CDEC FINAL RECOMMENDATION

RIOCIGUAT
(Adempas — Bayer HealthCare)
Indication: Chronic Thromboembolic Pulmonary Hypertension

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that riociguat be listed for the management of inoperable chronic thromboembolic pulmonary hypertension (CTEPH, World Health Organization [WHO] Group 4) or persistent or recurrent CTEPH after surgical treatment in adult patients (≥ 18 years of age) with WHO Functional Class (FC) II or III pulmonary hypertension (PH), if the following conditions are met:

Conditions:
- Riociguat should be prescribed by a clinician with experience in the diagnosis and treatment of CTEPH.
- A substantial reduction in price is required.

Reasons for the Recommendation:
1. A double-blind, randomized, placebo-controlled trial (CHEST-1; N = 262) demonstrated that riociguat resulted in a statistically significant and clinically relevant improvement in six-minute walking distance (6MWD) compared with placebo (mean difference [MD] of 45.7 m; 95% confidence interval [CI], 24.7 m to 66.6 m).
2. At the submitted price ($128.25 per day), riociguat is not considered to be cost-effective relative to appropriate comparators for the treatment of CTEPH.

Background:
Riociguat is the first drug in the class of soluble guanylate cyclase stimulators to be marketed in Canada and the first medication specifically indicated for use in the treatment of CTEPH. Riociguat is indicated for the management of inoperable CTEPH (WHO Group 4) or persistent or recurrent CTEPH after surgical treatment in adult patients at least 18 years of age with WHO FC II or III PH.

Riociguat is available as 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets for oral administration. The recommended starting dose of riociguat is 1 mg three times daily for two weeks. The dosage should be increased in two-week intervals by 0.5 mg increments to a maximum of 2.5 mg three times daily.

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

Patient Input Information
The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- Physical symptoms of PH, 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 CTEPH, as these patients may lose their ability to care for themselves and their children, and may be unable to work.

Clinical Trials
The CDR systematic review included one 16-week, double-blind, placebo-controlled RCT. CHEST-1 (N = 262) randomized patients (2:1) to either riociguat three times daily or placebo added to usual care. An individual dose titration protocol (initial dose: 1.0 mg three times daily) was employed during the first 8 weeks targeting a final dose of 2.5 mg three times daily or the maximally tolerated dose; dose adjustments were made every two weeks in 0.5 mg increments according to blood pressure readings. After the 8-week titration period, patients were continued for another 8 weeks on a dose maintenance phase.

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.
- Clinical worsening — Composite outcome designed to measure PH morbidity and mortality.
- WHO FC — PH severity classification system based on NYHA HF classification.
- Borg dyspnea scale — a self-reported scale used to measure difficulty breathing.
- Health-related quality of life — assessed using the Living with PH (LPH) questionnaire and the European Quality of Life-5 Dimensions (EQ-5D) questionnaire (visual analogue scale and index scores).
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

The primary efficacy outcome in CHEST-1 was change from baseline in 6MWD after 16 weeks.

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Efficacy

- Riociguat was statistically superior to placebo for change from baseline in 6MWD using both parametric (adjusted least square MD: 45.7 m; 95% CI, 24.7 m to 66.6 m) and non-parametric analyses (median difference: 39 m; 95% CI, 25 m to 54 m).
- Inoperable patients (n = 189) demonstrated an increase in 6MWD of 54 m (95% CI, 29 m to 79 m), and patients with recurrent or persisting CTEPH following pulmonary endarterectomy (n = 72) demonstrated an increase in 6MWD of 27 m (95% CI, –10 m to 63 m).
- There was no statistically significant difference between the riociguat group (2.3%) and the placebo group (5.7%) in the proportion of patients with clinical worsening.
- Compared with placebo, a statistically significantly greater proportion of patients in the riociguat group demonstrated improvement of one WHO FC (30.6% versus 14.9%) or two WHO FCs (2.3% versus 0%); *P* = 0.0026.
- Riociguat was statistically superior to placebo for change from baseline in LPH total score with a parametric analysis (MD: –5.8; 95% CI, –10.5 to –1.1); however, the difference was not statistically significant with a non-parametric analysis (*P* = 0.1220).
- Riociguat was statistically superior to placebo for change from baseline in EQ-5D utility with both parametric (MD: 0.1; 95% CI, 0.1 to 0.2) and non-parametric analysis (*P* < 0.0001).
- A statistically significant difference for the change from baseline in the Borg scale was reported in favour of riociguat (*P* = 0.0035).

Harms (Safety and Tolerability)

- The proportion of patients with at least one adverse event was 91.9% in the riociguat group and 86.4% in the placebo group. The most commonly reported adverse events in riociguat-treated patients as compared with placebo were headache (24.9% versus 13.6%) and dizziness (22.5% versus 12.5%) followed by dyspepsia (17.9% versus 8.0%), peripheral edema (15.6% versus 20.5%), nasopharyngitis (15.0% versus 9.1%), nausea (11.0% versus 8.0%), diarrhea (9.8% versus 4.5%), vomiting (9.8% versus 3.4%), and hypotension (9.2% versus 3.4%).
- The proportion of patients with at least one serious adverse event was 19.7% in the riociguat group and 15.9% in the placebo group. Serious adverse events were most often classified as cardiac disorders or respiratory, thoracic, and mediastinal disorders.
- Withdrawals due to adverse events were reported for 2.9% of patients in the riociguat group and 2.3% in the placebo group. Cardiac disorders were the most commonly reported reason for a withdrawal due to adverse event (0.6% with riociguat and 2.3% with placebo).

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis (CUA) from the Canadian public-payer perspective comparing riociguat with placebo, and riociguat with generic and brand name bosentan (Tracleer), during a 20-year time horizon. The Markov model included the following health states: WHO FC II, WHO FC III, WHO FC IV, and death. The clinical data from 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 values. After the first cycle, FC transitions were derived from the extrapolation of survival curves derived from the statistical fitting of CHEST-1 (placebo) and CHEST-2 (riociguat). Comparison between riociguat and bosentan was based on an indirect treatment comparison using CHEST-1 and the BENEFiT trial, which compared the efficacy of bosentan with placebo in CTEPH patients. It was

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assumed that FC transitions for bosentan remained constant throughout the remaining lifetime. Only liver toxicity and hypotension were included in the model as adverse events. Mortality data by FC were obtained from a European chart review commissioned by the manufacturer.

The manufacturer reported an incremental cost per quality-adjusted life-year (QALY) for riociguat compared with placebo of $173,524. The probabilistic sensitivity analysis indicated there is 0% probability that the incremental cost-utility ratio (ICUR) of riociguat compared with placebo would fall below a $50,000 per QALY threshold. The incremental cost per QALY for riociguat compared with generic bosentan was $187,347. Riociguat dominated Tracleer (i.e., was more effective and less costly).

CDR identified a number of limitations with the manufacturer's pharmacoeconomic submission:

- It is not established that long-term differences in FC will occur. If the treatment effect is not durable or attenuates, the cost-effectiveness ratio will be greater.
- Mortality is assumed to increase by worsening FC and is also affected by treatment strategy regardless of FC health state (informed by the indirect comparison). This might lead to double counting of the mortality benefit associated with riociguat.
- The comparative efficacy of riociguat and bosentan is uncertain. The indirect comparison submitted by the manufacturer reported a non-statistically significant increased odds of being in a better FC at study end point when treated with riociguat compared with bosentan (odds ratio 1.15, 95% credible interval, 0.51 to 2.61).

When considering shorter time frames, CDR noted that the ICURs increased to $434,311 per QALY compared with placebo or $492,361 per QALY compared with generic bosentan, as the majority of the incremental benefit associated with riociguat is accrued well beyond the time frame of the available RCTs. Where only mortality risk by FC class is considered, the ICUR increased to $350,519 per QALY compared with placebo, and riociguat was dominated by generic bosentan. Riociguat dominated Tracleer in all time horizons tested, and was less costly but less effective than Tracleer when mortality risk by FC class only was considered.

At the submitted price, riociguat is $42.75 per 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg or 2.5 mg tablet, or a daily cost of $128.25 (1 mg to 2.5 mg three times daily). This is similar to the daily cost of Tracleer ($128.36; 62.5 mg or 125 mg twice daily), but exceeds the daily cost of generic bosentan ($44.93; 62.5 mg or 125 mg twice daily).

Other Discussion Points:

CDEC noted the following:

- The clinical expert consulted by CDR during the review suggested that 60% to 80% of CTEPH patients in Canada are prescribed off-label pharmacotherapies for the condition and the majority of these patients would receive bosentan.
- The forced titration protocol (targeting a final dose of 2.5 mg three times daily) used during the first 8 weeks of the CHEST-1 trial was relatively rapid and unlikely to be reflective of routine clinical practice, due to concerns regarding hypotension.
- The ICUR of riociguat compared with bosentan is uncertain due to the lack of direct comparative evidence, lack of long-term clinical data, and the other limitations of the manufacturer's submission.

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- In addition to the 6MWD test, CDEC noted that riociguat demonstrated improvements in WHO FC health states and hemodynamic parameters compared with placebo.

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 CTEPH.
- The primary outcome of CHEST-1 is a surrogate end point (i.e., 6MWD); therefore, the long-term efficacy of riociguat on important clinical end points is uncertain.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

June 18, 2014 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 not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

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