Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH Therapeutic Review Report

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Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety, and Cost-Effectiveness — Recommendations Report

Supporting Informed Decisions

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ABBREVIATIONS

6MWD	six-minute walk distance
AE	adverse event
BDI	Borg dyspnea index
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	CADTH Common Drug Review
CI	cardiac index
CDEC	Canadian Drug Expert Committee
ERA	endothelin receptor antagonist
FC	functional class
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
MCID	minimal clinically important difference
mPAP	mean pulmonary artery pressure
NMA	network meta-analysis
NYHA	New York Heart Association
PAH	pulmonary arterial hypertension
PDE-5	phosphodiesterase-5
PVR	pulmonary vascular resistance
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SAE	serious adverse event
sGC	soluble guanylate cyclase
WHO	World Health Organization

BACKGROUND

Pulmonary arterial hypertension (PAH) is a chronic and progressive disease characterized by the elevation of the mean pulmonary arterial pressure (mPAP) that leads to morbidity and premature mortality.[1] Although PAH affects males and females of all ethnicities and ages,[2] the disease most commonly affects women and people between 20 and 40 years of age.[3] In adults, the prevalence of PAH is approximately 12 to 50 cases per million people.[4-6] Epidemiological data for PAH in Canada are not available. Based on published registry data from France, Scotland, Spain, and the US,[7] the prevalence of PAH in Canada may be estimated to be between 10.6 cases and 26 cases per million people. The number of adult Canadians with PAH is therefore estimated to be between 313 and 767. There is a paucity of trial data in children, despite the fact that children also experience PAH.

PAH is classified as Group 1 of the pulmonary hypertension (PH) classification.[8] Four subgroups of Group 1 include idiopathic PAH, heritable or familial PAH, drug- and toxin-induced PAH, and PAH associated with concurrent medical conditions such as connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis.

PAH is associated with poor overall prognosis. A US national registry study (conducted prior to the availability of PAH-specific pharmacological treatments) found that the median survival was 2.8 years if untreated.[9,10] At present, the average survival in adults after diagnosis is estimated at five to seven years.[11-13] Improvement in pharmacological treatments and care for patients with PAH is thought to have played a role in this survival gain.[13]

The mechanisms contributing to disease progression involve vasoconstriction, endothelial dysfunction, dysregulated smooth muscle cell growth, inflammation, and thrombosis that typically lead to overload of right ventricle and progressive right-sided heart failure.[14] The therapeutic objectives of drugs for PAH are to normalize these mechanisms. Treatment of PAH is generally categorized as supportive therapy or advanced therapy. Supportive therapy includes use of diuretics, oxygen, anticoagulants, and digoxin. Many patients with PAH initially receive supportive therapy despite limited or no evidence of effectiveness. Consequently, the majority of patients with PAH will ultimately require advanced therapy, which is directed at the disease itself. Eight drugs are approved in Canada for advanced therapy of PAH. They belong to four classes:

- prostanoids (injectables: epoprostenol, treprostinil)
- endothelin receptor antagonists (ERAs) (oral: bosentan, ambrisentan, macitentan)
- phosphodiesterase type-5 (PDE-5) inhibitors (oral: sildenafil [oral and injectable], tadalafil)
- soluble guanylate cyclase (sGC) stimulator (oral: riociguat).

Macitentan and riociguat are new drugs that received Health Canada approval for treatment of PAH in November 2013 and March 2014, respectively. Of note, epoprostenol, treprostinil, and bosentan are indicated for treatment of PAH patients with World Health Organization (WHO) functional class (FC) III or IV symptoms, while the other drugs are indicated for treatment of those with WHO FC II or III symptoms.

In patients who do not adequately respond to advanced monotherapy, sequential addition of a second drug is usually recommended by PH specialists in Canada. Approximately 22% of PAH patients in Ontario used combination therapy between 2010 and 2012;[15] however, the estimate may be closer to 50%, depending on the PAH clinic.

Evidence-informed recommendations were developed by the Canadian Drug Expert Committee (CDEC) to address the following policy questions:

1. How do new drugs for advanced therapy of PAH compare with currently available drugs?
2. How does (add-on) combination therapy compare with monotherapy in patients with PAH?
3. Are there subgroups of patients (based on disease severity or other disease characteristics) who benefit more from specific drugs when used either as monotherapy or (add-on) combination therapy?

As described in the CADTH Therapeutic Review Framework, the depth and scope of a CADTH therapeutic review is determined by CADTH in consultation with the jurisdictions. CADTH therapeutic reviews are evidence based, and use the highest level of publicly available evidence. Therapeutic reviews are conducted to coincide with key CADTH Common Drug Review (CDR) submission(s) relevant to the scope of the therapeutic review.

The recommendations listed in this report are intended to be used in conjunction with the Therapeutic Review Clinical and Economic Report as well as the recommendations made for individual drugs. Individual drug reviews and recommendations are made through the CDR process.

PREAMBLE TO THE RECOMMENDATIONS

CDEC recognizes that PAH is an uncommon and serious condition. The numbers of medications and treatment strategies for PAH have rapidly evolved in recent years, and this trend is expected to continue in the future. Given the rapid expansion in therapeutic options for PAH, the public drug plans require recommendations and advice regarding the currently approved and available treatments. While these advances provide clinicians and patients with additional treatment options, they necessitate an assessment of their comparative effectiveness and safety to ensure pharmacological interventions are used optimally, accounting for both their respective clinical and economic value. In developing recommendations on drugs for PAH, CDEC attempted to reach a balance between these two important values. CDEC also discussed input from patients and clinical experts. Of note, to ensure optimal care is provided, CDEC recognized that medical practitioners caring for patients with PAH should refer these patients to one of the designated PH centres in Canada.

To inform the development of recommendations, CADTH undertook a therapeutic review that includes both a comprehensive comparative analysis of the clinical evidence and an economic evaluation of drugs used to treat patients with PAH. CDEC noted that the published clinical evidence that met the therapeutic review inclusion criteria is still quite limited, as reflected in the findings and conclusions. CDEC also acknowledges efforts to improve the quality of randomized clinical trials (RCTs) recently conducted to assess the efficacy of pharmacological interventions for the treatment of PAH, such as increased duration of follow-up. Clinical evidence is also expanding with respect to combination therapy regimens, although only four RCTs assessing such treatment strategies met the inclusion criteria for the therapeutic review. There were no published studies identified for inclusion into the CADTH therapeutic review that investigated the use of combination therapy as initial treatment for patients with PAH. Lastly, although the scope of the therapeutic review and recommendations are for adults, a lack of high-quality comparative studies conducted in pediatric populations was noted.

CDEC discussed the evidence and its limitations primarily from a population perspective (as opposed to individual patient-level perspective). The anticipated absolute benefits, harms, and

cost-effectiveness of the therapies compared with each other, along with patient group input, were considered to be fundamental in the development of system-level recommendations. The Committee also recognized that clinical practice guidelines related to the treatment of PAH have been developed.[16,17] Clinical practice guidelines are generally based on clinical judgment and consideration of individual patient characteristics, but often do not take into account the cost or cost-effectiveness of these treatments.

The PACES-1 trial was excluded because the dose of sildenafil used in the study (80 mg three times daily) is not approved by Health Canada. However, the key results of the PACES-1 trial were summarized and contextualized in the CADTH therapeutic review and discussed by CDEC. In addition, two upcoming combination therapy trials — i.e., COMPASS-2 and AMBITION — were not included in the CADTH therapeutic review because the final trial findings had not been published at the time the therapeutic review was completed. As a result, CDEC did not discuss the results of these new trials, although the Committee noted there may be a need to reassess the recommendations as new data become available.

The evidence for developing CDEC recommendations was derived from the following reports:

1. Canadian Agency for Drugs and Technologies in Health. CADTH Therapeutic Review. Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety, and Cost-Effectiveness [Internet]. Ottawa: The Agency; 2014
2. Patient input to CADTH Therapeutic Review: Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety, and Cost-Effectiveness [Internet]. Ottawa: The Agency; 2014.

ADDRESSING STAKEHOLDER FEEDBACK TO THE DRAFT RECOMMENDATIONS

The draft recommendations were posted to the CADTH website on November 14, 2014, for 14 days. Several stakeholders responded to the request for feedback on the draft recommendations. Minor changes were made to the recommendation document to enhance clarity. In addition, key components of stakeholder feedback were addressed as follows:

- CDEC discussed the expressed preference of patient groups, clinicians, and industry that initial therapy for adult patients with FC II and III PAH not be limited to sildenafil and tadalafil (Recommendation 1). CDEC reaffirmed that the high cost of currently available treatments in conjunction with the progressive nature of PAH, which often necessitates combination drug therapy, supports judicious use of available therapies at this time.
- Based on jurisdictional feedback, CDEC provided additional context with regard to initiating intravenous epoprostenol in patients with FC IV PAH.

SUMMARY OF RECOMMENDATIONS

1. CDEC recommends that sildenafil or tadalafil be the preferred initial therapy for adult patients with FC II and III PAH.
2. CDEC recommends that add-on therapy should be used in adult PAH patients who are unable to achieve disease control with a single drug.
3. CDEC could not make a specific recommendation pertaining to subgroups of patients (based on disease severity or other disease characteristics) who may benefit more from specific drugs or combinations of drugs based on the evidence reviewed.

CANADIAN DRUG EXPERT COMMITTEE VALUES AND PREFERENCES

CDEC sought to balance patient perspectives, clinical evidence, and economic evidence. CDEC identified the values of efficacy, safety, cost-effectiveness, and patient preferences as particularly important in making these recommendations. In considering patient perspectives, CDEC noted patients' desire for treatments that slowed the progression and alleviated the symptoms of their disease, and that reduced the burden of treatment and adverse events (AEs).

RECOMMENDATIONS

Recommendation 1:

CDEC recommends that sildenafil or tadalafil be the preferred initial therapy for adult patients with FC II and III PAH.

Reasons for Recommendation 1

- CADTH network meta-analyses (NMAs) demonstrated that the available drugs used in monotherapy are similarly efficacious for improving the key trial outcomes of FC worsening and clinical worsening.
- CADTH cost-utility analysis demonstrated that sildenafil and tadalafil, when either is used as monotherapy, were the most cost-effective drugs for treatment-naive patients with PAH.
- There was insufficient evidence to make a recommendation for patients with FC I and IV PAH at this time.

Of Note

- CDEC noted that sildenafil and tadalafil should be avoided in patients with specific contraindications identified in the respective product monographs (e.g., concurrent nitrate use). CDEC was unable to identify potential additional criteria because of evidence gaps.
- CDEC noted there was no evidence to guide the duration of treatment with sildenafil or tadalafil before changing to or adding another drug. The decision to change from or add to initial therapy with either sildenafil or tadalafil should be based on patient-specific factors and response (effectiveness and harms), and should be determined by PAH specialists working in one of Canada's designated PH centres.

- For patients who are unable to receive sildenafil or tadalafil, no recommendation with respect to specific alternative initial therapies could be made within the context of the therapeutic review because of insufficient evidence.
- Substantial heterogeneity was noted across the studies included in the NMA; this is an important limitation of the therapeutic review.
- The specific inclusion criteria of the RCTs that formed the evidence base of the therapeutic review did not include all types of PAH patients seen in clinical practice, in terms of disease stability and presence of comorbidities.
- Only a very small proportion of patients enrolled in the included RCTs were classified as FC I PAH (< 1%). This low number of patients did not allow for a conclusion to be reached or a recommendation developed for this patient group.
- Intravenous epoprostenol is the only drug that has shown reduced mortality compared with placebo. This effect was predominantly observed in patients with more severe disease, i.e., FC III and IV, who made up a large portion of the patients in all epoprostenol studies (74% FC III and 26% FC IV).
- In most RCTs assessing drugs for PAH, the key outcome studied was the change from baseline in six-minute walk distance (6MWD), a measure that does not reliably reflect the benefit in such clinical outcomes as death, hospitalization, and initiation of PAH rescue therapy.
- The effect of treatment on FC was incorporated as the measure of treatment efficacy within the economic model because it is the only measure of clinical efficacy that has been demonstrated to be associated with quality of life in PAH. However, this may not capture the full quality of life benefits of treatment, which would be better reflected through direct measurement of quality of life in patients receiving PAH therapies.
- CDEC acknowledges that doses of sildenafil exceeding those recommended in the product monograph are used in Canadian clinical practice in order to adequately treat patients with PAH.
- In the feedback received from patients, the preference, mentioned several times, for using an oral medication rather than an injectable medication was noted.
- Based on how harms data were reported in RCTs, it was not possible to identify patients at greater risk for AEs.

Recommendation 2:

CDEC recommends that add-on therapy should be used in adult PAH patients who are unable to achieve disease control with a single drug.

Reason for Recommendation 2

- Four RCTs demonstrated that add-on therapy can improve outcomes in patients with PAH; all RCTs assessed add-on combination therapy versus monotherapy. No RCTs assessing triple combination therapy were identified.
- CDEC acknowledges that patients with PAH may not achieve satisfactory disease control on a single drug and may require additional medications due to the progressive nature of the disease.
- When considering combination therapy in patients with PAH, CDEC noted the need to balance the potential benefits against the potential increased risk of AEs.
- CDEC acknowledges that medical specialists working in PH clinics are best suited to prescribe these medications for adults with PAH, given the nature of the disease as well as the complexity and costs of drug regimens.

Of Note

- CDEC noted that it would be desirable to update the therapeutic review once the COMPASS-2 and AMBITION combination therapy trials are published. In particular, the AMBITION trial is the first to assess the efficacy of initial combination therapy in patients with PAH.
- The data available do not allow conclusions to be drawn about the comparative cost-effectiveness of add-on therapy versus monotherapy. Add-on therapies have only been compared with an ERA alone, which was not shown to be a cost-effective therapy.

Recommendation 3:

CDEC could not make a specific recommendation pertaining to subgroups of patients (based on disease severity or other disease characteristics) who may benefit more from specific drugs or combinations of drugs based on the evidence reviewed.

Reason for Recommendation 3

- There were no head-to-head RCTs comparing any of the drugs.
- No trials were specifically designed to assess patients who had failed or were intolerant to previous treatments.
- The subgroup analyses in the NMA conducted by CADTH did not influence the efficacy estimates.

Of Note

- CDEC noted it is likely that patients may benefit differently from specific drugs, as heterogeneity of patient response is common with all drug therapy.

PATIENT GROUP INPUT

CDEC discussions were informed by submissions to CADTH by four patient groups: the Pulmonary Hypertension Association of Canada (PHA Canada), the Edmonton Pulmonary Arterial Hypertension Society (EPAHS), the British Columbia Pulmonary Hypertension Society (BCPHS), and the Scleroderma Society of Canada. The following points summarize the key concerns of patients and caregivers, as documented in the patient group submissions:

- PAH has a significant impact on the lives of patients. Learning that one has this progressive and typically terminal illness is a shock. It forces immediate and drastic lifestyle changes on the part of the person with the disease.
- Patients with PAH have a day-to-day life that is difficult, exhausting, and challenging. Patients commonly experience depressed mood, anxiety, and feelings of helplessness and hopelessness as they are faced with a serious illness with a high risk of death within a few years.
- Patients progressively lose the ability to care for themselves and increasingly need the help of caregivers. Patients with children have limited ability to care for them, and once diagnosed with PAH, pregnancy is contraindicated. Many patients have to give up careers and dreams of starting a family in the prime of their lives.
- Therapy generally results in the reduction in the severity of PAH, but response is highly variable from day to day and person to person. While drug therapy delays the progression of the disease, alleviates some of the symptoms, and makes certain tasks easier, patients are frustrated by the fact that there is still no cure for PAH.
- Patients are also frustrated by the difficulties in gaining access to drug therapy, particularly combination therapy, depending on their residential location in Canada. This has resulted in some patients staying on monotherapy with suboptimal control of their disease.
- The impact on caregivers can be severe. They take the brunt of the work around the home, face increased financial responsibilities, and become psychological support systems for the patients. They give up considerable amounts of their own personal time and resources to care for the patient.

SUMMARY OF THE EVIDENCE

Clinical Evidence

CDEC discussed the results of a systematic review conducted to assess the comparative clinical efficacy and safety of PAH drugs used as monotherapy or add-on combination therapy. The PAH drugs included oral ERAs (ambrisentan 5 mg once daily, ambrisentan 10 mg once daily, bosentan 125 mg twice daily, macitentan 10mg once daily), sGC stimulators (riociguat max 1.5 mg three times daily and max 2.5 mg three times daily), PDE-5 inhibitors (sildenafil 20 mg three times daily, tadalafil 40 mg once daily), and prostanoids (intravenous epoprostenol, subcutaneous or intravenous treprostinil). Studies were selected for inclusion in the systematic review and subsequent analyses if they were RCTs or comparative observational studies (i.e., cohort or case-control) published in English, involving adults with PAH, had a treatment group consisting of a Health Canada–approved drug and dose, and reported any of the protocol-specified outcomes related to efficacy or safety.

The systematic review included 20 unique studies, of which 15[18-31] studies had treatment-naive populations and five[32-36] had mixed populations (i.e., PAH drug treatment-naive and treatment-experienced). Of the five studies with mixed populations, three[33-35] provided data for certain clinical outcomes in naive and experienced subpopulations. One study[32] with a mixed population did not provide data by treatment history subpopulations. Thus, 18[18-31,33-35] studies provided comparisons of PAH treatments in treatment-naive populations (i.e., monotherapy) and four[33-36] provided comparisons between dual combination (add-on) therapy and background therapy. All included studies were RCTs (15 double-blinded and 19 placebo-controlled); no published comparative observational studies were identified in the literature search that met the inclusion criteria for the systematic review. No published trials were identified in the literature search that directly compared the PAH drugs of interest.

Evidence on monotherapy was available for the following drug therapies: macitentan (one RCT), riociguat (one RCT), ambrisentan (three RCTs), bosentan (four RCTs), sildenafil (one RCT), tadalafil (one RCT), epoprostenol (three RCTs), and treprostinil (four RCTs). Evidence of dual (add-on therapy) was available from the following combinations: macitentan added to PDE-5 inhibitors or prostanoids (one RCT), riociguat added to ERA (one RCT), and tadalafil added to ERA (two RCTs).

The severity of PAH was based on a number of clinical parameters, including the New York Heart Association (NYHA) or WHO FC, which ranges from class I to IV, with class IV representing patients with the most severe symptoms. The outcomes of interest were mortality, hospitalization, clinical worsening, WHO FC (improved, unchanged, worsened), 6MWD, Borg dyspnea index (BDI), pulmonary hemodynamics (pulmonary vascular resistance [PVR], mPAP cardiac index [CI]), health-related quality of life (HRQoL), and safety data (serious adverse events [SAEs], discontinuation due to AEs, total AEs).

Traditional pairwise meta-analyses were conducted for the effects of the drugs of interest on all the listed outcomes. Because the therapeutic review was primarily interested in the comparative efficacy and safety of drugs to treat PAH, in the absence of head-to-head comparisons, indirect comparisons were performed. NMAs were conducted for four outcomes only: clinical worsening, WHO FC improvement, WHO FC worsening, and 6MWD. Planned subgroup analyses included age (e.g., < 65 years, ≥ 65 years), baseline NYHA or WHO FC (II, or III, IV), baseline 6MWD (e.g., < 350 m, ≥ 350 m), gender (male, female), background pharmacotherapy (Yes, No), and disease etiology subtype of PAH (e.g., idiopathic PAH and heritable PAH or other).

Additional meta-regression, subgroup, and sensitivity analyses were conducted for the NMA, based on patient treatment history (treatment-naive and patients on background PAH therapy), patient covariates (NYHA or WHO FC and PAH etiology at baseline) and treatment duration. Meta-regressions were performed when the variable was continuous in order to incorporate the maximum amount of information available from trials. Subgroup analyses were performed when the variable could be dichotomized (e.g., patient population was treatment-naive or on background PAH therapy). Sensitivity analyses were performed by removing macitentan (a long-term study) or by removing studies with different outcome definitions.

Monotherapy (Treatment-Naive Population)

For clinical worsening, data from eight treatment options (macitentan 10 mg, riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, and placebo) were subjected to meta-analyses. Despite the slight difference in definition among studies, clinical worsening (a mortality and morbidity composite outcome) was generally defined as time to first occurrence of all-cause death, worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, heart or lung transplantation, or atrial septostomy. Direct pairwise meta-analysis showed that all treatments were numerically favoured in reducing the risk of clinical worsening compared with placebo. Treatment effects (relative risk [RR]) ranged from 0.25 (tadalafil) to 0.59 (macitentan). A statistically significant difference versus placebo was reached for macitentan, ambrisentan 5 mg, and bosentan, but not for riociguat, ambrisentan 10 mg, sildenafil, and tadalafil in a treatment-naive population. The treatment effects versus placebo estimated from NMA were similar, in both magnitude and direction, to the results of direct pairwise estimates, with RRs ranging from 0.21 for tadalafil to 0.46 for macitentan. There were no statistically significant differences between drugs with respect to clinical worsening outcomes. Excluding the study examining the efficacy of macitentan (a long-term study with median follow-up of 115 weeks) from the analysis did not affect the effect sizes of other treatments. Likewise, sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect, suggesting the robustness of the results. Clinical worsening has been recommended for use as a clinically relevant primary outcome in studies evaluating drugs for the treatment of PAH because it measures treatment effects on mortality and morbidity. It is reasonable for clinical worsening to be a composite outcome, largely because of the low event rates for the individual mortality and morbidity components.[37] However, the definition of a clinically important difference between treatment groups with respect to clinical worsening in these studies has yet to be determined.

For FC improvement, data from nine treatment options (riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil, and placebo) were subjected to meta-analyses. Data for macitentan were not available for the treatment-naive population; only results for the total study population (i.e., treatment-naive plus treatment-experienced) regarding the proportion of patients with FC improvement were available from published sources for macitentan. Direct pairwise meta-analysis showed that, for naive populations, epoprostenol, sildenafil, and tadalafil showed statistically significant improvement in FC compared with placebo, while riociguat, ambrisentan, bosentan, and treprostinil did not. The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. Epoprostenol, which had the largest treatment effect versus placebo, was statistically significantly superior compared with all other treatments in the naive populations. Sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect, suggesting the robustness of the

results. The minimal clinically important difference (MCID) of WHO FC improvement is unknown.

For FC worsening, data from eight treatment options (riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and placebo) were subjected to meta-analyses. Data for macitentan were not available for the treatment-naive population; only results for the total study population (i.e., treatment-naive plus treatment-experienced) regarding the proportion of patients experiencing FC worsening were available from published sources. Direct pairwise meta-analysis showed that all treatments were numerically favoured in the reduction of FC worsening compared with placebo. Statistically significant differences were reached only for ambrisentan (5 mg and 10 mg) and riociguat (max 2.5 mg) in naive populations. The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. There were no statistically significant differences between riociguat and other drugs or between other drugs themselves. Sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect, suggesting the robustness of the results. The MCID of WHO FC worsening is unknown.

For 6MWD, data for all 11 treatment options (macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil, and placebo) were subjected to meta-analyses. The 6MWD measures the distance a patient can walk in six minutes. Change from baseline in 6MWD is the most widely used outcome in trials of drugs for PAH. However, while some evidence suggests baseline 6MWD and absolute distance walked in six minutes are correlated with mortality and morbidity outcomes in PAH, change from baseline in 6MWD has been inconsistently correlated with these outcomes. Change in 6MWD from baseline was used as the primary outcome in many of the included studies, except for the macitentan study, in which it was a secondary outcome. Direct pairwise meta-analysis showed that all drugs, except macitentan, statistically significantly increased 6MWD compared with placebo in the naive populations. The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. Increase in 6MWD with riociguat (both doses) was not statistically significantly different compared with all other drugs. Numerically, epoprostenol showed the highest increase in 6MWD compared with all remaining drugs. The mean differences in 6MWD relative to other drugs ranged from 18.3 m (compared with ambrisentan 5 mg) to 56.9 m (compared with macitentan 10 mg). The MCID for the change in 6MWD from baseline has been estimated to be 33.0 m (range: 25.1 m to 38.6 m). Sensitivity analysis was not performed for this outcome.

In summary, of the four outcomes analyzed using NMA, there were no statistically significant differences between drugs with respect to clinical worsening and FC worsening. For FC improvement and 6MWD, epoprostenol had highest activity in treatment-naive populations, while there were no apparent differences among the remaining treatments. Acknowledging the limitations in the available evidence, these findings suggest that there may not be statistically or clinically meaningful differences between drugs currently available in Canada for the treatment of PAH. There is, however, an exception with epoprostenol, which appears to be the most effective in improving clinical status, as measured by FC improvement and 6MWD.

Combination Therapy (Add-on)

Evidence of clinical worsening, FC improvement, FC worsening, and 6MWD was available for riociguat max 2.5 mg or tadalafil 40 mg added to ERA background therapy of ambrisentan or bosentan that had been stable for at least three months. Evidence for clinical worsening and

6MWD was also available for addition of macitentan onto PDE-5 inhibitor or prostanoid background therapy. However, the macitentan data could not be combined with those of riociguat or tadalafil in the NMA because of different background therapies and the much longer study duration of the macitentan RCT. The following findings addressed the comparison of dual therapy versus monotherapy:

- Addition of macitentan 10 mg to PDE-5 inhibitor or prostanoid background therapy statistically significantly reduced clinical worsening compared with background therapy alone.
- Addition of riociguat max 2.5 mg to ERA background therapy reduced clinical worsening versus ERA monotherapy, but this effect was not statistically significant. However, addition of tadalafil 40 mg to ERA background therapy statistically significantly reduced clinical worsening versus ERA monotherapy.
- For FC improvement, there were no statistically significant differences between combination therapy of riociguat max 2.5 mg and ERA or of tadalafil 40 mg and ERA versus ERA alone.
- Addition of riociguat max 2.5 mg or tadalafil 40 mg to ERA background therapy reduced FC worsening versus ERA alone; however, neither combination resulted in a statistically significant difference versus monotherapy.
- Addition of macitentan 10 mg, riociguat max 2.5 mg, or tadalafil 40 mg to corresponding background therapy numerically improved 6MWD compared with background therapy alone. Statistically significant differences were reached for macitentan and tadalafil, but not for riociguat.
- There were no statistically significant differences between combination therapy of riociguat + ERA and tadalafil + ERA for clinical worsening, FC improvement, FC worsening, and 6MWD.

Other Efficacy Outcomes

Direct pairwise meta-analyses were performed for hospitalization, mortality, BDI, hemodynamics (PVR, mPAP, CI), and HRQoL. These outcomes were mostly available for total populations; i.e., including both treatment-naive and treatment-experienced patients.

The number of deaths in all studies was relatively low, except in one study of epoprostenol and one study of treprostinil, where the percentage of patients who died in the placebo groups reached 25% and 36%, respectively, albeit among patients with more severe disease (predominantly NYHA or WHO FC III or IV). Epoprostenol showed a statistically significant lower risk of mortality compared with placebo, while there were no statistically significant differences between other drugs and placebo.

Of all drugs, except epoprostenol, macitentan 10 mg was the only drug that showed a statistically significant reduction in hospitalization compared with placebo.

Compared with placebo, all drugs improved breathlessness (measured by BDI), PVR, mPAP, and CI. However, statistically significant improvements were less consistent across drugs for improved BDI scores as compared with hemodynamic parameters and CI.

HRQoL was reported in most studies using different instruments such as the Short-Form 36-Item health survey (SF-36), EuroQol 5-Dimensions questionnaire (EQ-5D), Living with Pulmonary Hypertension questionnaire, Minnesota Living with Heart Failure questionnaire, Chronic Heart Failure questionnaire, Nottingham Health Profile, and Dyspnea-Fatigue Rating. Overall, all drugs showed improvement in HRQoL compared with placebo. Statistically significant differences were not reached for bosentan.

Subgroup Analyses

The results for subgroup analyses with respect to age, baseline FC, baseline 6MWD, gender, PAH etiology, and PAH therapies at baseline were reported as point estimates in forest plots. Raw data were not available to perform meta-analysis. The macitentan study reported subgroup analyses on clinical worsening and 6MWD, while the riociguat, bosentan, sildenafil, and tadalafil studies reported subgroup analyses on 6MWD only. Overall, all five drugs showed improvement in clinical worsening and/or 6MWD in all patient subgroups.

Safety

Safety data from the published studies included in this review were available only for total populations; i.e., including both treatment-naive and treatment-experienced patients.

- SAEs were less frequent with macitentan (45% versus 55%), riociguat (11% versus 18%), ambrisentan (9% versus 16%), and tadalafil (9% versus 15%) compared with placebo. In contrast, treprostinil (62% versus 20%) had frequent SAEs related to injection-site reactions. Bosentan, sildenafil, and epoprostenol showed no differences in SAEs compared with placebo.
- Discontinuation of treatment was more frequent with treprostinil than placebo (7.7% versus 0.4%). This was mainly because of abdominal subcutaneous injection-site pain. There was no apparent difference between other drugs and placebo with respect to discontinuation of treatment due to AEs.
- Treatment-related AEs compared with placebo:
    - Risk of liver toxicity: bosentan (12% versus 2%)
    - Risk of peripheral edema: riociguat (18% versus 11%), ambrisentan (22% versus 11%), bosentan (13% versus 8%), and treprostinil (9% versus 3%)
    - Risk of anemia: macitentan (13% versus 3%), riociguat (8% versus 2%), and ambrisentan (68% versus 17%)
    - Risk of hypotension: riociguat (10% versus 2%), epoprostenol (13% versus 0%), and treprostinil (5% versus 2%)
    - Epoprostenol and treprostinil were frequently associated with nausea, diarrhea, jaw pain, headache, and injection-site reactions.

Economic Evidence

CDEC discussed the results of an economic model developed to assess the comparative cost-effectiveness of PAH drugs used as monotherapy or add-on combination therapy. The model was in the form of a cost-utility analysis with treatments compared in terms of the incremental cost per quality-adjusted life-year (QALY) gained during a lifetime horizon (30 years), from a Canadian Ministry of Health perspective. A cohort of patients 50 years of age diagnosed with NYHA FC II, III, or IV PAH (ratio of females to males 2.3:1) was modelled within the analysis, as this was reflective of the average age of patients, severity of PAH, and gender distribution within PAH registries.[5,38] Separate analyses were conducted for cohorts of patients beginning with FC II, FC III, and FC IV PAH. For the comparison of monotherapy, the analysis was based on a treatment-naive population, meaning that patients had not previously received treatment for PAH with PDE-5 inhibitors, prostaglandins, sGC stimulators, or ERAs. The comparison of add-on therapies included a mixed population of both treatment-naive patients and those who had previously received therapy for PAH. The medications modelled included prostaglandin inhibitor (epoprostenol), ERAs (bosentan, ambrisentan), PDE-5 inhibitors (sildenafil and tadalafil), and sGC stimulator (riociguat). The prostaglandin inhibitor treprostinil was not included within the model due to a lack of clinical data on the relevant end points. The ERA macitentan was evaluated within a separate sensitivity analysis, as the results of the clinical trial were reported

only in a mixed population of both treatment-naive and treatment-experienced patients, thereby precluding its inclusion within the NMA.

A Markov model with a three-month cycle length was created to estimate the long-term costs, life-years, and QALYs associated with PAH treatments. None of the included clinical trials for PAH therapies directly measured quality of life using a method that would allow for the calculation of utility values at baseline or throughout the duration of the trials. Consequently, the calculation of the utility gained with treatment must be inferred from a relationship between an improvement in a clinical measure and in quality of life. The only PAH clinical measure that has been shown to be related to quality of life is the FC.[39] Patients enter the model with FC II, III, or IV PAH, as these are the most common stages of the illness for diagnosis and initiation of treatment. Efficacy estimates of the treatments were derived from the NMA conducted by CADTH, based on the relative risk of improving and worsening in FC with treatment versus placebo. The nature of economic modelling is such that inclusion of more than one outcome measure can often lead to double counting. Other outcomes from the NMA were therefore not included within the analysis as the inclusion of other outcomes aside from FC, which have similar indirect effects, will lead to overestimation of the benefits to be gained from treatment. A mortality rate, adjusted based on the impact of FC on the age-specific mortality rate for the general population, was applied within each of the states in the model.[40] An independent effect of treatment on mortality was not incorporated, to avoid double counting and a consequent overestimation of the survival benefit with treatment.

Other parameters were sourced from the published literature and clinical expert opinion. Drug costs were derived from the Saskatchewan Provincial Drug Formulary or from the manufacturer if not listed within the formulary (Table 1).

Table 1: PAH Drug Costs per Cycle Within the Economic Model		
Drug/Comparator	**Dosing Used in the Model**	**Drug Cost per Three-Month Cycle[a]**
Stimulators of sGC		
Riociguat (Adempas)	1 mg three times daily increased to 2.5 mg three times daily	$12,639[b]
ERA		
Macitentan (Opsumit)	10 mg once daily	$12,656[b]
Ambrisentan (Volibris)	5 mg for two weeks, then 10 mg once daily	$12,074
Bosentan (Tracleer)	62.5 mg twice daily increased to 125 mg twice daily after four weeks	$12,650[c]
PDE-5 inhibitors		
Sildenafil (Revatio)	20 mg three times daily	$3,288
Tadalafil (Adcirca)	40 mg once daily	$2,634
Parenteral prostanoids		
Epoprostenol (Flolan)	First cycle: 2 ng/kg/min increased to 4 ng/kg/min by day 7, and then increased at a rate of 2.5 ng/kg/min every 21 days Subsequent cycles: 27 ng/kg/min, with increases of 5 ng/kg/min every two years until a ceiling of 50 ng/kg/min is reached	First cycle: $5,274[d,e] Subsequent cycles: $11,247[d,e]

ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase-5; sGC = soluble guanylate cyclase.
[a] Includes 8% markup and $8.83 dispensing fee for a three-month supply.
[b] List price confirmed by the manufacturer.
[c] Assumes a 70 kg patient and includes the cost of diluent.
[d] The base-case analysis used the price of Tracleer (brand-name bosentan, $64.18 per tablet, based on Saskatchewan Formulary, April 2014).
[e] Unused medication discarded after 24 hours.
Source: Saskatchewan Drug Plan (April 2014) unless otherwise indicated.

Extensive deterministic sensitivity analyses were conducted to assess the impact of changes in parameter inputs (parameter uncertainty) and model assumptions (structural uncertainty). A probabilistic sensitivity analysis was also conducted to estimate the extent of uncertainty surrounding the estimates.

For monotherapy versus supportive care, the results of the base case show that sildenafil would be considered the most cost-effective therapy for PAH in patients with FC II, III, or IV. In patients with FC II and III, sildenafil was both less costly and more effective than all comparator treatments including supportive care — sildenafil is therefore the dominant therapy. In FC IV, supportive care was less costly than treatment with sildenafil; however, provided a payer's

willingness to pay per QALY was greater than $19,188, sildenafil would be the most cost-effective therapy.

Although sildenafil dominated treatment with tadalafil in FC II and III, being both more effective and less costly, when compared with supportive care, tadalafil was dominant over supportive care in patients with FC II and FC III PAH. In FC IV, the incremental cost-utility ratio (ICUR) for tadalafil versus supportive care was $211,923 per QALY. In FC IV, all other treatments in comparison with supportive care produced ICURs of greater than $1,000,000 per QALY.

There were no studies comparing monotherapy with a PDE-5 inhibitor, the most cost-effective therapy based on the monotherapy analysis, with (add-on) therapy. There were, however, studies examining the use of add-on therapy with either an ERA plus tadalafil or an ERA plus riociguat versus an ERA alone. In interpreting the results of this analysis, one should bear in mind that an ERA alone was not cost-effective at a willingness to pay of $50,000 per QALY, as compared with supportive care for any PAH FC within the monotherapy analysis.

At a decision-maker's willingness to pay of less than approximately $88,000 per QALY, neither add-on therapy with an ERA plus tadalafil nor add-on therapy with an ERA plus riociguat would be considered cost-effective in PAH patients with FC II, III, or IV disease relative to an ERA alone. The ICUR for an ERA plus tadalafil versus an ERA alone in FC II patients was the lowest at $88,506 per QALY, followed by FC III at $156,513 per QALY and significantly higher in FC IV at $1,568,400 per QALY. The combination of an ERA plus riociguat was both more costly and more efficacious than an ERA plus tadalafil, resulting in comparative cost-effectiveness ratios of more than $500,000 per QALY in all three PAH FCs.

In deterministic sensitivity analyses, results were insensitive to changes in assumptions regarding discount rates, utility values, treatment costs, and health care costs in FC I; however, they were sensitive to the time horizon of the model, the percentage of patients initiating epoprostenol upon deteriorating to FC IV, and the incorporation of unadjusted estimates for the RR of improvement and worsening in FC with treatment only within FC IV.

The probabilistic sensitivity analysis suggests that there is a great deal of uncertainty surrounding the estimates of costs and effectiveness associated with the PAH therapies under study. This uncertainty is primarily due to the significant uncertainty in the estimates produced from the NMA for the improvement and worsening in FC, which is reflected in the wide credible intervals reported for the RRs. Even given the uncertainty within the clinical inputs, apart from sildenafil and tadalafil, the other PAH therapies had negligible probability of being the most cost-effective.

Limitations of the Evidence

The therapeutic review of the comparative efficacy, safety, and cost-effectiveness of drug therapies for PAH was limited by important gaps in the available evidence, including the small number of studies in relation to the number of treatment strategies, the lack of head-to-head comparisons, short-term follow-up, limited evidence on combination therapy, and restriction to the Health Canada–recommended dosage regimen. For instance, the Health Canada–approved dose of sildenafil is 20 mg three times daily; however, in practice clinicians may increase the dose to 80 mg three times daily or more. In addition, there were no trials specifically designed to assess the comparative efficacy and safety of new treatments in patients who had failed or were intolerant to previous treatments; thus, it is uncertain to what extent the results of the current review are applicable to this patient population. According to the clinical experts involved in this

review, in the clinical practice setting the decision to intensify therapy by adding a new therapy to the existing one is proactive, made when patients do not meet specific targets of response rather than waiting for a bad outcome to occur. Several studies on combination therapy did not meet the review inclusion criteria and were therefore excluded from data analysis. Two studies on combination therapy, one comparing sildenafil plus bosentan versus sildenafil alone (COMPASS-2) and the other comparing first-line ambrisentan plus tadalafil versus ambrisentan and tadalafil monotherapies (AMBITION), were ongoing at the initiation of this review; the final results these studies are not yet published.

Furthermore, substantial heterogeneity in study designs, patient demographics, and disease characteristics (i.e., WHO FC at baseline and PAH etiology) may present as a threat to the validity of this review. However, these potential sources of bias were assessed early in the development of this review and methods to deal with these were determined a priori. To address the heterogeneity, meta-regression and subgroup analyses were performed using patient characteristics as covariates. However, the small number of studies in relation to the number of treatment strategies may not have allowed for complete control of confounding.

Several subgroups were identified as important for this review: age, gender, baseline 6MWD, baseline PAH etiology, baseline WHO FC, and background PAH therapy. Treatment outcomes according to these subgroups were not reported in the published articles. We were therefore unable to estimate the comparative treatment effects of PAH therapies based on these subgroups in the analysis to identify which treatment is better for specific subgroups and to account for related potential sources of bias.

Finally, safety data and data on hemodynamics were often reported without stratifying into treatment-naive or treatment-experienced populations in trials having mixed populations, such as the studies of macitentan, riociguat, tadalafil, and bosentan. This would largely compromise the interpretation of the comparative safety of different therapeutic regimens. Therefore, in this review, we were not able to conduct an NMA for those outcomes.

Economic modelling requires a number of assumptions to be made as a result of limitations in data availability. This was the case also within the model for this analysis, which required the use of a clinical marker, specifically FC, to model disease progression and required that short-term clinical trial data be extrapolated to predict longer-term outcomes. Where possible, assumptions have been tested within sensitivity analyses.

The economic analysis was limited by the lack of data regarding the impact of treatment on patients' HRQoL. As change in FC is the only measure of clinical efficacy that has been demonstrated to be associated with quality of life in PAH, the impact of treatment on FC was incorporated as the measure of treatment efficacy within the economic model. This may not capture the full benefit of treatment, which would be better reflected through direct measurement of quality of life in patients receiving PAH therapies. A major limitation in the economic analysis is the low quantity and quality of the clinical trials. The uncertainty regarding the effectiveness estimates from the NMA was the most significant contributing factor to the uncertainty in the results of the economic estimates. The short-term nature of the clinical trials required assumptions regarding the long-term impacts of treatment, which may have introduced additional uncertainty within the results.

DISCUSSION POINTS

Efficacy and Cost-Effectiveness

- CDEC discussed the therapeutic trends in PAH and acknowledged that PAH is a condition in which the treatment offered in specialized clinics evolves more rapidly than the evidence base. This at least partly reflects the need for clinicians to intervene aggressively in some patients, due to the severe and fatal nature of PAH.
- CDEC discussed the definition of time to clinical worsening, which is a composite outcome of mortality and morbidity. The effect of PAH therapies on this outcome was affected by change in FC and 6MWD. CDEC heard from clinical experts that, in practice, a non-responder to a particular treatment is identified by assessing the impact of therapy on several indicators and clinical events. In that context, FC improvement is less reliable than FC worsening.
- CDEC heard from clinical experts that there are two types of non-responders: those who do not improve, but remain clinically stable; and those who continue to deteriorate. Whereas there may be more time to assess the impact of drug therapy in the first group, in the latter case, optimization of therapy needs to occur rapidly in order to prevent serious consequences for the patients. In both situations, options include increasing the dose of the drug being used; discontinuing the drug being used and replacing it with a new one; or initiating combination therapy by adding a second drug to the first one.
- CDEC discussed the dose of sildenafil used in clinical practice. The clinical experts agreed that sildenafil can be started at 20 mg three times daily. However, this dose often needs to be increased as treatment effect plateaus; the time required for optimizing therapy varies depending on the clinical status of the patient.
- CDEC discussed the availability of generic sildenafil on some of the drug plans' formularies. CDR economic analysis used the listed price of brand-name sildenafil. Using the generic cost would not change the conclusions of the analysis, as sildenafil would remain the most cost-effective option for adult patients with FC II and III PAH.
- CDEC discussed the selection of different drug therapies based on the clinical status of the patient. According to the clinical expert, the FC status is a common criterion used to make such decisions.
- Although sildenafil was found to be the most cost-effective PAH therapy in FC IV based on the economic analysis, its role as monotherapy in FC IV has been questioned. Epoprostenol or combination therapy is normally used for patients with FC IV, while treatment with any orally available drug is typically considered in patients with stable FC II. Many patients seen in clinical practice are in FC III, for whom intensified therapy needs to be considered. Sildenafil monotherapy would not typically be considered in these cases unless, possibly, they are stable FC III.
- CDEC noted that higher quality evidence on combination therapy is limited to only four RCTs that did not address whether combination therapy could be used in patients who did not have an adequate response or were intolerant to their previous treatment.
- CDEC also noted that there is a lack of evidence available on the value of particular treatment options for specific subgroups of patients based on disease severity or other disease characteristics.
- CDEC noted that there are a number of important limitations to the economic evaluation. These are a consequence of the lack of high-quality evidence on the efficacy of drugs currently used for the treatment of PAH, which resulted in uncertainty in the estimates of clinical effects. Given that the clinical consequences used in the economic model are based on the available clinical evidence, there is also uncertainty in the economic evaluation results.

- Among the important limitations of the economic evaluation, CDEC noted the lack of support for the assumption of long-term benefits of PAH therapies, given that the duration of most RCTs was limited to a few months.

Other Discussion Points

CDEC noted that several stakeholders responded to the request for feedback on the therapeutic review and sent detailed submissions. Many issues were raised by stakeholders; among these, CDEC particularly noted the following:

- The quantity and quality of evidence on the effectiveness of these drugs are limited, but the amount of such evidence has increased in recent years. As such, CDEC deems the current evidence base to be sufficient to develop recommendations on drugs to treat patients with PAH.
- The dose of sildenafil evaluated in the therapeutic review (and approved by Health Canada for PAH) does not reflect the higher doses used in clinical practice, particularly in specialized treatment centres; this limits the interpretation of the therapeutic review findings.
- The presence of significant heterogeneity in the included studies represents an important limitation of the NMA, requiring cautious interpretation of its findings.

RESEARCH GAPS

CDEC proposed that the following issues be addressed through research as a high priority:

- Head-to-head RCTs to assess the comparative efficacy and safety of all drugs for the treatment of PAH.
- Comparative RCTs to determine the efficacy and safety of add-on combination therapy used in patients who failed or deteriorated with monotherapy, in particular sildenafil monotherapy.
- RCTs to determine whether particular treatments may provide incremental benefits to specific patient subgroups based on disease severity or other disease characteristics.
- High-quality comparative studies to assess the long-term efficacy and safety of PAH drug therapies.

Committee Members:

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

Regrets:

Conflicts of Interest: None.

One external clinical expert attended the meeting and participated in the discussion, but did not vote on the recommendations.

About This Document:

The Therapeutic Review Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication's efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic Review clinical and economic reports are based on published information available up to the time that CDEC made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations, is considered in the preparation of this recommendation document.

CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). It makes recommendations and provides advice to Canadian jurisdictions to use in making informed decisions. It is made up of experts in drug evaluation and drug therapy, and public members.

The Final CDEC Therapeutic Review Recommendations or Advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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The Therapeutic Review Framework describes the Therapeutic Review process in detail.[41]

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