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CADTH

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CADTH Reimbursement Recommendation

Macitentan and Tadalafil (Opsynvi)

Indication: For the long-term treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to reduce morbidity in patients of WHO functional class II or III whose PAH is idiopathic, heritable, or associated with connective tissue disease or congenital heart disease. Opsynvi should be used in patients who are currently treated concomitantly with stable doses of macitentan 10 mg and tadalafil 40 mg (20 mg × 2) as separate tablets.

Sponsor: Janssen Inc.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Opsynvi?

CADTH recommends that Opsynvi should be reimbursed by public drug plans for the long-term treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to reduce morbidity in patients in WHO functional class (FC) II or III whose PAH is idiopathic, heritable, or associated with connective tissue disease or congenital heart disease if certain conditions are met.

Which Patients Are Eligible for Coverage?

Opsynvi should only be covered for patients who are currently treated simultaneously with stable doses of macitentan 10 mg and tadalafil 40 mg as separate tablets.

What Are the Conditions for Reimbursement?

Opsynvi should only be reimbursed if prescribed by a specialist with expertise in managing and treating patients with PAH and if the price of Opsynvi is negotiated to ensure cost savings in comparison with separate macitentan and tadalafil tablets.

Why Did CADTH Make This Recommendation?

- Three clinical studies in healthy volunteers showed that Opsynvi has similar blood concentration levels as macitentan and tadalafil given separately.
- At its submitted price, Opsynvi was cost-saving in comparison with the regimen of macitentan and tadalafil administered as individual components using public list prices.
- Based on public list prices, Opsynvi is expected to save public drug plans $8,601,826 over 3 years.

Additional Information

What Is Pulmonary Arterial Hypertension?

PAH is a condition in which the small blood vessels in the lungs become narrow and thick. This leads to high blood pressure within the lungs and the side of the heart that sends blood to the lungs. Patients with this condition can develop shortness of breath, dizziness, chest pain, and other symptoms. In some cases, this condition will get worse and can become life-threatening. In Canada, it is estimated that PAH affects 29 in every 100,000 persons.

Unmet Needs in PAH

There is a need for a more effective treatment with fewer side effects.

How Much Does Opsynvi Cost?

Treatment with Opsynvi is expected to cost approximately $48,202 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that macitentan-tadalafil be reimbursed for the long-term treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to reduce morbidity in patients in WHO functional class (FC) II or III whose PAH is idiopathic, heritable, or associated with connective tissue disease or congenital heart disease only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

The results from 3 bioequivalence studies in healthy volunteers suggest that the fixed-dose combination (FDC) of macitentan-tadalafil is bioequivalent to the individual components administered separately. One randomized controlled trial (SERAPHIN; N = 742) demonstrated that treatment with macitentan 10 mg resulted in reduced morbidity and mortality (as a composite end point) compared with placebo in patients with WHO FC II or III PAH (hazard ratio [HR] = 0.55; 97.5% confidence interval [CI], 0.39 to 0.76).

Using the sponsor-submitted price for macitentan-tadalafil FDC and publicly listed prices for macitentan and tadalafil individually, the FDC was less costly compared with the individual components and considered similarly effective.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Macitentan-tadalafil FDC must only be used in patients who are currently treated concomitantly with stable doses of macitentan 10 mg and tadalafil 40 mg as separate tablets.	Macitentan-tadalafil FDC has shown bioequivalence to its individual components administered separately. This is also consistent with the Health Canada indication.
Prescribing	
2. Must be prescribed by a specialist with expertise in managing and treating patients with PAH.	Accurate diagnosis and management of PAH is important to ensure that macitentan-tadalafil FDC is prescribed to the appropriate patients.
Pricing	
3. Macitentan-tadalafil FDC should provide cost savings for drug programs relative to the cost of treatment with macitentan and tadalafil as individual components reimbursed for the treatment of patients with PAH who are currently treated concomitantly with macitentan 10 mg and tadalafil 40 mg per day.	At its submitted price, macitentan-tadalafil FDC was cost-saving in comparison with the regimen of macitentan and tadalafil administered as individual components. This analysis considered publicly available list prices and did not consider potential confidential negotiated prices. The price of macitentan-tadalafil FDC should be negotiated to ensure suggested cost savings are maintained.

FDC = fixed-dose combination; PAH = pulmonary arterial hypertension.

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by CDEC and the drug plans are summarized in Table 2.

Table 2: Implementation Guidance From CDEC

Condition #	Implementation considerations and guidance
1	The duration at which a patient needs to be on stable doses of macitentan and tadalafil as separate tablets before switching to macitentan-tadalafil can be addressed at the individual jurisdiction level in consultation with clinical experts.

Discussion Points

- CDEC acknowledged that recommendations to reimburse with conditions were previously issued to each of the individual components of macitentan and tadalafil, separately.
- CDEC discussed the lack of evidence of the clinical efficacy of macitentan-tadalafil FDC compared with its individual components administered separately in patients with PAH.
- The FDC of macitentan-tadalafil has a hypothesized benefit of reducing pill burden and improving adherence; however, such outcomes have not been evaluated in the submitted studies.

Background

Macitentan-tadalafil is an FDC of macitentan 10 mg and tadalafil 40 mg. It has a Health Canada indication for the long-term treatment of PAH (WHO Group 1) to reduce morbidity in patients in WHO FC II or III whose PAH is either idiopathic, heritable, or associated with connective tissue disease or congenital heart disease. The product monograph states that the FDC of macitentan and tadalafil should be used in patients who are currently treated concomitantly with stable doses of macitentan 10 mg and tadalafil 40 mg (20 mg × 2) as separate tablets. The dosage is 1 tablet of the FDC daily.

Tadalafil was reviewed by CADTH in 2010 and macitentan was reviewed in 2014, and both drugs received recommendations to reimburse with conditions for patients with WHO Group 1 PAH in WHO FC II or III. The condition for reimbursing tadalafil was similar to the reimbursement of sildenafil, and at a cost not to exceed that of sildenafil. The conditions for the reimbursement of macitentan were that the patient has a contraindication or inadequate response to sildenafil or tadalafil and that the price be reduced to ensure that the drug plan cost for macitentan does not exceed the drug plan cost for bosentan. Both drugs have restricted reimbursement in some of the CADTH participating drug plans.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of the summary of pivotal trials submitted by the sponsor, which included 3 phase I bioequivalence studies in healthy volunteers and 1 supportive phase III randomized controlled trial in patients with WHO FC II or III PAH
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with PAH
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

No patient group submission was received for the review of macitentan-tadalafil FDC.

Input From the Clinical Expert Consulted by CADTH

One clinical expert with expertise in the diagnosis and management of PAH was consulted by CADTH.

The clinical expert indicated that the macitentan-tadalafil FDC will primarily be prescribed to patients switching from existing dual therapy with tadalafil and macitentan. Patients would be switched to the macitentan-tadalafil FDC for convenience to reduce overall pill burden unless the individual components have not been tolerated by the patient. There would be consideration for switching from other dual therapy combinations, such as tadalafil plus ambrisentan, sildenafil plus ambrisentan, sildenafil plus bosentan, sildenafil plus macitentan, or tadalafil plus bosentan, but this would be a much smaller proportion of patients because of concerns of clinical destabilization, patient preference, and cost.

Although trial data and clinical experience suggest that macitentan has fewer side effects leading to treatment discontinuation than ambrisentan or bosentan, it is not prescribed as the other endothelin receptor antagonists in part because of issues of access; in some provinces, macitentan is not reimbursed or has only recently been reimbursed . Tadalafil plus ambrisentan is currently the most commonly prescribed dual therapy based on the results of the AMBITION trial (for starting newly diagnosed patients on combination therapy).

Of the phosphodiesterase type 5 (PDE-5) inhibitors, tadalafil 40 mg daily is currently prescribed more than sildenafil because clinicians consider it to be more potent than sildenafil 20 mg 3 times per day and it is more convenient in terms of pill burden.

Initiation of the macitentan-tadalafil FDC in newly diagnosed patients would be of interest, pending data from the A DUE study on initial therapy with the FDC. However, this is outside of the Health Canada switch indication and reimbursement request from the sponsor. At the moment, most newly diagnosed patients who are identified as appropriate for initial dual therapy would be prescribed ambrisentan plus tadalafil because there are data supporting the long-term efficacy of that specific combination from the AMBITION trial.

Clinician Group Input

CADTH received no clinician group submission for the review of macitentan-tadalafil FDC.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. Input from drug programs explored the questions of generalizability to patients with PAH, and the lack of comparators in the clinical studies. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for macitentan-tadalafil FDC:

- considerations for initiation of therapy
- considerations for prescribing of therapy.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 3: Responses to Implementation Questions From the Drug Programs

Implementation issues	Advice from CADTH
Considerations for initiation of therapy	
The proposed indication submitted to Health Canada appears to contain 2 groups: initial combination therapy and switching therapy to the combination as FDC. The sponsor's reimbursement request is for macitentan-tadalafil FDC to be funded only for patients previously treated with the individual components only (i.e., macitentan and tadalafil), and not the initiation of macitentan-tadalafil FDC in patients not previously treated with the individual components. How will clinicians use the FDC in practice?	A communication was received from the sponsor confirming that the current proposed Health Canada indication and the reimbursement request is for macitentan-tadalafil FDC in patients who are currently treated concomitantly with stable doses of macitentan 10 mg and tadalafil 40 mg (20 mg × 2) as separate tablets. In addition, the clinical expert indicated that the macitentan-tadalafil FDC will mostly be prescribed to patients switching from existing dual therapy with tadalafil and macitentan. CDEC noted that sponsor-submitted economic information does not take into account potential future changes in indication or mandatory switching policies.
Considerations for prescribing of therapy	
Would clinicians prescribe the FDC to pediatric patients with PAH?	PAH in children is exceedingly rare, and pediatric use of macitentan-tadalafil FDC is outside the Health Canada indication. Special authorization in extreme circumstances would be an appropriate route.

FDC = fixed-dose combination; PAH = pulmonary arterial hypertension.

Clinical Evidence

Description of the Study

The CADTH clinical review was based on a summary of clinical evidence provided by the sponsor with the CADTH tailored review process, including bioequivalence studies and the SERAPHIN study. The SERAPHIN trial was previously evaluated as part of the CADTH review of macitentan, which received a recommendation to reimburse in 2015 with the clinical

condition of a contraindication or inadequate response to sildenafil or tadalafil. Therefore, the combination use of macitentan and tadalafil was previously established and recommended by CADTH. The data on macitentan 3 mg group was not presented for this submission because this dose is not aligned with the Health Canada–approved dose.

SERAPHIN was a multinational study that included 5 centres in Canada. A total of 742 patients were randomly assigned (1:1:1) to receive placebo (250 patients), macitentan 3 mg (250 patients), or macitentan 10 mg (242 patients) and were included in the intention-to-treat population. Patients were aged 12 years or older at study entry, with a hemodynamically confirmed diagnosis of symptomatic PAH with WHO FC II to IV. Idiopathic PAH, familial PAH, and PAH associated with collagen vascular disease, congenital heart disease, HIV infection, or drugs and toxins were eligible. Patients were required to have a 6-minute walk test (6MWT) distance of at least 50 m at screening and randomization. Importantly, concomitant treatment with oral PDE-5 inhibitors, oral or inhaled prostanoids, calcium channel blockers, or L-arginine was allowed at study entry and could continue throughout the study, provided that the patient had been receiving a stable dose for at least 3 months before randomization and remained on a stable dose. Patients receiving IV or subcutaneous prostanoids were excluded. At baseline of the SERAPHIN study, 61% of patients had been treated with a PDE-5 inhibitor and 5% with oral or inhaled prostanoids. Sildenafil was the most common PAH therapy at baseline (58%).

The primary end point was a composite outcome of the time to first morbidity event or all-cause death. Morbidity events were atrial septostomy, lung transplantation, initiation of treatment with IV or subcutaneous prostanoids, or worsening of PAH atrial septostomy, lung transplantation, initiation of IV or subcutaneous prostanoids, or worsening of PAH. Secondary efficacy end points included the change from baseline to month 6 in the 6MWT, the percentage of patients with an improvement in WHO FC from baseline to month 6, time to death due to PAH or hospitalization for PAH up to the end of treatment, and time to death from any cause up to end of treatment and up to the end of the study.

Efficacy Results

A total of 287 patients in the full population of the SERAPHIN study had a composite primary end point event over a median treatment period of 115 weeks: 116 patients (46.4%) in the placebo group and 76 patients (31.4%) in the macitentan 10 mg group. Worsening of PAH was the most frequent primary end point event (37.2% versus 24.4% for placebo and macitentan 10 mg, respectively). The HR for the time to first morbidity event or mortality was 0.55 (97.5% CI, 0.39 to 0.76; log rank $P < 0.001$) in favour of macitentan versus placebo.

SERAPHIN included a mixed population of patients who received monotherapy (macitentan or placebo) or dual therapy (baseline PAH therapy plus macitentan or placebo). More than 60% of patients were in the latter group, with most patients treated with macitentan plus sildenafil; a minority of patients (approximately 4%) were treated with macitentan plus tadalafil. In the subgroup of patients receiving background PAH therapy, the HR for the composite primary end point of time to first morbidity event or mortality was 0.62 (95% CI, 0.43 to 0.89) in favour of the macitentan group. The most frequent event was clinical worsening.

Harms Results

The overall frequency of adverse events (AEs) was similar between the groups in the full population of the SERAPHIN trial (94.6% macitentan 10 mg; 96.4% placebo). Worsening of PAH was the most frequently reported AE (21.9% macitentan 10 mg; 34.9% placebo). Serious AEs (SAEs) were reported less frequently in the macitentan 10 mg group compared with the

placebo group. During the study, 45% of patients in the macitentan 10 mg group and 55% of patients in the placebo group experienced SAEs. Worsening of PAH reported as "pulmonary arterial hypertension" and right ventricular failure were the most frequently reported SAEs, and both occurred at lower frequencies in the macitentan group than in the placebo group. SAEs of anemia occurred more frequently in the macitentan 10 mg group (2.5%) compared with placebo (0.4%). Withdrawals due to AEs were similar between the macitentan 10 mg arm (10.7%) and the placebo arm (12.4%). Consistent with the overall AE profile and the SAE profile, the most frequently reported AEs that led to discontinuation of study treatment across the groups were PAH (1.7% macitentan 10 mg, 4.0% placebo) and right ventricular failure (1.7% macitentan 10 mg; 2.4% placebo). The frequency of alanine transaminase or aspartate transaminase more than 3 times the upper limit of normal was lower in the macitentan 10 mg group (3.4%) compared with the placebo group (4.5%). Edema occurred at a similar frequency in both groups (macitentan 10 mg: 21%; placebo: 20%). More patients in the macitentan group than in the placebo group had laboratory findings of decreased hemoglobin (4.3% versus 0.4%, respectively). The study report for the SERAPHIN clinical study did not include overall AEs, SAEs, or withdrawals due to AEs by subgroup. Data provided in the macitentan-tadalafil FDC submission indicated that the AEs in the subgroup of patients on background therapy plus macitentan were similar to that expected with the individual components and consistent with AEs observed in the overall SERAPHIN population. The percentage of patients within the background therapy plus macitentan group and placebo group who experienced an AE was 93.5% and 97.4%, respectively. Withdrawals due to AEs were similar between those receiving macitentan and those receiving placebo (9.1% versus 11.8%, respectively).

Bioequivalence Studies

Results from 3 bioequivalence studies were included in the sponsor's submission to CADTH. These studies compared the FDC with treatment by 10 mg macitentan and 40 mg tadalafil as separate tablets. The studies were phase I trials conducted in healthy individuals with a crossover design. The primary objective was to demonstrate bioequivalence of the maximum plasma concentration (C_{max}), the area under the curve (AUC) for the plasma concentration-time curve from time 0 to time t (AUC_{0-t}) of the last measured concentration above the lower limit of quantification and AUC from time 0 to infinity (AUC_{0-inf}) of macitentan-tadalafil FDC and as a free combination of macitentan and tadalafil. The secondary objectives were to evaluate the safety and tolerability of concomitant macitentan and tadalafil administered as an FDC product or as a free combination and to investigate other pharmacokinetic parameters of concomitant macitentan and tadalafil administered as an FDC product or as a free combination. Determination of bioequivalence was based upon the 90% CI for the ratios of the geometric means (test/reference) for macitentan and tadalafil AUC_{0-inf}, AUC_{0-t}, and C_{max}. The results of these studies suggested bioequivalence between FDC and treatment by 10 mg macitentan and 40 mg tadalafil as separate tablets. No individual died or reported SAEs. Most of the AEs were mild, and the proportion of individuals who had at least 1 AE was similar for the FDCs and the free combinations for both groups and varied between 70.0% and 78.7%.

Critical Appraisal

The evidence to support the indication and reimbursement request for macitentan-tadalafil FDC includes bioequivalence data. The SERAPHIN study was provided as supportive efficacy and safety data and was not submitted as the primary study. The SERAPHIN trial has been previously evaluated as part of the macitentan CADTH review and received a positive recommendation in 2015, with the clinical condition of a contraindication or inadequate

response to sildenafil or tadalafil. Therefore, the combination use of macitentan and tadalafil has been previously established and recommended by CADTH.

The overall design of the SERAPHIN study appears to be appropriate with respect to randomization and standardized assessment of the efficacy and safety outcomes. Based on the information available in the sponsor's summary of the clinical evidence, the trial appeared to be generally well balanced in terms of baseline demographic and disease characteristics. The main analyses for the primary and secondary end points were performed by intention-to-treat approach, which included all patients who had undergone randomization. The clinical study report stated that no imputation method was used for the primary efficacy end point because of the time-to-event design. The last observation carried forward approach was used to impute missing values of secondary and exploratory outcomes. More patients in the placebo group versus the macitentan group prematurely discontinued treatment (59.4% versus 44.2%, respectively) and the study (22.0% versus 16.9%, respectively), mostly due to death (17.6% versus 14.0%, respectively) and loss of follow-up (2.8% versus 0.8%, respectively). These differences may impact the validity of the secondary analyses with last observation carried forward imputation because the method relies on data missing at random, which does not appear to have been met. Bonferroni correction was applied to ensure an overall alpha level of 0.01 for the primary outcome analysis. Overall, the handling of multiplicity in the outcome comparison is reasonably presented and acceptable due to the hierarchical testing procedure for the secondary end points.

No data were provided from a higher-level study such as a randomized controlled trial on the efficacy and safety of the FDC itself and that the whole submission is based on extrapolation from existing trial data and bioequivalence data. Given that only approximately 4% of patients received tadalafil plus macitentan and the study did not use a treatment switch design, the results do not directly apply to the target patient group for the submission. Nonetheless, the subgroup analyses, in combination with evidence from the CADTH therapeutic review on drugs for PAH, support the notion that combination use of macitentan and tadalafil improves outcomes for patients with WHO FC II or III PAH. Bioequivalence data suggest that the FDC is equivalent to the individual components administered separately.

The HRs reported for the time-to-event outcomes have been interpreted as a relative risk reduction, which is incorrect. The HRs represent instantaneous risk over the study time period which was lower for the treatment group.

A total of 158 centres participated in this trial, and 492 eligible PAH patients were randomized into the 2 arms (242 to macitentan 10 mg arm and 250 to placebo arm). Given the large number of centres involved, if there were differences in quality of care in the participating centres, the overall results may not be balanced because stratification by centre procedures was not employed in the randomization scheme. However, PAH is a rare disease, and the reason that so many countries and centres participated in this study was to ensure that the study has sufficient sample size to measure a clinically important outcome.

The total observation period was 728 days. This time period may not be realistic for some outcome measures such as lung transplantation.

The proportion of patients who discontinued from the trial was high (44.2% in macitentan 10 mg arm and 59.4% in placebo arm). However, most discontinuations were outcome related so it would not affect the primary end point, although secondary assessments that relied on complete case analysis would be expected to be affected by the dropouts.

Economic Evidence

Cost and Cost-Effectiveness

At the submitted price of $132.06 per tablet, macitentan-tadalafil FDC costs $48,202 per patient annually. The annual cost savings associated with macitentan-tadalafil FDC compared with macitentan and tadalafil taken as individual products at the same dose range from $7,388 to $9,140 per patient, depending on the list price of tadalafil. The incremental savings are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

The sponsor's cost comparison assumes clinical similarity between macitentan-tadalafil FDC and macitentan and tadalafil taken as individual products. The clinical review conducted by CADTH identified several limitations with the submitted clinical evidence, but it was concluded the FDC is similar to its components taken as individual products based on bioequivalence information. Should the clinical effectiveness of macitentan-tadalafil FDC be different than that of macitentan and tadalafil taken as individual products in real-world use, the cost-effectiveness of macitentan-tadalafil FDC is unknown.

The sponsor's submission and CADTH re-analyses focused on the sponsor's proposed Health Canada indication and reimbursement request population, which consisted solely of patients previously treated with macitentan and tadalafil taken as individual products.

Budget Impact

CADTH identified 2 key limitations with the sponsor's analysis. There is uncertainty in the estimated market size due to the use of a claims-based approach and that the list price of tadalafil varies across jurisdictions and the analysis relies on publicly available list prices.

CADTH did not conduct a base-case analysis because the issues related to uncertainty in the potential market size could not be addressed by CADTH. Instead, CADTH presented a series of scenario analyses to test the impact of alternative assumptions that could be altered in the sponsor's model. The sponsor's base case suggested 3-year budgetary savings of $8,601,826, which decreased to $7,589,631 when considering a lower list price for tadalafil. The savings also varied depending on the proportion of macitentan claims that were assumed to be made in combination with tadalafil, highlighting the impact of increasing and decreasing the estimated population size. However, the presence of confidential prices paid by the jurisdictions is likely to reduce or eliminate these savings, depending on the discounts in place.

The sponsor's submission focused on their reimbursement request, with the target population consisting solely of patients already on macitentan and tadalafil taken as individual products and switching to the FDC product. The budget impact when considering patients on other combinations of an ERA and a PDE-5 inhibitor, or patients who are naive to dual therapy combinations, is unknown.

CADTH

CADTH Canadian Drug Expert Committee Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: October 27, 2021

Regrets: Two expert committee members did not attend

Conflicts of interest: None