Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	riociguat (Adempas)
Indication	Management of inoperable chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4) or persistent or recurrent CTEPH after surgical treatment in adult patients ≥ 18 years of age with WHO functional class II or III pulmonary hypertension.
Listing request	As per indication
Manufacturers	Bayer HealthCare

Riociguat (Adempas) 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.

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ABBREVIATIONS

6MWD	six-minute walk distance
AE	adverse event
CCA	cost-consequence analysis
CDR	Common Drug Review
CEA	cost-effectiveness analysis
CI	confidence interval
CrI	credible interval
CTEPH	chronic thromboembolic pulmonary hypertension
CUA	cost-utility analysis
EQ-5D	EuroQol 5-Dimensions Questionnaire
FC	functional class
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
ITC	indirect treatment comparison
LPH	living with pulmonary hypertension questionnaire
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OCCI	Ontario Case Costing Initiative
OR	odds ratio
PAH	pulmonary arterial hypertension
RCT	randomized controlled trial
QALY	quality-adjusted life-year
TTCW	time to clinical worsening
WHO FC	World Health Organization functional class

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Riociguat (Adempas)
Study Question	*"What is the incremental cost per QALY gained, from a provincial government payer perspective for Adempas compared to placebo for the management of CTEPH in Canadian patients in WHO functional class II or III with inoperable CTEPH, or patients with persistent or recurrent pulmonary hypertension following pulmonary endarterectomy, over a patient lifetime horizon (maximum 20 years)?"*
Type of Economic Evaluation	• CUA • CCA
Target Population	Inoperable CTEPH patients or CTEPH patients with persistent or recurrent pulmonary hypertension after pulmonary endarterectomy
Treatment	0.5 to 2.5 mg three times a day
Outcomes	• CUA: cost per LY gained, cost per QALY gained • CCA: 6MWD, PVR, NT-proBNP, WHO FC, TTCW, Borg Dyspnea Index, EQ-5D, LPH, and SF-36
Comparators	• Placebo • Bosentan (generics and brand-name)
Perspective	Canadian ministry of health
Time Horizon	Lifetime (max 20 years)
Manufacturer's Results (Base Case)	• Riociguat vs. placebo: $173,524 per QALY • Riociguat vs. generic bosentan: $187,347 per QALY • Riociguat vs. Tracleer: riociguat dominates brand-name bosentan
Key Limitations and CDR Estimate(s)	• Riociguat is priced at $42.75 per tablet, or $128.25 daily. • Generic and brand-name bosentan are priced at $44.93 daily and $128.36 daily, respectively. The utilization of brand-name vs. generic bosentan varies across drug plans (from 0% to 95% of claims are for brand-name bosentan). **Riociguat vs. Placebo** • The long-term efficacy of riociguat is unclear. ICURs are robust in the CDR analyses, based on different assumptions on the relative efficacy of transition probabilities (± 20%). ICURs increase when a shorter time horizon is used, which indicates that much of the benefit occurs in the future. • The potential benefit of riociguat on mortality may be double counted. ICUR increases to $350,519 per QALY in the CDR analyses when mortality is mediated only through FC health status. **Riociguat vs. Generic/Brand-Name Bosentan (Most Relevant Comparator)** • The true relative efficacy is unknown. A manufacturer-funded ITC was performed, but the results were not used to inform transition through the FC health states. However, ICURs are robust (versus generic bosentan) in the CDR analyses, based on different assumptions on the relative efficacy of transition probabilities (± 20%). ICURs increase when a shorter time horizon is used (and indicate that much of the benefit occurs over a long time frame).

[redacted]	• The potential benefit of riociguat on mortality may be double counted and the ITC showed no statistically significant difference between riociguat and bosentan for this outcome. Where mortality risk is mediated only through FC health state status, riociguat is dominated by generic bosentan (more costly and less effective) and riociguat is less costly but less effective than Tracleer (CDR analysis). The true differences in mortality between riociguat and bosentan are unknown.

6MWD = six-minute walk distance; CCA = Cost-consequence analysis; CDR = Common Drug Review; CTEPH = chronic thromboembolic pulmonary hypertension; CUA = cost-utility analysis; EQ-5D = EuroQol 5-Dimensions Questionnaire; FC = functional class; ICUR = incremental cost-utility ratio; ITC = indirect treatment comparison; LPH = living with pulmonary hypertension questionnaire; LY = life-year; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PVR = pulmonary vascular resistance; QALY = quality-adjusted life-year; SF-36 = Short-Form 36 Health Survey; TTCW = time to clinical worsening; vs. = versus; WHO FC = World Health Organization functional class.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Riociguat (Adempas) is being reviewed for the treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment in adult patients (≥ 18 years of age) with World Health Organization functional class (WHO FC) II or III pulmonary hypertension. Riociguat is administered based on an individual dose titration of between 0.5 to 2.5 mg taken three times a day. The manufacturer submitted a price of $42.75 per tablet (0.5 mg, 1 mg, 1.5 mg, 2 mg, or 2.5 mg), or $128.25 daily.[1]

Summary of Economic Analysis

The manufacturer conducted a cost-utility analysis (CUA) from a Canadian public-payer perspective, over a 20-year time horizon, comparing riociguat with placebo and riociguat with generic and brand-name bosentan (Tracleer).

The 16-week cycle Markov model included the following health states: WHO FC II, WHO FC III, WHO FC IV, and death. WHO FC I was not included in the model since the CHEST-1 trial did not recruit patients in that health state. The clinical data from Phase III CHEST-1 and CHEST-2 trials were used to establish the characteristics of patients entering the economic model, transition probabilities between FC for placebo (CHEST-1) and riociguat (CHEST-2) for the first model cycle (16 weeks), the frequency of adverse events, and utility measurement. Comparison between riociguat and bosentan was performed with an indirect treatment comparison (ITC) using CHEST-1 and the BENEFiT trial.[2] Within each Markov cycle, patients can remain in the same health state, improve by one FC, worsen by one FC, or die. After the first cycle, FC transitions were derived from the extrapolation of survival curves derived from statistical fitting of the trial data. Only liver toxicity and hypotension were included in the model as adverse events. Mortality data by FC were from a European chart review commissioned by the manufacturer.[1]

Utilities associated with FC status were collected from CHEST-1. Disutilities associated with adverse events were not considered in the model. Drug costs for riociguat were provided by the manufacturer, while costs for Tracleer and generic bosentan were obtained from the Quebec Formulary (June 2013). Treatment-specific one-off initiation costs were based on discussions with clinical experts. Supportive care use (such as supplemental oxygen, warfarin, and diuretics) was based on the European chart review, with the unit cost derived from Canadian sources such as the Ontario Drug Benefit (ODB) Formulary and a study on the cost of management of warfarin.[3] Similarly, ongoing health care resource utilization associated with CTEPH (hospitalizations, specialists visits, and examination and diagnostic testing) were also based on the European chart review, with the unit costs estimated from Canadian sources (Ontario Schedule of Benefits, Ontario Case Costing Initiative (OCCI), and BC Medical Services Commission payment schedule).

Results of Manufacturer's Analysis

Using the health-payer perspective, the manufacturer reports an incremental cost per quality-adjusted life-year (QALY) for riociguat compared with placebo of $173,524. The incremental cost per QALY for riociguat compared with generic bosentan is $187,347. Riociguat dominates Tracleer.

Interpretations and Key Limitations

Short Duration of Clinical Trials and Assumption of Long-Term Relative Efficacy

Given the duration of existing trials (16 weeks for CHEST-1 and approximately one year for CHEST-2), it is not established that long-term differences will occur in the clinically important outcome of FC (the major factor driving quality of life and disease costs). If the treatment effect is not durable or attenuates, the cost-effectiveness ratio will be greater.

Mortality and Relative Efficacy

In the model, mortality is assumed to increase by worsening FC (which, according to the clinical expert, is a reasonable assumption), but mortality is also impacted by treatment strategy, regardless of FC health state (informed by the ITC, but not stratified by FC status). This might lead to double counting of the potential mortality benefit of riociguat. True differences in mortality between riociguat and comparators are not known.

Transition Probabilities

The manufacturer states that it was not possible to derive the odds ratio (OR) from a formal indirect comparison between riociguat and bosentan for each FC health state, since individual patient data were not available. Therefore, the ORs for transition to FC health states in patients treated with bosentan were estimated from the BENEFiT study (bosentan group only) using a calibration approach. Of note, the ITC[4] submitted by the manufacturer reported non-significantly increased odds of being in a better functional class (FC I or II versus FC III, IV, or death) at the study end point when treated with riociguat compared to bosentan (OR 1.15, 95% credible interval [CrI], 0.51 to 2.61). The true relative efficacy of riociguat and bosentan is not clear. This is a key limitation, as in Canada bosentan is currently used in the majority of patients who would be eligible for riociguat.

Titration Cost Not Included in the Cost-Utility Analysis

There were four nursing visits for treatment initiation with riociguat in the cost-consequence analysis (CCA), but only one visit in the CUA model. However, given the high drug cost, the impact of the titration cost on the incremental cost-utility ratio (ICUR) is minimal.

Results of CADTH Common Drug Review Analysis

Riociguat Versus Placebo

- Uncertainty in long-term efficacy: Shortening the time horizon to five years, the incremental QALYs associated with riociguat compared with placebo decreased from 0.887 to 0.275, and the cost per QALY increased to $434,311 for riociguat versus placebo, highlighting that a majority of the incremental benefit accrued in the model is well beyond the timeframe of current randomized controlled trials (RCTs).
- Mortality might be double counted. ICUR increases to $350,519 per QALY in the CADTH Common Drug Review (CDR) analyses when mortality risk by FC class only is considered.
- Uncertainty in transition probabilities through FC. Exploring the ± 20% for the transition probabilities did not significantly alter results.

Riociguat Versus Generic Bosentan

- Uncertainty in long-term efficacy: When shortening the time horizon to five years, the incremental QALYs decreased from 0.416 to 0.137 for riociguat compared with generic bosentan, and the cost per QALY increased to $492,361.
- Mortality might be double counted. Riociguat is dominated by generic bosentan (more costly and less effective: 5.387 versus 5.839 QALYs, respectively) in the CDR analyses when mortality risk by FC class only is considered, although true differences in mortality are not known.
- Uncertainty in transition probabilities through FC. Exploring the ± 20% for the transition probabilities did not significantly alter results.

Riociguat Versus Brand-Name Bosentan (Tracleer)

- Uncertainty in long-term relative efficacy: Riociguat dominated Tracleer in all time horizons tested.
- Mortality might be double counted. Riociguat is less costly but less effective than Tracleer when mortality risk by FC class only is considered in sensitivity analyses. The cost per QALY for Tracleer is $227,457 compared with riociguat.

Issues for Consideration

- According to the clinical expert, the majority of eligible patients are currently treated with bosentan (through special authorization programs). There is wide variation in the proportion of patients treated with Tracleer versus generic bosentan (from 0 to approximately 95%), which has important implications for incremental cost. Riociguat and Tracleer have almost the same daily cost ($128.25 versus $128.36, respectively). Tracleer appears to be favoured by clinical experts due to industry-supported patient programs, concerns around the range of bioavailability of generics, and switching "stable" patients to generic. The true difference in efficacy and side effects of generic versus brand-name bosentan is not known. As the proportion of patients on Tracleer versus generics increases, incremental drug costs for riociguat become smaller.
- According to the clinical expert, since there is currently no Health Canada–approved drug for this indicated patient group, riociguat will become first-line treatment if listed by drug plans.
- This medication, if approved, is unlikely to modify consideration of surgical management which, if feasible, is considered optimal treatment.
- Riociguat is also indicated for treatment in patients with pulmonary arterial hypertension (PAH), and is likely to be used in non-CTEPH PAH.

Conclusions

In the CDR reanalysis, eliminating the possible double counting of mortality benefit, the ICUR increases to $350,519 per QALY for riociguat versus placebo, and riociguat results in lower QALYs than bosentan (riociguat is dominated by generic bosentan; riociguat is less costly, but less effective than Tracleer). However, true differences in mortality between riociguat and bosentan are unclear. There is significant uncertainty in the ICUR given lack of head-to-head trials of riociguat versus bosentan, the approach to modelling relative efficacy, and lack of data on long-term outcomes. Several scenarios result in greater ICURs than the base case presented by the manufacturer.

If drug costs of riociguat versus bosentan only are examined, riociguat has similar costs in jurisdictions where all patients are receiving Tracleer, but incremental costs of riociguat versus bosentan rise as this proportion falls.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

"What is the incremental cost per quality-adjusted life-year (QALY) gained, from a provincial government payer perspective for Adempas compared with placebo for the management of chronic thromboembolic pulmonary hypertension (CTEPH) in Canadian patients in World Health Organization functional class (WHO FC) II or III with inoperable CTEPH, or patients with persistent or recurrent pulmonary hypertension following pulmonary endarterectomy, over a patient lifetime horizon (maximum 20 years)?"

(Manufacturer's submission,[1] page 57.)

1.2 Treatment

An individual dose titration of between 0.5 mg and 2.5 mg, orally, three times a day.

1.3 Comparators

Placebo or bosentan (generic) and Tracleer (brand-name bosentan). According to the clinical expert, 60% to 80% of the indicated patient group are on off-label treatment, bosentan being the most commonly used, although not approved by Health Canada. As such, it is appropriate to consider bosentan as the most appropriate comparator in the cost-utility analysis (CUA). Please refer to Table 3 for the proportion of brand-name versus generic bosentan across provinces and drug plans.

1.4 Type of Economic Evaluation

A CUA was undertaken and is appropriate according to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines. The primary perspective utilized in the model is that of the Canadian public payer.

In addition, a cost-consequence analysis (CCA) was conducted when the costs and consequences of the alternative treatments are listed separately in a disaggregated format. A summary of the CCA is presented in Appendix 3.

1.5 Population

The population comprised adult patients (≥ 18 years old) with 1) inoperable CTEPH, or 2) persistent or recurrent pulmonary hypertension after pulmonary endarterectomy.

2. METHODS

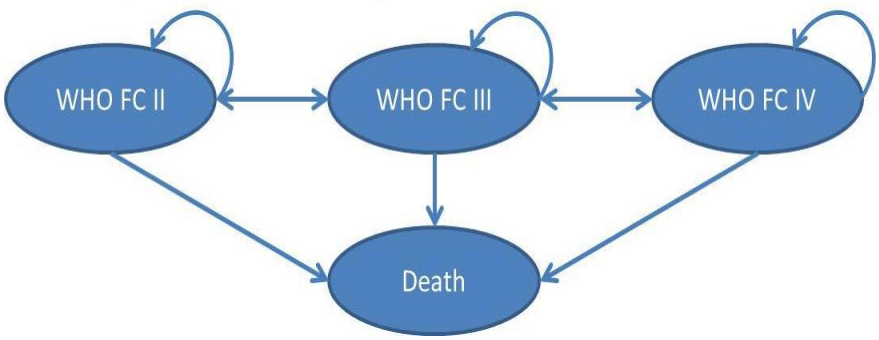
Please see Table 8 for a summary of the key limitations associated with the methodology used by the manufacturer.

2.1 Model Structure

The CUA consists of a 20-year Markov model that utilizes efficacy data from a phase III RCT (CHEST-1[5]) comparing riociguat with placebo, and an ongoing open-label extension study (CHEST-2). The Markov health states included WHO FC II, WHO FC III, WHO FC IV, and death (Figure 1). FC I was not included as the CHEST-1 clinical trial did not recruit patients in FC I. The cycle length in the Markov model was four

months (16 weeks) to correspond with the length of the CHEST-1 study. In each model cycle, patients can remain stable (i.e., in the same FC health state), improve by one FC, worsen by one FC, or die. The transition probability of FC change was based on data from the CHEST-1 (riociguat and placebo) and CHEST-2 (riociguat) trials.

FIGURE 1: MARKOV MODEL STRUCTURE



Source: Manufacturer's submission.[1]

2.2 Clinical Inputs

2.2.1 Efficacy

The clinical data from Phase III CHEST-1 and CHEST-2 trials were used to establish transition probabilities between FC for placebo (CHEST-1) and riociguat (CHEST-1 and CHEST-2). A survival analysis–based approach using CHEST-1 and CHEST-2 data was used to estimate transition probabilities over a longer time frame (lifetime horizon [20 years]). For the first model cycle (first 16 weeks), FC transitions were obtained from the CHEST-1 clinical trial for both placebo and riociguat. After the first 16 weeks, FC transitions were derived from the extrapolation of survival curves derived from statistical fitting of the CHEST-2 data for riociguat. Data from all patients treated with riociguat in the open-label CHEST-2 extension study were included in the analysis. The transition probabilities for patients treated with placebo beyond 16 weeks were based on extrapolations of data from CHEST-1 placebo-treated patients. Odd ratios (ORs) for FC change in patients treated with riociguat in the first 16-week cycle of the model were calculated by comparing the Kaplan-Meier curves for each CHEST-1 treatment group. ORs for riociguat for cycles of the model after the initial 16 weeks were calculated by comparing extrapolations of patients on riociguat in CHEST-2 to the extrapolations of the placebo group in CHEST-1.

A secondary analysis comparing riociguat with bosentan using an indirect treatment comparison (ITC) was also undertaken. Published cohort-level data from the BENEFiT trial[2] were used to estimate ORs for each FC transition for bosentan versus placebo. The ORs for bosentan were assumed to remain constant from the first 16-week cycle and throughout the remaining lifetime of the patient.

2.2.2 Harms

Adverse event (AE) rates were collected from the CHEST-1 and CHEST-2 trials. Only AEs with an incidence of 5% or more were included in the model. In the manufacturer-conducted CTEPH tracking study, the top three AEs of concern to physicians were liver toxicity, hypotension, and arrhythmia. Since riociguat did not increase the risk of arrhythmia (as confirmed by the CHEST-2 study), only liver-function test abnormalities and hypotension were included in the model. AE rates for patients treated with bosentan were collected from the drug's US package inserts.

2.2.3 Natural History

The patient registry data were deemed insufficient to determine robust natural history of CTEPH disease progression since all patients in the registry were on treatment and treatment groups were usually pooled. As such, the long-term outcomes were modelled from the extrapolation of trial data as described in 2.2.1.

2.2.4 Mortality

Mortality rates by FC were derived from a European chart review commissioned by the manufacturer that included 19 pulmonary hypertension specialist–treatment sites in six countries and a total of 119 CTEPH and 285 PAH patients. These rates were converted to a per-cycle probability of death. FC III and IV mortality rates were assumed to be the same, as the European chart review data suggested that the probability of mortality was lower in FC IV than in FC II or FC III), which lacked face validity. The risk of mortality for patients treated with riociguat was derived from the CHEST-1 clinical trial. The OR for riociguat versus bosentan was based on an ITC of the CHEST-1 trial data against BENEFiT trial.[4]

2.2.5 Quality of Life

Utility values were determined using EQ-5D scores of patients in the CHEST-1 study, as determined for each FC health state.

More details on how the utility scores were assigned are listed in section 2.2.9. _Utilities_1

2.2.6 Costs

Resource use was considered from the perspective of the public payer in the base-case models.

2.2.7 Drug Costs

The price of riociguat is $42.75 per 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, or 2.5 mg tablet. Riociguat is administered based on an individual dose titration between 0.5 to 2.5 mg taken orally, three times a day. This corresponds to a daily cost of $128.25 or $46,811.25 annually.

Bosentan is available as Tracleer (brand-name bosentan) and generic bosentan. The manufacturer used the Quebec Formulary list price for Tracleer ($64.18 per 62.5 mg or 125 mg tablet) and generic bosentan ($22.46 per 62.5 mg or 125 mg tablet). Bosentan is administered at a dose of 62.5 mg twice daily for 4 weeks and 125 mg twice daily thereafter. This corresponds to a daily cost of $128.36 for Tracleer ($46,851.40 annually) and a daily cost of $44.92 for generic bosentan ($16,395.80 annually).

The model also included one-off initiation costs that were drug-specific. At treatment initiation, all patients receiving drugs spend one hour with a nurse specialist who will provide patients with information on drug dose and drug administration, etc. Patients prescribed bosentan also undergo an initial liver-function test to monitor hepatic enzymes. The cost of a liver-function test (ALT or AST) is $18.82 and was obtained from the British Columbia Medical Services Commission Payment Schedule.

Supportive care costs comprised of supplemental oxygen, warfarin, and diuretics were also included. Based on the European chart review, oxygen use was assumed to be 26% for all patients in all FCs. The daily dosage was assumed to be 1,360 litres for FC II and III, and 2,122 litres for FC IV. The cost of oxygen ($0.003/L) was obtained from an oxygen supplier in Ontario. The daily dose of warfarin was assumed to be 5 mg for all patients, with a unit cost of $0.0675 per tablet from the Ontario Drug Formulary. A monthly cost of warfarin monitoring ($31.13) derived from a Canadian study[3] was also included. All patients were also treated with hydrochlorothiazide (HCTZ) at 25 mg per day, with a unit cost of $0.0157 from the Ontario Drug Formulary.

2.2.8 Event Treatment Costs

Ongoing costs associated with CTEPH included hospitalizations, visits with treating specialists, and examination and diagnostic testing (ventilation/perfusion scan, echocardiogram, 6MWD test, blood test [specifically, B-type natriuretic peptide test] [BNP or NT-proBNP test]). The resource utilization per cycle was based on discussions with Canadian CTEPH experts and data from the European chart review and the unit costs were obtained from Canadian sources (Ontario Schedule of Benefits, OCCI, and BC Medical Services Commission payment schedule). Based on the European chart review, patients would be hospitalized 1.8 times on average per year, corresponding to 0.6 hospitalizations per cycle for all FC classes. It was also assumed that patients would undergo routine examination and diagnostic tests during each follow-up visit in each cycle based on experts' opinions. Same event treatment costs ($1,619.35 per cycle) were applied to all FC. However, patients prescribed bosentan incurred additional costs ($76.60 per cycle) as they underwent routine liver-function tests to monitor hepatic enzymes at each follow-up visit.

AE costs were broken down into two types: one-time cost in the first cycle and ongoing costs in subsequent cycles. Patients with liver abnormalities were assumed to receive additional liver-function tests above the routine tests captured in ongoing monitoring costs, both in the first and subsequent cycles. Hypotension was assumed to involve potential drug dose reductions, and assumed to incur a one-time cost for a follow-up visit to the treating specialist in 50% of cases, given that not all patients would require such a visit.

2.2.9 Utilities

Utility values were assigned according to FC status. CHEST-1 reported utilities by baseline FC, change over time by treatment group, and change over time by FC. Pooled baseline (pre-treatment) utilities from the riociguat and placebo arms of CHEST-1 stratified by FC were used to determine a utility score for each health state in the model. These values were validated by published studies in PAH.

2.2.10 Time Horizon

The time horizon was based on the lifetime of CTEPH patients with a maximum of 20 years. The time horizon in the model can also be modified from four months to 30 years.

2.2.11 Discounting

According to the CADTH guidelines, costs and consequences occurring after 12 months were discounted at an annual rate of 5%. The results were presented in 2013 Canadian dollars.

2.2.12 Validation

Information on model validation was not provided in the submission.

3. RESULTS

3.1 Manufacturer's Base Case

In the reference case, the manufacturer reported that the total cost for riociguat was $191,214, an incremental cost of $153,904 compared with placebo. Riociguat resulted in additional drug costs of $147,809 compared with placebo. Treatment with riociguat resulted in a total of 5.387 QALYs, an additional 0.887 QALY compared with placebo; therefore, the incremental cost per QALY gained was $173,524.

For riociguat versus generic bosentan, the manufacturer reported that the total cost for riociguat was $191,214, an incremental cost of $77,848 compared with generic bosentan. Riociguat resulted in additional drug costs of $75,634 compared with generic bosentan. Treatment with riociguat resulted in 5.387 total QALYs, an additional 0.416 QALY compared with generic bosentan; therefore, the incremental cost per QALY gained was $187,347.

For riociguat versus Tracleer, riociguat dominates Tracleer as it has a lower drug cost (–$58,409) and is more effective. While the daily drug costs are the same for Tracleer and riociguat, the savings in drug costs are due to the fact that a higher proportion of patients continued on drug treatment in the Tracleer-treated group compared with those treated with riociguat, as the withdrawal rates were lower for Tracleer (3.8% versus 8% for riociguat).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

Comparators	Total Costs ($)	Incremental Cost of Riociguat ($)	Total QALYs	Incremental QALYs of Riociguat vs. Comparator	Incremental Cost Per QALY of Riociguat vs. Comparator
Riociguat	191,214		5.387	Reference	Reference
Placebo	37,311	153,904	4.500	0.887	173,524
Bosentan (generic)	113,366	77,848	4.971	0.416	187,347
Tracleer (brand-name)	247,409	–56,195	4.971	0.416	Dominant

QALY = quality-adjusted life-year; vs. = versus.
Source: Manufacturer's submission.[1]

3.2 Summary of the Manufacturer's Sensitivity Analyses

Uncertainty was addressed using a Monte Carlo simulation analysis and one-way deterministic sensitivity analyses that varied model parameters by using alternative values.

3.2.1 One-Way Sensitivity Analyses

A series of one-way sensitivity analyses (95% confidence interval [CI] of the parameter, unless specified) was conducted by the manufacturer comparing riociguat with placebo. The parameters included starting age (47.6 years, 71.4 years); change in the utility score of each FC; time horizon (10, 15 years); mortality OR; discount rates; baseline FC status (proportion of patients in each FC); percentage of male; transition probabilities; drug costs (± 20%); and ongoing costs (± 20%).

The reference case result for riociguat compared with placebo was $173,524 per QALY. The following parameters increased the incremental cost per QALY gained by more than 25% for riociguat:

- increased starting age to 71.4 years — cost per QALY was $276,904
- decreased time horizon to 10 years — cost per QALY was $240,109
- decreased utility of FC II (lower 95% CI) — cost per QALY was $235,969
- mortality OR, riociguat versus placebo (0.93 instead of 0.31) — cost per QALY was $220,784.

Sensitivity analyses by the manufacturer comparing riociguat with bosentan were not described in the submission but were included in the economic model. The reference case result for riociguat compared with bosentan was $187,347 per QALY. The following parameters increased the incremental cost per QALY gained by more than 25% for riociguat:

- increased mortality OR, riociguat versus bosentan (0.96) — cost per QALY was $979,263
- decreased mortality OR, riociguat versus placebo (0.1033) — cost per QALY was $468,277
- decreased the starting age to 47.6 years — cost per QALY was $452,508
- decreased mortality in FC III for bosentan — cost per QALY was $248,539.

The reference case result for riociguat compared with Tracleer was that riociguat was dominant (more QALYs and lower cost). Manufacturer's sensitivity analyses on the parameters above did not change this conclusion.

3.2.2 Probabilistic Sensitivity Analysis

According to the acceptability curves from the probabilistic sensitivity analyses, there is 0% probability that the incremental cost-effectiveness ratio (ICER) would fall below a $50,000 per QALY threshold for riociguat versus placebo.

3.3 CADTH Common Drug Review Analyses

3.3.1 Riociguat Versus Placebo

a) Functional Class Transition Probabilities

Transition probabilities between functional classes (FC II to FC III, FC III to FC II, FC III to FC IV, FC IV to FC III) at different cycles of the model were tested. When the lower and upper 95% CIs of the OR for transition for riociguat in the first 16 weeks are used (assuming CI bounds are 20% above and below mean), the ICUR is between $172,985 to $174,392 per QALY. When ± 20% is used after the first 16 weeks, the ICUR is between $173,204 to $174,093 per QALY. When ± 20% is used for both periods, the ICUR is between $173,652 to $174,294 per QALY. When it is assumed there is no change in transition probabilities after two years (patients transition through FC health states in same manner), the ICUR increases to $209,518 per QALY.

b) Mortality

In the manufacturer's economic model, mortality varies by FC health state, as well as by treatment. If the risk of mortality is fully reflected by increases in mortality by FC health state (additional mortality benefit is excluded: OR for riociguat versus placebo is set to unity, and same mortality risk applied for each treatment within the same FC), the ICUR increases to $350,519 per QALY. If same mortality is assumed in all FC health states, and the OR for mortality from the ITC is used, the ICUR increases to $187,397 per QALY.

c) Titration Cost

There were four nursing visits for treatment initiation with riociguat in the CCA, but only one visit in the CUA model. If 4 nursing visits are used in the model, the ICUR increases to $173,590 per QALY.

3.3.2 Riociguat Versus Generic Bosentan

FC Transition Probabilities

When ± 20% of the OR for transition for riociguat in the first 16 weeks is explored, the ICUR ranges between $185,841 to $188,335 per QALY. When the ± 20% is used after the first 16 weeks, the ICUR is between $179,939 to $196,626 per QALY. When the ± 20% is used for both periods, the ICUR is between $180,741 to $194,654 per QALY.

a) Mortality

If the mortality risk is fully captured by FC health state (the OR for mortality is set to unity for riociguat versus bosentan, and the same mortality risk applied for each treatment within the same FC), generic bosentan is the dominant strategy (less costly and more effective). If mortality is equal across all FC health states and the OR of mortality from the ITC is used, the ICUR decreases to $134,865 per QALY.

b) Titration Cost

There were four nursing visits for treatment initiation with riociguat in the CCA, but only one visit in the CUA model. If 4 nursing visits are used in the model, the ICUR increases to $187,486 per QALY.

3.3.3 Riociguat Versus Tracleer

a) Discontinuation Rate

It is not clear that discontinuation rates are truly different between riociguat and Tracleer (ITC reported discontinuation due to AE with a credible interval (CrI) overlapping unity: OR riociguat versus Tracleer: 2.53; 95% CrI, 0.23 to 27.73). If set to be equal (3.8%), there is no longer cost savings associated with riociguat, and incremental costs increase to $47,358, resulting an ICUR of $49,099 per QALY.

b) Mortality

If the mortality risk is fully captured by FC health state (the OR for mortality set to unity for riociguat versus Tracleer and same mortality risk applied for each treatment within the same FC), riociguat is less costly, but less effective than Tracleer. The ICUR for Tracleer is $227,861 per QALY when compared with riociguat.

3.3.4 Riociguat Versus Mix of Generic Bosentan and Tracleer

Even if bosentan is available in generics, many provincial drug plans still cover Tracleer under exceptional access program (please refer to the Drug Plan Benefit Listings Table). According to the clinical expert, patients and physicians with CTEPH and PAH are reluctant to switch from Tracleer to generics because they are concerned by the potential variability in bioavailability between generics and lack of patient-support program. 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 across provinces, ranging from 0% to 96% of claims. (PharmaStat data from IMS Health Canada Inc., 2013). However, the PharmaStat data does not differentiate the indication; claims above likely include PAH patients as well as CTEPH patients (Table 3).

TABLE 3: PROPORTION OF CLAIMS FOR 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%)

NIHB = Non-Insured Health Benefits.

There were no data available for Alberta and Manitoba. According to the clinical expert, approximately 100% in Alberta and 80% of patients in Manitoba are on Tracleer.

The annual drug cost per patient of riociguat versus different mix of generic bosentan (Tracleer) is listed in Table 4.

TABLE 4: ANNUAL DRUG COSTS OF RIOCIGUAT VERSUS DIFFERENT MIX OF GENERIC BOSENTAN (TRACLEER)

Annual Drug Cost Per Patient ($)		
Scenario	**Mix of Bosentan and Tracleer**	**Riociguat**
100% bosentan versus 0% Tracleer	16,399	46,811
90% bosentan versus 10% Tracleer	19,445	
80% bosentan versus 20% Tracleer	22,490	
70% bosentan versus 30% Tracleer	25,535	
60% bosentan versus 40% Tracleer	28,580	
50% bosentan versus 50% Tracleer	31,625	
40% bosentan versus 60% Tracleer	34,671	
30% bosentan versus 70% Tracleer	37,716	
20% bosentan versus 80% Tracleer	40,761	
10% bosentan versus 90% Tracleer	43,806	
0% bosentan versus 100% Tracleer	46,851	

CDR also estimated the cost per QALY with a different mix of patients on generic versus brand-name drugs based on the manufacturer's base-case results (Table 5).

TABLE 5: CADTH COMMON DRUG REVIEW REANALYSIS OF INCREMENTAL COST-UTILITY RATIOS FOR RIOCIGUAT VERSUS BOSENTAN FOR VARYING UTILIZATION OF TRACLEER

Scenario	ICUR ($/QALY) Based on Manufacturer's Analysis Riociguat vs. Mix of Bosentan and Tracleer	ICUR ($/QALY) Based on CDR Reanalysis Assuming Mortality Based on FC Only Riociguat vs. Mix of Bosentan and Tracleer
90% bosentan vs. 10% Tracleer	155,104	Dominated
80% bosentan vs. 20% Tracleer	122,861	Dominated
70% bosentan vs. 30% Tracleer	90,618	Dominated
60% bosentan vs. 40% Tracleer	58,375	Less costly (–$7,219), less effective (–0.453 QALYs)
50% bosentan vs. 50% Tracleer	26,131	Less costly (–$23,189), less effective (–0.453 QALYs)
40% bosentan vs. 60% Tracleer	Dominant	Less costly (–$39,158), less effective (–0.453 QALYs)
30% bosentan vs. 70% Tracleer	Dominant	Less costly (–$55,128), less effective (–0.453 QALYs)
20% bosentan vs. 80% Tracleer	Dominant	Less costly (–$71,098), less effective (–0.453 QALYs)
10% bosentan vs. 90% Tracleer	Dominant	Less costly (–$87,068), less effective (–0.453 QALYs)

FC = functional class; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Although the drug costs of riociguat and Tracleer are similar (daily cost of $128.25 versus $128.36, respectively), there are additional monitoring costs associated with Tracleer (one additional liver-function test per month at an additional cost of $225.84 annually). As such, assuming equal efficacy between the two drugs (as true relative efficacy is unknown), riociguat is slightly less costly than Tracleer.

A summary of key CDR reanalyses is presented in Table 6. The CDR reanalyses, which accounted for potential double counting of the benefit of riociguat on mortality, showed that the base-case analysis submitted by the manufacturer likely underestimated the ICUR of riociguat compared with placebo or generic bosentan.

TABLE 6: SUMMARY OF CADTH COMMON DRUG REVIEW REANALYSES OF INCREMENTAL COST-UTILITY RATIOS FOR RIOCIGUAT VERSUS PLACEBO AND RIOCIGUAT VERSUS GENERIC BOSENTAN

	ICURs for Riociguat vs. Placebo	ICURs for Riociguat vs. Generic Bosentan
Manufacturer's base case	173,524	187,347
Cost per life-year	134,217	120,075
Time horizon		
1 year	1,616,001	2,771,047
5 years	434,311	492,361
10 years	240,109	253,476

	ICURs for Riociguat vs. Placebo	ICURs for Riociguat vs. Generic Bosentan
Transition probabilities (± 20%) First 16 weeks After 16 weeks Both times Same efficacy after 2 years	 172,985 to 174,392 173,204 to 174,093 173,652 to 174,294 209,518	 185,841 to 188,335 179,939 to 196,626 180,741 to 194,654 NA
Same mortality across FC	187,397	134,865
OR mortality = 1 and same mortality risk within same FC	350,519	Dominated (more costly and less effective)
Titration cost (4 visits)	173,590	187,486

FC = functional class; ICURs = incremental cost-utility ratios; NA = not applicable; OR = odds ratio; vs. = versus.

Note: Tracleer was dominated in all scenarios except when OR mortality = 1 and when the mortality risk is the same for both riociguat and Tracleer within the same FC (ICUR is $227,861 when compared with riociguat [riociguat is less costly but less effective]).

Several price-reduction scenarios were explored using the manufacturer's base-case analysis for riociguat compared with placebo and generic bosentan, respectively (Table 7). Of note, when the CDR reanalysis — which accounted for potential double counting of the benefit of riociguat on mortality — is used as a reference, a price reduction of more than 80% would be needed for the ICUR of riociguat compared with placebo to fall below $50,000 per QALY, and a price reduction of more than 60% would be needed for riociguat to be less costly (but still less effective) than generic bosentan.

TABLE 7: CADTH COMMON DRUG REVIEW ANALYSIS OF INCREMENTAL COST-UTILITY RATIOS BASED ON VARIOUS PRICE-REDUCTION SCENARIOS

Scenario	ICUR ($/QALY) Based on Manufacturer's Analysis Riociguat vs. Placebo	ICUR ($/QALY) Based on Manufacturer's Analysis Riociguat vs. Generic Bosentan
Manufacturer's base case ($128.25/day)	173,524	187,347
10% price reduction ($115.43)	156,859	151,776
20% price reduction ($102.60)	140,194	116,205
30% price reduction ($87.78)	123,529	80,634
40% price reduction ($76.95)	106,863	45,063
50% price reduction ($64.13)	90,198	9,491
60% price reduction ($51.30)	73,533	Dominant
70% price reduction ($38.48)	56,868	Dominant
80% price reduction ($25.65)	40,203	Dominant

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.
Note: Tracleer was dominated in manufacturer's base case.

4. DISCUSSION

The conducted trials are short and, in the base-case analysis, the manufacturer assumed that differences observed at the end of the trials persist throughout the patient's lifetime, leading to slower progression to worse FC health states, with attendant relative improvement in quality of life and mortality for riociguat-treated patients. However, there is significant uncertainty in long-term outcomes. In the model, much of the benefit of riociguat occurs over a very long time frame. Using shorter time horizons exemplifies this: the reference case reports total incremental QALYs of 0.887 for riociguat versus placebo, but only 0.004 occur in the first four months (and 0.025 at one year). The ICUR increases to $240,109 and $434,311 per QALY when using a time horizon of 10 and 5 years. This underscores the importance of assumptions influencing long-term relative efficacy.

The model uses the pooled EQ-5D scores from the CHEST-1 study to inform the utility values based on the FC status in the model. A statistically significant improvement in EQ-5D utility score was observed from baseline, favouring riociguat in the CHEST-1 trial but, due to pre-specified hierarchical testing rules, the results of this analysis cannot be considered statistically significant (see details in the CDR clinical report). If the EQ-5D score by treatment allocation as reported in the trial is used (instead of the score by pooled FC), the incremental QALY gained at one year is larger (0.13 versus 0.025 QALY), and thus the ICUR at one year ($309,813 versus $1,616,001 per QALY) is reduced. However, it is not unreasonable to assign quality of life by health status. Further, the long-term differences in quality of life are unknown.

Potential benefit of riociguat on mortality might be double counted in the model, as it was assumed that mortality increased by worsening FC (an assumption that was thought to be reasonable by the clinical expert), but mortality also increased by treatment (independent of FC status). When the risk of mortality by FC health status only was used (risk was equal among treatments within same FC status), the ICUR increased to $350,519 per QALY for riociguat versus placebo, and riociguat resulted in lower QALYs than bosentan (riociguat is dominated by generic bosentan; riociguat is less costly, but less effective than Tracleer). Note that the ITC comparing riociguat versus bosentan reports a wide credible interval for the OR of mortality that crosses unity (0.32 with 95% CrI, 0.01 to 8.86). Nevertheless, true differences in mortality are not known.

While the manufacturer uses the primary comparison of riociguat versus placebo, most patients in Canada are treated with pharmacologic therapy, with the most common being bosentan. Therefore, the analysis and sensitivity analysis comparing these two drugs are most relevant. However, this is significantly hindered by the lack of direct evidence comparing these treatment strategies. While an ITC of riociguat versus bosentan was conducted, the model was selective in what data were used in the model. While the OR of mortality was used (which, as noted earlier, may double count the impact on mortality and, in addition, had a wide CrI, including unity), the transition between health states was taken from the bosentan group of the BENEFiT trial. (Simply using data from two treatment arms from two different trials is a very low-quality approach to determining effectiveness.) There is significant uncertainty regarding the relative efficacy and harms of riociguat versus bosentan.

A key issue is the proportion of patients receiving brand-name versus generic bosentan. Riociguat drug cost are almost identical to Tracleer (approximately $128 per day), but far greater than generics ($45 per day). According to available data, there is evidence of large variation in the proportion of patients on Tracleer by drug plans — from 0% to 95% of claims. The rationales for brand-name use, according to the clinical expert, are: industry-funded patient-support programs, concerns of variable bioavailability of generics, and attendant efficacy and side effects. And, if patients are on the brand-

name formulation and are "stable," there is prescriber and patient reticence to switch. Anecdotally, in some provinces, patients started on a brand-name formulation may be left on that drug, but new patients are started on generic bosentan. The incremental cost of riociguat for any given drug plan will be dependent on the proportion of patients on brand-name versus generic bosentan, and the proportion that would be switched from their current treatment to riociguat.

The key limitations associated with the manufacturer's submission are summarized in Table 8.

TABLE 8: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Long-term relative efficacy of riociguat	Conducted trials were short and assumed differences observed at the end of the trials persist throughout the patients' lifetime.	May overestimate cost-effectiveness. CDR reanalysis shows robust results using different assumptions on relative efficacy.
Mortality risks differ by both FC and by treatment	Might double count mortality, as mortality increases by worsening FC health status in the model.	May overestimate the efficacy of riociguat. CDR estimate of ICUR is $350,519 per QALY for riociguat vs. placebo, and riociguat dominated by generic bosentan when mortality is equal across treatments.
OR for FC change in patients treated with bosentan	Estimated from the cohort-level data from the BENEFiT study instead of the indirect treatment comparison.	True relative efficacy between riociguat and bosentan is unknown (CDR unable to perform reanalysis due to lack of data).

CDR = CADTH Common Drug Review; FC = functional class; ICUR = incremental cost-utility ratio; OR = odds ratio; QALY = quality-adjusted life-year; vs. = versus.

4.1 Issues for Consideration

- According to the clinical expert, the majority of eligible patients are currently treated with bosentan (through special authorization programs). There is wide variation in the proportion of patients treated with Tracleer versus generic bosentan (from 0 to approximately 95%), which has important implications for incremental cost. Tracleer appears to be favoured by clinical experts due to industry-supported patient programs, concerns around the range of bioavailability of generics, and switching "stable" patients to generic. The true difference in efficacy and side effects of generic bosentan versus Tracleer is not known. As the proportion of patients on Tracleer versus generic bosentan increases, incremental drug costs for riociguat become smaller.
- According to the clinical expert, since there is currently no Health Canada–approved drug for this indicated patient group, riociguat will become first-line treatment if listed by drug plans.
- This medication, if approved, is unlikely to modify consideration of surgical management, which is considered optimal treatment, if feasible.
- Riociguat is also indicated for treatment in patients with pulmonary arterial hypertension (PAH), and is likely to be used in non-CTEPH PAH.

4.2 Patient Input

Quality of life in terms of mobility, self-care, usual activities, and anxiety or depression, are important outcomes to CTEPH patients that were included by the manufacturer in the economic submission.

5. CONCLUSIONS

In the CDR reanalysis, eliminating the possible double counting of mortality benefit, the ICUR increases to $350,519 per QALY for riociguat versus placebo, and riociguat results in lower QALYs than bosentan (riociguat is dominated by generic bosentan; riociguat is less costly, but less effective than Tracleer); however, true differences in mortality are unclear. There is significant uncertainty in the ICUR given the lack of head-to-head trials of riociguat versus bosentan; the approach to modelling the relative efficacy; and the lack of data on long-term outcomes. Several scenarios result in greater ICURs than the base case presented by the manufacturer.

If drug costs of riociguat versus bosentan only are examined, riociguat has similar costs in jurisdictions where all patients are receiving Tracleer, but the incremental costs of riociguat versus bosentan rise as this proportion falls.

APPENDIX 1: COST-COMPARISON TABLE FOR DRUGS USED FOR THE TREATMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Clinical experts have deemed the comparators presented in Table 9 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.

The clinical expert indicated that most patients with chronic thromboembolic pulmonary hypertension (CTEPH) are currently treated with drugs for pulmonary arterial hypertension used off-label. Clinicians use the recommended for pulmonary arterial hypertension for CTEPH patients.

TABLE 9: COST-COMPARISON TABLE FOR MEDICATIONS USED FOR THE TREATMENT OF CTEPH

Drug/ Comparator	Strength	Dosage Form	Price ($)	Average Use	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Riociguat (Adempas)	0.5 mg 1.0 mg 1.5 mg 2.0 mg 2.5 mg	Tablet	42.7500[a]	1.0 to 2.5 mg three times daily	128.25	46,811
Comparators (Used Off-Label)						
Endothelin Receptor Antagonist						
Ambrisentan (Volibris)	5 mg 10 mg	Tablet	122.5200	5 to 10 mg once daily	122.52	44,720
Bosentan (Tracleer and generics)	62.5 mg 125 mg	Tablet	64.1786 (Tracleer) 22.4625 (generics)	62.5 mg twice daily for four weeks then 125 mg twice daily	128.36 (Tracleer) 44.93 (generics)	46,851 (Tracleer) 16,398 (generics)
Phoshodiesterase-5 Inhibitors						
Sildenafil (Revatio)	20 mg	Tablet	11.1219	20 mg three times daily	33.37	12,178
Tadalafil (Adcirca)	20 mg	Tablet	13.3633	40 mg once daily	26.73	9,755
Parenteral Prostanoids						
Epoprostenol (Flolan)	0.5 mg/vial 1.5 mg/vial 50 mL diluent	Vial	18.6400 37.2800 10.6500	15 to 30 ng/kg/min Up to 50 ng/kg/min has been reported	58.88 to 96.46[c] Up to 146.56	21,491 to 35,208[b,c] Up to 53,494
Treprostinil (Remodulin)	1.0 mg 2.5 mg	20 mL multi-	45.0000 114.2500	30 to 60 ng/kg/min[e]	142.81 to 281.25[b]	52,126 to 102,656[b]

Drug/ Comparator	Strength	Dosage Form	Price ($)	Average Use	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
	5.0 mg 10.0 mg	use vial[f]	225.0000 450.0000	Up to 100 ng/kg/min has been reported	Up to 473.68	Up to 172,893

[a] Manufacturer's submitted price.
[b] Assumes a 70 kg patient.
[c] Unused medication discarded after 24 hours.
[d] Should be prepared using two vials of the specific sterile diluent for use during a 24-hour period.
[e] Clinical experts indicated that treprostinil average doses and ceilings are about twice that of epoprostenol.
[f] Stable 30 days after the initial puncture of the rubber stopper.
Source: Saskatchewan Drug Plan (May 2014) unless otherwise indicated.

APPENDIX 2: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

The Institut National en Santé et Services Sociaux (INESSS) has published a recommendation regarding riociguat for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH; April 2014).

Riociguat is priced at $42.75 per tablet ($46,811 annually), which is the same as the price submitted to the CADTH Common Drug Review (CDR). The manufacturer submitted both a cost-utility analysis (CUA) and cost-consequence analysis (CCA).

For the CUA, similar to the CDR pharmacoeconomic review, INESSS noted the following limitations with the manufacturer's health economic model:

- results of CHEST-1 at 16 weeks are extrapolated over lifetime horizon
- uncertainty in the comparative efficacy of riociguat and bosentan
- assumption of reduced mortality risk with riociguat versus bosentan, while no clinical trial showed a reduction of mortality risk with riociguat.

Because of these limitations, no further reanalyses were performed by INESSS.

The CCA submitted by the manufacturer was based on the CHEST-1/CHEST-2[5] trial for riociguat versus placebo, and the BENEFiT trial[2] for bosentan versus placebo, over a 16-week period.

INESSS noted some limitations with the CCA, such as a short time horizon, considering that CTEPH is a chronic disease, and a potential double counting of costs associated with bosentan. The INESSS reanalysis of the CCA reports total health care costs over a 16-week period of $14,866 for riociguat, compared with $310 for best supportive care, and total health care costs of $14,948 for Tracleer ($5,602 for generic bosentan), compared with $450 for best supportive care.

APPENDIX 3: SUMMARY OF KEY OUTCOMES

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS RIOCIGUAT COMPARED WITH PLACEBO AND BOSENTAN (GENERIC)?

Riociguat vs. Placebo	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X (slightly unattractive vs. bosentan in some CDR analyses)				
Quality of life		X (slightly unattractive vs. bosentan in some CDR analyses)				
ICER or net benefit calculation	Manufacturer's base case: • $173,524 per QALY (riociguat vs. placebo) • $187,347 per QALY (riociguat vs. generic bosentan) CDR reanalyses: • $350,519 per QALY in the CDR analyses when mortality is mediated only through FC health status (riociguat vs. placebo) • riociguat is dominated by generic bosentan					

CDR = Common Drug Review; FC = functional class; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

The above is based on both the manufacturer's results and the reanalysis.

TABLE 11: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS RIOCIGUAT COMPARED WITH BRAND-NAME BOSENTAN (TRACLEER)?

Riociguat vs. Placebo	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes		X				
Quality of life		X				
ICER or net benefit calculation	Manufacturer's base case: Riociguat dominates Tracleer CDR reanalyses: True differences in mortality between riociguat and bosentan are unclear. If drug costs of riociguat versus Tracleer only are examined, riociguat has similar costs in jurisdictions where all patients are receiving Tracleer.					

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; vs. = versus.

The above is based on both the manufacturer's results and the reanalysis.

APPENDIX 4: ADDITIONAL INFORMATION

TABLE 12: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments			
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 13: AUTHOR INFORMATION

Authors	Affiliations
Eva Chan[1], Brandon Levac,[1] Warren Chin[2]	1. Bayer Inc.; 2. ILEX Consulting Inc.

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 5: SUMMARY AND APPRAISAL OF THE MANUFACTURER-SUBMITTED COST-CONSEQUENCE ANALYSIS

OBJECTIVE

The objective of this review is to summarize the methods and results, and to conduct a critical appraisal of the manufacturer-provided cost-consequence analysis (CCA) comparing the costs and consequences of riociguat with placebo, and bosentan with placebo.

SUMMARY OF COST-CONSEQUENCE ANALYSIS

Rationale

The manufacturer indicated that complex economic evaluations are difficult to understand and highly susceptible to both error and introduction of bias. CCA can be made more useful to most clinicians and decision-makers as the costs and consequences of the alternative treatments are listed separately in a disaggregated format.

Methods

Target Population

The target population consisted of patients who have inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment.

Treatment Comparators

The CCA is based on the CHEST-1/CHEST-2[5] trial for riociguat versus placebo (primary analysis), and the BENEFiT trial[2] for bosentan versus placebo (secondary analysis). A comparison with sildenafil was not conducted given the very limited data available on the efficacy and safety of sildenafil in CTEPH patients.

Perspective, Resource Costing, and Time Horizon

This CCA was conducted from the perspective of a provincial ministry of health. The resource use and costs to the health system in the economic evaluation included drug costs, treatment initiation costs, maintenance costs, patient-monitoring test costs, and adverse event (AE) management costs. A time horizon of 16 weeks was chosen because it was the clinical trial duration for the CHEST-1 and BENEFiT trials. Discounting was not conducted in the economic evaluation due to the short time horizon. The costs were presented in 2013 Canadian dollars.

Results

Results of the manufacturer's CCA are summarized in Table 14.

TABLE 14: SUMMARY OF KEY OUTCOMES COMPARISON — RIOCIGUAT AND BOSENTAN IN CTEPH

Outcome	Riociguat vs. Placebo	Bosentan vs. Placebo
Background Information		
Health Canada approval	Yes	No
RCT	Yes	Yes
Type of trial	Phase III	Phase III
Multi-centre	Yes	Yes
Number of patients studied	261 (173 for riociguat and 88 for placebo)	157 (77 for bosentan and 80 for placebo)
Length of trial	16 weeks	16 weeks
Long-term data	Yes – CHEST-2 (OL, ongoing, n = 194)	Yes – BENEFiT OL (OL, up to 3.3 years, n = 151)
Dosage	Individual dose titration, 0.5 mg to 2.5 mg t.i.d. oral	62.5 mg b.i.d. oral 4 weeks, 125 b.i.d. thereafter
Consequences — Efficacy		
Primary end point(s) met	Yes Change in 6MWD met	No Change in PVR met Change in 6MWD not met
6MWD	46 m[a]	2 m
PVR	–246[a]	–176[a]
NT-proBNP	–444[a]	[a]
WHO FC improved	32.9% riociguat vs. 14.9% placebo[a]	14.5% bosentan vs. 11.3% placebo
TTCW	2% riociguat vs. 6% placebo	3.9% bosentan vs. 6.3% placebo
Borg Dyspnea Index	–0.83 riociguat vs. 0.17 placebo[a]	[a]
EQ-5D	0.1[a]	NR
Consequences — Safety		
Most common serious adverse events	Right ventricular failure (3.5% riociguat vs. 3.4% placebo) and syncope (2.3% riociguat vs. 3.4% placebo)	Right ventricular failure (2.6% bosentan vs. 3.8% placebo) and worsening of PH (2.6% bosentan vs. 1.3% placebo)
Costs (16 Weeks)		
Drug, treatment initiation, maintenance, and patient-monitoring test costs	Riociguat: $14,678 Placebo: $0	Tracleer: $14,774 Generic bosentan: $5,429 Placebo: $0
Adverse events management costs	Riociguat: $232 Placebo:$115	Tracleer: $802 Generic bosentan: $802 Placebo: $680
Overall cost per patient, first	Riociguat: $14,909	Tracleer: $15,577

Outcome	Riociguat vs. Placebo	Bosentan vs. Placebo
16 weeks of treatment	Placebo: $115	Generic bosentan: $6,231 Placebo: $680

6MWD = six-minute walk distance; b.i.d. = twice daily; CTEPH = chronic thromboembolic pulmonary hypertension; EQ-5D = EuroQol 5-Dimensions Questionnaire; LPH = Living with pulmonary hypertension questionnaire; NR = not reported; NT-proBNP = N-terminal prohormone brain natriuretic peptide; OL = open label; PVR = pulmonary vascular resistance; SF-36 = Short Form 36 Health Survey; NR = not reported; t.i.d. = three times a day; TTCW = time to clinical worsening; vs. = versus; WHO FC = World Health Organization functional class.
[a]Statistically significant.
Source: Manufacturer's submission.[1]

Critical Appraisal of Cost-Consequence Analysis

CCA is "a form of cost-effectiveness analysis that presents costs and outcomes in discrete categories, without aggregating or weighting them."[6] It does not necessarily provide more information for decision-making, and may lead to confusion given the multiple end points (with varying degrees of clinical importance). In this CCA, the primary end point from the trials' 6MWD is an ambiguous outcome as, according to the clinical expert, it is not proven to be a surrogate for survival, which is one of the important factors for resource allocation in health care. In addition, compared with the single outcome (QALY) generated from a CUA, in a CCA, decision-makers need to consider all the surrogate outcomes from the trials that would not make the process easier.[7] Although complex economic models may be susceptible to error and bias, this can be attenuated by adherence to clear methodology, reasonable assumptions, and robust sensitivity analyses to explore any uncertainties.[8,9] That is why CUA is still the preferred method to evaluate health technology as recommended by the National Institute for Health and Care Excellence (NICE), CADTH and other similar agencies around the world.

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