

CDEC FINAL RECOMMENDATION

Macitentan (Opsumit — Actelion Pharmaceuticals Canada Inc.)

Indication: Pulmonary Arterial Hypertension

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that macitentan be listed for the long-term treatment of pulmonary arterial hypertension (PAH) to reduce morbidity in patients of World Health Organization (WHO) Functional Class II or III whose PAH is either idiopathic or heritable, or associated with connective tissue disease or congenital heart disease, if the following clinical criterion and condition are met:

Clinical Criterion:

- Contraindication or inadequate response to sildenafil or tadalafil.

Condition:

- Reduction in price to ensure that the drug plan cost for macitentan does not exceed the drug plan cost for bosentan.

Reasons for the Recommendation:

1. One randomized controlled trial (RCT) (SERAPHIN; N = 742) demonstrated that treatment with macitentan resulted in reduced morbidity and mortality (as a composite end point) compared with placebo in patients with WHO Functional Class II or III PAH. However, there are no comparative head-to-head trials with any other treatments for PAH.
2. At the submitted price of \$128.33 per tablet (\$128.33 per day), macitentan is priced similarly to brand-name bosentan (Tracleer; \$128.36 per day), but is more expensive than generic bosentan (\$44.93 per day), ambrisentan (\$122.52 per day), generic and brand-name sildenafil (\$18.76 to \$33.36 per day, based on the recommended dose of 20 mg three times daily), and tadalafil (\$26.72 per day).

Of Note:

CDEC noted the following:

- Sildenafil and tadalafil are the least-costly options available as the initial treatment of PAH.
- The Health Canada-approved indication states that macitentan is effective when used as monotherapy or in combination with phosphodiesterase-5 (PDE-5) inhibitors.

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Background:

Macitentan (Opsumit) is indicated for long-term treatment of PAH (WHO Group I) to reduce morbidity in patients of WHO Functional Class II or III whose PAH is either idiopathic or heritable, or associated with connective tissue disease or congenital heart disease. Macitentan is available as 10 mg film-coated tablets and the recommended dose is 10 mg once daily as monotherapy or in combination with PDE-5 inhibitors.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of macitentan, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with PAH.

Patient Input Information

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

- Pulmonary hypertension has a considerable life-changing impact on the lives of patients and caregivers. Frequent medical appointments, tests, and hospitalizations are burdensome for patients and their caregivers.
- Patients commonly experience depressed mood, anxiety, and feelings of helplessness and hopelessness as they are faced with a high risk of death within a few years. The condition-related symptoms and problems that affect the day-to-day life of a patient are difficulty breathing with or without exertion; palpitations or pounding of the chest; chest pain; ankle, leg, and abdomen swelling due to fluid retention; dizziness; fainting; and tingling of hands and feet.
- Experience with currently available therapy, while not a cure, is generally positive, with most responders reporting taking combination therapy. The medications (particularly intravenous [IV] therapies) help to keep pulmonary hypertension stable and increase quality of life. However, the effectiveness of therapy varies considerably from patient to patient.

Clinical Trials

The CDR systematic review included one phase 3 study (SERAPHIN), which was a randomized, double-blind, placebo-controlled, event-driven trial in patients with symptomatic PAH. The objective of the trial was to demonstrate that macitentan reduces the risk of morbidity and mortality. A total of 742 patients with WHO Functional Class II or III were randomized (1:1:1) to macitentan 3 mg once daily, macitentan 10 mg once daily, or placebo. The mean duration of study treatment was 96.2 weeks. The SERAPHIN study population comprised both treatment-experienced patients (63.7%) and treatment-naive patients (36.3%). The proportion of patients with prior exposure to PDE-5 inhibitors and prostanoids was 61.4% and 5.4%, respectively. Sildenafil was the most common PAH therapy at baseline (58%).

Outcomes

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

- Time to first morbidity or mortality event — time from the initiation of treatment to the first event defined as a composite of all-cause death, atrial septostomy, lung transplantation, initiation of treatment with IV or subcutaneous prostanoids, or worsening of PAH.

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- Six-minute walk distance (6MWD) — distance that a patient can walk unencouraged on a flat, hard surface in a time of six minutes. The minimal clinically-important difference (MCID) for 6MWD in PAH has been estimated to be 33.0 m (range 25.1 m to 38.6 m).
- Proportion of patients with improvement in WHO Functional Class.
- Borg Dyspnea Index — a measure of perceived breathlessness on a scale of 0 to 10, in which 0 is no breathlessness and 10 is maximal breathlessness.
- Pulmonary hemodynamics — including mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), mean right atrial pressure (mRAP), and cardiac index.
- Health-related quality of life using the SF-36 questionnaire — a 36-item, general health status measure having eight dimensions measuring physical functioning, role functioning (work or other activities) affected by both physical and emotional symptoms, pain, general health, vitality, social functioning, and mental health, which may be collapsed into two domain scores reflecting physical and mental components. The score is from 0 to 100 with higher scores indicating better quality of life. The MCID for the SF-36 has been estimated to be a change of 5 to 10 points in each dimension or 2.5 to 5 points in each component summary.
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

The primary efficacy outcome in SERAPHIN was time from the initiation of treatment to the first event defined as all-cause death, atrial septostomy, lung transplantation, initiation of treatment with IV or subcutaneous prostanoids, or worsening of PAH.

Efficacy

- Macitentan was superior to placebo for time to first morbidity or mortality event up to 36 months with a hazard ratio of 0.547 (97.5% confidence interval [CI], 0.39 to 0.76; $P < 0.0001$). The difference was mainly driven by lower rates of worsening of PAH (24.4% versus 37.3%) and prostanoid initiation (0.4% versus 2.4%), but not due to a reduction in death rate (6.6% versus 6.8%) (macitentan versus placebo, respectively).
- Macitentan statistically significantly increased 6MWD from baseline to month six compared with placebo; difference in mean change was 22.0 m (standard deviation, 92.6); $P = 0.0078$.
- There was no difference in the proportion of patients whose WHO Functional Class remained unchanged from baseline to month six (70.7% for macitentan and 65.9% for placebo).
- The proportion of patients who demonstrated WHO Functional Class improvement was statistically significantly greater in the macitentan group compared with the placebo group from baseline to month six (22.3% versus 12.9%, $P = 0.007$).
- The proportion of patients whose WHO Functional Class worsened from baseline to six months was statistically significantly lower in the macitentan group compared with placebo (7.0% versus 21.6%; $P < 0.0001$).
- Compared with placebo, macitentan was associated with a statistically significant improvement in breathlessness, as measured by the Borg Dyspnea Index, with a difference in mean change of -0.5 (97.5% CI, -1.0 to -0.1).
- Relative to placebo, macitentan treatment resulted in statistically significant improvements in the following measures of pulmonary hemodynamics: PVR (mean change 61.8% [97.5% CI, 49.9% to 76.5%]) and cardiac index (difference in mean change was 0.61 [97.5% CI, 0.28 to 0.93]). There was no statistically significant difference between macitentan and placebo for mPAP (difference in mean change -2.7 [97.5% CI, -11.7 to 6.3]) and mRAP (difference in mean change 0.4 [97.5% CI, -9.1 to 9.9]).

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- Macitentan statistically significantly improved both the physical and mental component summaries (PCS and MCS) of the SF-36 questionnaire from baseline to month six; the between-group differences for PCS and MCS were 3.0 (97.5% CI, 1.3 to 4.7) and 3.4 (97.5% CI, 0.9 to 5.9), respectively.

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event was 45.0% with macitentan and 55.0% with placebo.
- The proportion of patients with at least one adverse event was 94.6% with macitentan and 96.4% with placebo.
- Compared with placebo, macitentan was associated with a higher frequency of the following adverse events: anemia (13.2% versus 3.2%), headache (13.6% versus 8.8%), upper respiratory tract infection (15.3% versus 13.3%), urinary tract infection (8.7% versus 5.6%), bronchitis (11.6% versus 5.6%), influenza (5.8% versus 1.6%), and thrombocytopenia (5.0% versus 2.8%).
- The proportion of patients with liver disorders and abnormal liver function was lower in macitentan than in the placebo group (8.7% versus 14.5%).
- The proportion of patients who withdrew from the trial due to adverse events was 10.7% with macitentan and 12.4% with placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing macitentan with brand-name bosentan (Tracleer), over a one-year time frame. Drug costs, physician visits, and monitoring costs were included in the analysis. The manufacturer concluded that macitentan is cost saving (by \$33.26 annually), driven by the lower non-drug costs for macitentan compared with brand-name bosentan, as the manufacturer assumed patients on bosentan would necessitate more physician visits and monitoring, due to a higher incidence of liver dysfunction and edema compared with macitentan. However, the differences in cost between macitentan and brand-name bosentan are very small (< 0.1% of annual total cost). The manufacturer reported that macitentan is more costly when compared with ambrisentan (by \$3,873 annually) or “multi-sourced” generic bosentan (by \$25,878 annually).

No direct or indirect evidence comparing macitentan with other drugs indicated for the treatment of PAH was provided by the manufacturer; consequently, the comparative effectiveness and safety of macitentan with other drugs for PAH is uncertain. Furthermore, in the base-case analysis, the manufacturer did not account for patients receiving generic bosentan. CDR reanalysis, considering only drug costs and using the generic bosentan price of \$44.93 per day in 100% of patients, demonstrated that macitentan costs \$30,441 more per patient per year.

At the submitted price of \$128.33 per tablet (\$128.33 per day), macitentan is priced similarly to brand-name bosentan (Tracleer; \$128.36 per day), but is more expensive than generic bosentan (\$44.93 per day), ambrisentan (\$122.52 per day), generic and brand-name sildenafil (\$18.76 to \$33.36 per day, based on the recommended dose of 20 mg three times daily), and tadalafil (\$26.72 per day).

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Other Discussion Points:

CDEC noted the following:

- The incidence of liver disorders and abnormal liver function was lower in the macitentan group compared with placebo. This is in contrast to other endothelin receptor antagonists, which are associated with increased incidence of hepatotoxicity.
- The manufacturer requested a recommendation to list macitentan in a manner similar to bosentan; however, these two drugs have different Health Canada–approved indications. Bosentan is indicated for use in WHO Functional Class II, III, and IV PAH and macitentan is indicated for use in patients with WHO Functional Class II and III PAH.
- Due to limited clinical experience, the product monograph indicates that macitentan should be used with caution in patients who are 75 years of age or older or are younger than 18 years.
- The listing status of endothelin receptor antagonists for PAH varies across the CDR-participating drug plans.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Long-term comparative efficacy and safety data for use of macitentan compared with other endothelin receptor antagonists.
- Comparative efficacy and head-to-head trials with other endothelin receptor antagonists such as bosentan or ambrisentan or other treatments for advanced PAH.

CDEC Members:

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

Regrets:

October 15, 2014: None

January 21, 2015: None

Conflicts of Interest:

October 15, 2014: None

January 21, 2015: 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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