CADTH THERAPEUTIC REVIEW REPORT

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Drugs for Pulmonary Arterial Hypertension — Project Protocol

Supporting Informed Decisions

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ABBREVIATIONS

CDEC	Canadian Drug Expert Committee
HF	heart failure
HPAH	heritable pulmonary arterial hypertension
IPAH	idiopathic pulmonary arterial hypertension
PAH	pulmonary arterial hypertension
PCH	pulmonary capillary hemangiomatosis
PDE-5	phosphodiesterase type 5
PH	pulmonary hypertension
PVOD	pulmonary venoocclusive disease
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management

1   INTRODUCTION AND RATIONALE

Pulmonary arterial hypertension (PAH) — a form of pulmonary hypertension (PH) — is   a progressive disease characterized by elevation of pulmonary artery pressure of greater than 25 mm Hg, leading to restricted flow through pulmonary arterial circulation.[1] It is a complex, multifactorial disorder that typically leads to overload of the right ventricle, progressive right-sided heart failure (HF), and premature death.[2] In adults, the prevalence of PAH is approximately 12 to 50 per million people.[3-5] Although PAH affects males and females of all ethnicities and ages,[6] the disease is more common among women and people between 20 and 40 years of age.[7] Overall, it has been estimated that between 2,000 and 10,000 Canadians have pulmonary hypertension (PH); between 250 and 500 new cases develop annually.[8] Given that the population in Canada is currently about 35 million,[9] the estimated number of Canadians with PAH ranges from 420 to 1,750.

PH is currently classified into five groups; Group 1 is synonymous with PAH and its subcategories (Table 1).[1,10] Idiopathic PAH is the most common form of the disease (46%).[10] Additional subcategories of PAH include a heritable form, a form induced by drugs and toxins, a form in newborns, and forms associated with concurrent medical conditions such as connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, and chronic hemolytic anemia. With the revisions to the PH classification system that occurred in 2008, a supplemental Group 1 (i.e., Group 1' pulmonary venoocclusive disease [PVOD] and/or pulmonary capillary hemangiomatosis [PCH]) was created. However, because of the particular nature of PVOD and PCH, Group 1' will be excluded from the scope of this therapeutic review.

Table 1: Pulmonary Arterial Hypertension
1.1 IPAH
1.2 HPAH
1.2.1   BMPR2
1.2.2   ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3   Unknown
1.3 Drug- and toxin-induced
1.4 APAH:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.4.6 Chronic hemolytic anemia
1.5 Persistent PH in the newborn

ALK1= activin receptor-like kinase type 1; APAH = associated (with) pulmonary arterial hypertension; BMPR2 = bone morphogenetic protein receptor type 2; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PH = pulmonary hypertension.

PAH is associated with poor overall prognosis. A US national registry conducted in the early 1980s, which included 187 patients with IPAH followed for up to 5 years, found that the median survival was 2.8 years.[11,12] At present, the average survival in adults after diagnosis is estimated at 5 to 7 years.[13-15] From the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) data, the 1-year survival rate of PAH is approximately 91%.[16] The pathological changes of PAH include lesions in distal pulmonary arteries, medial hypertrophy, intimal proliferative and fibrotic changes, and adventitial thickening with perivascular

inflammatory infiltrates.[2] Vasoconstriction, endothelial dysfunction, dysregulated smooth muscle cell growth, inflammation, and thrombosis are contributory mechanisms to the disease progression.[2] The action of PAH drugs aim at normalizing these mechanisms.

Treatment of PAH is generally categorized as primary therapy or advanced therapy. Primary therapy refers to treatment directed at underlying causes of the disease and includes the use of diuretics, oxygen, anticoagulants, and digoxin. Advanced therapy is directed at the disease itself. As primary therapies are generally not effective in PAH, advanced therapy is often needed.[17]

There are seven approved drugs in Canada for advanced therapy of PAH. They belong to three classes of drugs: prostanoids (epoprostenol injectable, treprostinil injectable), endothelin receptor antagonists (ERAs) (bosentan tablet, ambrisentan tablet, macitentan tablet), and phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil tablet and injectable, tadalafil tablet). Macitentan received Health Canada approval for the treatment of PAH in November 2013.

A number of potential future therapies are in clinical development for the treatment of PAH. These include:

- the first representatives of two new drug classes intended for oral use:
  - a soluble guanylate cyclase (sGC) stimulator (riociguat)
  - an highly selective prostacyclin receptor agonist (selexipag)
- a new PAH indication for two existing drugs:
  - a PDE-5 inhibitor (vardenafil)
  - an oral tyrosine kinase inhibitor (imatinib)
- inhaled and oral formulations of treprostinil.

The availability of two new PAH drugs — macitentan and potentially riociguat — in Canada will augment the complexity of PAH therapy, including options for combination therapy; the latter being based on the concurrent use of drugs with different mechanisms of action. There are two possibilities for combination therapy: add a medication to an ongoing treatment (sequential [add-on] combination therapy), or begin with a combination therapy from the start of treatment (upfront combination therapy). Recent data from REVEAL indicate that combination therapy is routinely used in the US, with approximately 65% of PAH patients on such therapy. A recent survey indicates that a majority of PH specialists in Canada support the use of combination therapy in patients who do not adequately respond to monotherapy.[18] Recent revision to the reimbursement policy for PAH drugs in Ontario included changes in funding for certain drug combinations and restricting prescribing of these to recognized PH treatment centres; this has led to 22% of PAH patients using combination therapy.[19]

The emergence of novel drug therapies will necessitate consideration of their comparative effectiveness from both a clinical and an economic perspective, accounting for both monotherapy and combination therapy regimens.

CADTH will undertake a systematic review to compare the efficacy and safety of new and existing drug therapies for PAH, and will examine their cost-effectiveness. The review will include drug therapies that are available in Canada (epoprostenol, treprostinil, bosentan, ambrisentan, macitentan, sildenafil, tadalafil) and one for which the clinical development program is advanced but is not yet approved for the treatment of PAH in Canada (riociguat).

The clinical and cost-effectiveness evidence will be reviewed by the Canadian Drug Expert Committee (CDEC) for the purpose of making recommendations. Recommendations and advice delivered by CDEC are provided to CADTH participating jurisdictional drug programs to inform their policy decisions.

2 DELIVERABLES

The following deliverables are planned:
- a science report, including both a systematic review of comparative efficacy and safety of historical and new (i.e., riociguat and macitentan) therapies for PAH; and if sufficient data are available, an examination of their cost-effectiveness based on a cost utility analysis
- CDEC recommendations and/or advice based on the science report, and stakeholder feedback; recommendations and/or advice will be limited to drug therapies for PAH that are approved by Health Canada.

3 POLICY QUESTIONS

There are three policy questions for this project. These reflect the information needs of CADTH jurisdictional clients. Policy questions will also feed deliberations of the CDEC members when they develop the therapeutic review recommendations.
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 agents when used either as monotherapy or (add-on) combination therapy?

4 RESEARCH QUESTIONS

There are four research questions for this project. These were developed to address the aforementioned policy issues.
1. What is the efficacy, safety, and cost-effectiveness of monotherapy with macitentan or riociguat compared with monotherapy, with each other or with a PDE5 inhibitor, another ERA, or a prostanoid:
   a. in PAH patients, irrespective of disease severity or etiology?
   b. in PAH patients with class II HF?
   c. in PAH patients with class III or class IV HF?
   d. in PAH patients with different disease etiology, as defined in the Dana Point 2008 Classification?

2. What is the comparative efficacy, safety, and cost-effectiveness of dual (add-on) combination therapy involving either a PDE5 inhibitor, an ERA, an sGC stimulator, or a prostanoid versus monotherapy:
   a. in PAH patients, irrespective of disease severity or etiology?
   b. in PAH patients with class II HF?
   c. in PAH patients with class III or class IV HF?

    d. in PAH patients with different disease etiology, as defined in the Dana Point 2008 Classification?

3.   What is the comparative efficacy, safety, and cost-effectiveness of dual (add-on) combination therapy involving either a PDE5 inhibitor, an ERA, an sGC stimulator, or a prostanoid versus dual (add-on) combination therapy:
    a. in PAH patients, irrespective of disease severity or etiology?
    b. in PAH patients with class II HF?
    c. in PAH patients with class III or class IV HF?
    d. in PAH patients with different disease etiology, as defined in the Dana Point 2008 Classification?

4.   What is the comparative efficacy, safety, and cost-effectiveness of triple (add-on) combination therapy involving either a PDE5 inhibitor, an ERA, an sGC stimulator, or a prostanoid versus dual (add-on) combination therapy:
    a. in PAH patients irrespective of disease severity or etiology?
    b. in PAH patients with class II HF?
    c. in PAH patients with class III or class IV HF?
    d. in PAH patients with different disease etiology, as defined in the Dana Point 2008 Classification?

5   METHODS

5.1   Literature Search Strategy

The literature search will be performed by an information specialist using a peer-reviewed search strategy. Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946-) with In-Process records and daily updates via Ovid; Embase (1974-) via Ovid; the Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts are pulmonary arterial hypertension and riociguat, macitentan, epoprostenol, treprostinil, bosentan, ambrisentan, sildenafil, and tadalafil.

Methodological filters will be applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, clinical trials, and observational studies. Where possible, retrieval will be limited to the human population. Retrieval will not be limited by publication date but will be limited to English language results. Conference abstracts will be excluded from the search results. Regular alerts will be established to update the search until recommendations by the Canadian Drug Expert Committee (CDEC), based on this review, are finalized. Regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Search Tool for Evidence-Based Medicine* checklist (http://www.cadth.ca/resources/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials, and databases (free). Google and other Internet search engines will be used to search for additional

web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacting appropriate experts.

5.2 Selection Criteria

5.2.1 Clinical

Two reviewers will independently screen titles and abstracts relevant to the clinical research questions regarding available and emerging drug therapies for the treatment of patients with PAH. Full texts of potentially relevant articles will be retrieved and independently assessed for possible inclusion based on the predetermined selection criteria (Table 2). The two reviewers will then compare their chosen included and excluded studies; disagreements will be discussed until consensus is reached. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Table 2: Inclusion and Exclusion Criteria for Primary Studies	
Inclusion Criteria	
Study Design	Published RCTs and controlled observational studies will be considered to answer the 4 research questions. Only studies of ≥ 8 weeks in duration will qualify for inclusion. Observational studies will be limited to higher quality design, defined for the purpose of this therapeutic review as comparative (prospective or retrospective) cohort and case-control studies (including nested case-control studies).
Population	Adult patients (≥ 18 years) diagnosed with PAH[a], as defined in Table 1.
Interventions	• Macitentan – oral • Riociguat – oral

Comparators	• Drug therapies[b, c, d]
	  ▪ Epoprostenol – injectable
	  ▪ Treprostinil – injectable
	  ▪ Bosentan – oral
	  ▪ Ambrisentan – oral
	  ▪ Sildenafil – oral and injectable
	  ▪ Tadalafil – oral
	• Placebo or conventional medical treatment

Outcomes	*Ranking based on hierarchy of importance:* 1) Death (all-cause, PAH-related) 2) Hospitalization 3) Clinical worsening[e] 4) Improvement, unchanged, or worsening in NYHA or WHO HF functional class 5) 6MWD 6) Hemodynamic variables, including but not restricted to PVR, mPAP, and CO 7) Quality of life 8) Borg dyspnea score 9) Serious adverse events 10) Treatment-related adverse events 11) Laboratory abnormalities 12) Withdrawals due to adverse events

Table 2: Inclusion and Exclusion Criteria for Primary Studies
Exclusion Criteria
Studies will be excluded if they: are in languages other than English, do not meet the selection criteria aforementioned, provide results of a qualitative or a non-comparative study, are follow-up or extension studies, or present preliminary results in abstract form. Duplicate publications, narrative reviews, and editorials will also be excluded.   The following observational study designs will be excluded: before and after studies, single-arm cohort studies with historical controls, case series, and case reports. Studies that enrolled patients with diseases classified as Group 1' PH (i.e., PVOD or PCH) will be excluded. For the assessment of combination therapy, studies using upfront combination therapy will also be excluded.   Abstracts will be excluded unless they present supplementary data for an RCT that has another full-text publication that may be used to assess the risk of bias.

6MWD = 6-minute walk distance; CO = cardiac output; HF = heart failure; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; NMA = network meta-analysis; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary hemangiomatosis; PH = pulmonary hypertension; PPH = primary pulmonary hypertension; PVOD = pulmonary venoocclusive disease; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; WHO = World Health Organization.

[a]Older studies may have enrolled patients with PPH. For the purpose of this therapeutic review, these studies will be included and categorized as studies that enrolled patients with IPAH.
[b]Formulations and doses approved and available in Canada only will be included.
[c]Drug regimens will include monotherapy, dual (add-on) therapy, and triple (add-on) therapy.
[d]Studies of PAH drugs not approved for use in Canada (e.g., iloprost) will be excluded from the main analyses. Such studies may, however, be included in sensitivity analyses of an NMA should such analyses be performed. The effectiveness of PAH drugs not available in Canada will not be directly evaluated in this therapeutic review.
[e]The definition of clinical worsening may vary within the PAH literature; hence, the following definition will be used:
Clinical worsening is a composite end point of:
- death, or
- hospitalization (which is clearly predefined), or
- worsening of PAH requiring lung transplantation or atrial septostomy, or
- initiation of parenteral therapy (prostanoid, sildenafil), or
- discontinuation of the study treatment because of disease progression, or
- disease progression, or
where disease progression is defined as:
- 6MWD decrease of 15% (from baseline) and worsening of NYHA or WHO HF functional class, or
- 6MWD decrease of 15% (from baseline) and need for additional therapy (including oral and parenteral drugs).

It is anticipated that 6MWD will be a common primary outcome in the studies that will be included. This outcome will, however, not be the primary outcome in this therapeutic review as it appears that only a relatively small proportion of the "treatment to clinical benefits" relationship is explained by either baseline values or changes from baseline values of this surrogate outcome.[20-22]

As it is anticipated that a sizable amount of PAH drug therapy literature involves non-comparative observational studies, CADTH might commission a supplemental report in the form of a Rapid Response, summary of evidence with critical appraisal, to:
- identify and summarize this literature
- characterize the quality of the evidence available on PAH drug therapy
- provide background for future research, which could be submitted to the Drug Safety and Effectiveness Network (DSEN) or other similar research groups
- provide additional therapeutic context to members of CDEC and jurisdictional drug programs to inform their respective deliberations and policy work.

5.2.2 Economic

One reviewer will screen titles and abstracts relevant to the economic research questions on the use of available and emerging drug therapies for the treatment of patients with PAH that might inform data inputs in the health economic model. Full papers will be obtained for those that appeared to be potentially relevant.

5.3 Data Extraction and Critical Appraisal of Clinical Studies

One reviewer will perform data extraction for each article, using a data extraction form developed a priori covering the following items:
- baseline characteristics, demographics and treatment history of trial participants
- interventions evaluated, including dose, duration, and relevant concomitant medication
- efficacy and safety results for specified outcomes
- type of analysis (intention-to-treat [ITT] or per-protocol)
- description of withdrawals and dropouts.

All extracted data will be checked for accuracy by a second reviewer. Any disagreements will be resolved through discussion until consensus is reached.

Quality assessment of the included studies will be performed independently by two reviewers using a combination of Scottish Intercollegiate Guidelines 50 (SIGN-50) and Downs and Black instruments for internal validity. Additional critical appraisal will be performed based on input from clinical experts.

5.4 Data Analysis and Synthesis

5.4.1 Clinical

Included studies will be classified based on study populations and relevant comparisons. Prior to quantitative pooling of study-specific outcomes, a thorough qualitative analysis will be undertaken to assess clinical heterogeneity. In particular, a detailed assessment of event rates (and other relevant covariates) across the conventional therapy or placebo arm of each study will be conducted.[23,24] If substantial heterogeneity exists in certain comparisons or subsets of studies, then only narrative reviews of findings will be reported. Where appropriate, meta-analysis of direct comparisons and indirect/mixed-treatment comparisons employing a Bayesian network meta-analysis (NMA) may be performed.

Should a Bayesian NMA be conducted, WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) will be used. Binomial likelihood and normal likelihood models, which allow for the use of multi-arm trials, will be used for dichotomous and continuous outcomes, respectively.[25] Both fixed- and random-effects network meta-analyses will be considered, including both vague and informative priors on the between-study variance for random-effects meta-analyses. Choice of model will be based on assessment of model fit using the deviance information criterion (DIC) and by comparing residual deviance to number of unconstrained data points. Trace plots and the Brooks-Gelman-Rubin statistic will be used to assess convergence. Three chains will be fit in WinBUGS for each analysis, with at least 40,000 iterations and a burn-in of at least 40,000 iterations.

For studies that enrolled mixed populations (i.e., treatment-naive patients and patients on background PAH therapy), the analysis will target specific sub-populations rather than the entire study population. Access to subgroup analysis data may be required to do so. Subgroup analyses will also be conducted where appropriate; these will include age (treated as a continuous variable), baseline NYHA/WHO heart failure functional class (II, III, or IV), baseline 6MWD (treated as a continuous variable), gender (female or male), background pharmacotherapy, and disease etiology/subtype of PAH (IPAH/HPAH or other).

5.4.2 Economic

If sufficient data are available, an economic model will be constructed and the primary analysis will be in the form of a cost utility analysis. The primary outcome will be number of quality-adjusted life-years (QALY), with treatments compared in terms of the incremental cost per QALY (ICUR). The parameter uncertainty will be assessed through both deterministic and probabilistic sensitivity analysis.

5.5 Data Availability

In accordance with the CADTH *Therapeutic Review Framework*: *"The primary source of data is in the public domain. All stakeholders will be given the option of identifying and providing unpublished data on the condition that, if used, it would be included in publicly available reports and documents, related to the therapeutic review."* If the necessary clinical data required to address the research questions are not made publicly available by the manufacturers at the time of project initiation, there may be limited information available to address all of the research or policy questions listed in the protocol.

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