans.	The use of brand pricing or higher prices for generics for the comparator drugs underestimates the incremental cost of riociguat.
Underestimation of resource utilization	The clinical expert indicated some of the manufacturer's estimates may not represent clinical practice.	May result in underestimating the costs associated with treatment with riociguat or overestimating the costs associated with the comparator drugs.
Exclusion of relevant comparator	The manufacturer did not consider the ERA macitentan in its base-case analysis.	Inclusion of all comparators provides for a more complete analysis.
Unclear place in therapy of riociguat as first-line drug	Several public drug plans have a preferential listing for sildenafil or tadalafil.	In a situation where sildenafil or tadalafil are not used as first line of therapy, an ERA would be a less costly option than riociguat.
Limited evidence on the effectiveness and cost-effectiveness of riociguat as a second-line drug	Adding riociguat to an ERA is more costly than switching to another ERA. [redacted] The combination of generic bosentan + riociguat would be more costly than generic bosentan + epoprostenol, but less costly then generic bosentan + treprostinil. Although the inclusion criteria for the PATENT-1 trial included patients who were on a previous therapy (ERA or prostanoids), these were likely stable, prevalent cases that would be able to tolerate receiving a placebo drug if randomized to that group.	A cost-utility analysis would have been needed to fully assess the comparative cost-effectiveness of adding riociguat to an ERA versus switching to a different ERA. Additionally, the comparative efficacy when riociguat is used as add-on therapy in patients non-responsive to monotherapy remains unknown, introducing uncertainty when estimating the cost-effectiveness.
Issues with the manufacturer-submitted ITC	[redacted]	Introduces slight uncertainty in the manufacturer's overall ITC results in terms of comparative clinical efficacy of PAH drugs.

Identified Limitation	Description	Implication
	[redacted]	
Uninformative time horizon	The manufacturer used a time horizon of 4 months to report the overall costs of riociguat, the PAH comparator drugs, and incremental cost versus riociguat for its base-case analysis. Although this may be valid in terms of when patients may modify their treatment, a time horizon of 12 months (or 1 year) is more informative.	Overall costs are greater as they are incurred over a larger time frame. CDR reanalysis considered a time horizon of 1 year.
Incorrect costs associated with resources	The unit costs the manufacturer used for the following resources were off by a few cents/dollars: the hourly salary for a registered nurse, liver function test, and hematology blood test.	Inaccurate unit costs result in inaccurate overall treatment costs of riociguat and all of the comparator drugs.
Inaccurate recommended dose for PCs	The manufacturer used a dosage of 22 to 50 ng/kg/min for epoprostenol (3.63 mg per day, on average). However, the clinical expert noted that the dosage would be closer to 35 to 50 ng/kg/min (which CDR assumed to be an average of 4.284 mg per day – see cost comparison table). Similarly, the manufacturer used a dosage of 35 to 90 ng/kg/min for treprostinil (6.30 mg per day, on average). However, the clinical expert noted that dosage would more likely be between 50 to 60 ng/kg/min (which CDR assumed to be an average of 5.544 mg per day).	In the case of epoprostenol, overestimates the incremental costs of riociguat. In the case of treprostinil, underestimates the incremental cost of riociguat.

CDR = CADTH Common Drug Review; ERA = endothelin receptor antagonist; ITC = indirect treatment comparison; PAH = pulmonary arterial hypertension; PC = prostacyclin.

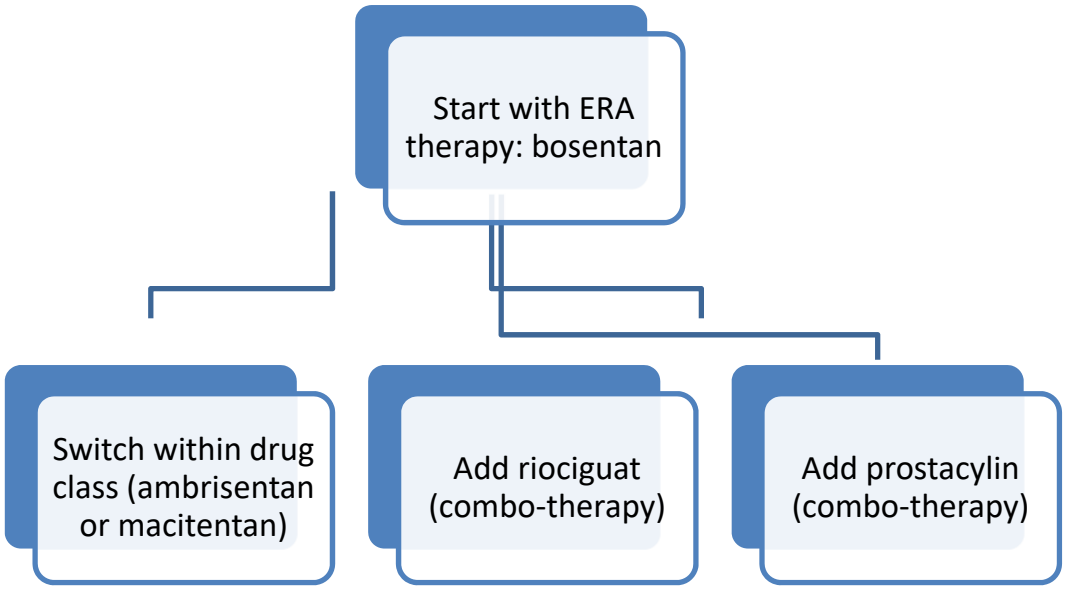
APPENDIX 3: TREATMENT PATHWAY DIAGRAMS

FIGURE 1: TREATMENT PATHWAY FOR PATIENTS WITH FUNCTIONAL CLASS II PULMONARY HYPERTENSION, IF INTOLERANT TO PHOSPHODIESTERASE TYPE 5 INHIBITORS, BASED ON FEEDBACK FROM CLINICAL EXPERT



ERA = endothelin receptor antagonist.

FIGURE 2: TREATMENT PATHWAY FOR PATIENTS WITH FUNCTIONAL CLASS III PULMONARY HYPERTENSION, IF INTOLERANT TO PHOSPHODIESTERASE TYPE 5 INHIBITORS, BASED ON FEEDBACK FROM CLINICAL EXPERT



ERA = endothelin receptor antagonist.

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