CADTH CANADIAN DRUG EXPERT REVIEW COMMITTEE FINAL RECOMMENDATION

RIOCIGUAT
(Adempas — Bayer HealthCare Inc.)
Indication: Pulmonary Arterial Hypertension

Recommendation:
The CADTH Canadian Drug Expert Review Committee (CDEC) recommends that riociguat be listed 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 functional class II or III pulmonary hypertension, if the following clinical criterion and condition are met:

Clinical criterion:
- Inadequate control with a first-line PAH therapy.

Condition:
- Prescribed by a clinician with experience in the diagnosis and treatment of PAH
- Drug plan cost for riociguat should not exceed the drug plan cost for the least costly second-line option for the treatment of PAH.

Reasons for the Recommendation:
1. One double-blind, placebo-controlled, randomized trial (PATENT-1; N = 443) demonstrated that treatment with riociguat was associated with statistically significant improvements in time to clinical worsening, six-minute walk distance (6MWD), and hemodynamic outcomes in adults with symptomatic PAH who were either treatment-naive or were receiving therapy with ERAs or prostanoids.
2. A network meta-analysis (NMA) suggested that riociguat has similar efficacy to other PAH treatments for individuals with PAH functional class II or III.
3. At the submitted price, riociguat is more costly than all other drugs, with total incremental costs ranging between $1,873 and $39,987 annually per patient.

Of Note:
- CDEC noted that there may be variation in the way first-line PAH therapies are defined and reimbursed across the CADTH Common Drug Review (CDR)-participating drug plans.
- Patients enrolled in the PATENT-1 trial had not been previously treated with a phosphodiesterase type 5 (PDE5) inhibitor.

Background:
Riociguat is indicated for the treatment of PAH (WHO Group 1) as monotherapy or in combination with ERAs in adult patients (≥ 18 years of age) with functional class II or III pulmonary hypertension.

Riociguat is initiated at a dose of 1.0 mg orally three times daily and adjusted by 0.5 mg increments every two weeks according to systolic blood pressure readings, to a maximum dose of 2.5 mg three times daily.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials (RCTs) focused on the use of riociguat for the treatment of PAH, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals with PAH.

Patient Input Information
One patient group, the Pulmonary Hypertension Association of Canada, responded to the CDR call for patient input. Information was obtained through interviews and surveys of patients and caregivers, and through experience working in the PAH community. The following is a summary of information provided by patients:

- Physical symptoms of PAH, such as difficulty breathing, dizziness, fatigue, peripheral edema, fainting, and chest pain, can be substantial and often unpredictable. Low tolerance for physical exertion can impede activities of daily living and caring for children.
- Emotional and psychological symptoms are common and include depression, anxiety, and feelings of helplessness and hopelessness.
- Caregivers play an important role in supporting those living with PAH, as these patients may lose their ability to care for themselves and their children, and may be unable to work.
- A majority of patients indicated that monotherapy with currently available treatments was ineffective and, as a result, were using combinations of more than one drug. Patients noted that a significant unmet need for more effective therapies exists.

Clinical Trials
The CDR systematic review included one randomized, double-blind study (PATENT-1; N = 443) that compared the safety and efficacy of 12 weeks of riociguat (titrated up to a maximum of 2.5 mg three times daily) with placebo in adults with symptomatic PAH. The study also included an exploratory lower-dose riociguat group (titrated up to a maximum of 1.5 mg three times daily). Randomization was stratified by the patients' prior treatment history: half of those enrolled were treatment-naive, and half were receiving ERA or prostanoid therapy, which was continued during the study period.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- 6MWD — change from baseline in the total distance walked in six minutes. The estimated minimal clinically important difference is 33.0 m.
- Clinical worsening — a composite outcome designed to measure PAH morbidity and mortality. Clinical worsening included any of the following: death; heart/lung transplantation; atrial septostomy; hospitalization due to persistent worsening of PAH; start of new PAH

specific treatment or modification of pre-existing prostacyclin analogue treatment due to worsening PAH; persistent decrease of more than 15% from baseline or more than 30% compared with the last study-related measurement in 6MWD due to worsening PAH; or persistent worsening of functional class due to deterioration of PAH or patients who deteriorate from class II or III to class IV.
- WHO functional class — a pulmonary hypertension severity classification system based on New York Heart Association heart failure classification.
- Borg CR10 dyspnea scale — a self-reported scale used to measure difficulty breathing.
- Health-related quality of life — assessed using the Living with Pulmonary Hypertension (LPH) questionnaire and the EuroQol 5-Dimensions Questionnaire (EQ-5D) (visual analogue scale [VAS] and index scores).
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

The primary efficacy outcome in PATENT-1 was change from baseline in 6MWD after 12 weeks.

Efficacy
- Riociguat up to 2.5 mg three times daily for 12 weeks demonstrated a statistically significant and clinically meaningful increase in 6MWD compared with placebo (mean difference 36 m; 95% confidence interval [CI], 20 m to 52 m).
- Riociguat 2.5 mg demonstrated statistically significant reductions in the time to clinical worsening compared with placebo ($P = 0.005$). Improvements in clinical worsening appeared to be driven by a decrease in hospitalization due to PAH.
- A statistically significant greater proportion of patients in the riociguat 2.5 mg group (21%) demonstrated an improvement in their functional class compared with the placebo group (14%); $P = 0.003$.
- The differences between riociguat 2.5 mg and placebo for dyspnea symptoms were statistically significant. The mean change (standard deviation) from baseline to week 12 was −0.4 (1.7) in the riociguat group and 0.1 (2.1) in the placebo group ($P = 0.002$).
- Subgroup analysis suggested that the treatment effect of riociguat 2.5 mg versus placebo was similar across outcomes for treatment-naive patients (i.e., monotherapy) and when administered as add-on therapy to stable ERA or prostanoid regimens.
- There was a statistically significant reduction in pulmonary vascular resistance in the riociguat 2.5 mg group compared with the placebo group (mean difference −226 $dyn \cdot s \cdot cm^{-5}$; 95% CI, −281 to −170; $P < 0.0001$).
- There were no statistically significant differences between the riociguat and placebo groups in the EQ-5D or LPH assessments. The mean differences for riociguat 2.5 mg versus placebo were:
  - EQ-5D utility: 0.06 (95% CI, 0.01 to 0.11)
  - EQ-5D VAS: [redacted]
  - LPH: −6 (95% CI, −10 to −3).

Harms (Safety and Tolerability)
- The most common adverse events in the riociguat groups were headache, dizziness, and gastrointestinal events. The incidence of anemia and hypotension were numerically greater in the riociguat 2.5 mg group than in the placebo and riociguat 1.5 mg groups. The incidence of any bleeding event was similar across treatments in PATENT-1; however, serious bleeding events occurred more frequently in the riociguat groups compared with the placebo

group. The proportions of patients who experienced at least one adverse event were: riociguat 2.5 mg, 89%; riociguat 1.5 mg, 92%; placebo, 86%.
- Serious adverse events were reported in 18%, 11%, and 18% of patients in the placebo, riociguat 2.5 mg, and riociguat 1.5 mg groups, respectively.
- More patients discontinued treatment due to adverse events in the placebo group (7%) than in the riociguat groups (2% and 3%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing riociguat (1 mg to 2.5 mg three times daily) with 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 daily); and prostanoids epoprostenol (22 to 50 ng/kg/min) and treprostinil (35 to 90 ng/kg/min), for the treatment of PAH (WHO Group 1) as monotherapy or in combination with ERAs in adults with WHO functional class II or III PAH. The perspective was that of a publicly funded health care system with a time horizon of four months. [redacted] The findings of the manufacturer's NMA were generally consistent with the NMA conducted by CADTH for the Therapeutic Review of PAH drugs. The manufacturer's analysis included drug costs and health care resource costs (e.g., time spent with a nurse, visits to a physician specialist, liver function tests, and hemoglobin blood tests).

CDR identified the following limitations with the manufacturer's pharmacoeconomic evaluation:
- Lack of consideration around the variability in the pricing of the comparator drugs across public drug plans
- Underestimation of the health care resources utilized
- Unclear place in therapy of riociguat as a first-line treatment
- Limited evidence on the effectiveness and cost-effectiveness of riociguat as a second-line drug.

When used as monotherapy, CDR reanalyses showed that riociguat is more costly than all other oral PAH drugs, with total incremental costs ranging from $1,873 to $39,987 per patient annually, but less costly than most parenteral prostanoids.

When used as add-on combination therapy, the place in therapy of riociguat is unclear and there is limited clinical evidence supporting the efficacy and cost-effectiveness versus other comparators. Riociguat is contraindicated for use with PDE5 inhibitors, so only the combination of an ERA + prostanoids is a relevant comparator; 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).

At the submitted price of $42.75 per tablet for all dosage strengths, riociguat ($128.25 per day) is more costly than ambrisentan ($122.52 per day), generic bosentan ($32.09 per day),

macitentan ($116.50 per day), generic sildenafil (based on the recommended dose of 20 mg three times daily, $18.76 per day), and tadalafil ($26.99 per day).

Other Discussion Points:
CDEC noted the following:

- As part of CADTH's 2014 Therapeutic Review of drugs for pulmonary arterial hypertension, CDEC recommended that sildenafil or tadalafil be the preferred initial therapy for adult patients with functional class II and III PAH.
- Riociguat requires a relatively long dose-titration period, which is an important limitation compared with other oral drugs.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There are no direct comparisons between riociguat and other treatment strategies used in the management of patients with PAH.
- The efficacy of riociguat in the management of patients who have experienced inadequate disease control with alternative treatments, including PDE5 inhibitors.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

November 18, 2015 Meeting

Regrets:
None

Conflicts of Interest:
None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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