Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

# CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

## TREPROSTINIL SODIUM RESUBMISSION
**(Remodulin™ – Innomar Strategies Inc.)**

**Description:**
Treprostinil is a tricyclic benzindene analog of prostacyclin, indicated for the long-term, subcutaneous treatment of pulmonary arterial hypertension in patients with New York Heart Association (NYHA) Class III and IV disease who do not respond adequately to conventional therapy.

**Dosage Forms:**
1 mg/mL, 2.5 mg/mL, 5 mg/mL, 10 mg/mL solution for subcutaneous injection

**Recommendation:**
The Canadian Expert Drug Advisory Committee (CEDAC) had previously recommended that treprostinil not be listed. A new randomized controlled trial (RCT) was the basis for the treprostinil resubmission. The Committee maintains its prior conclusion that treprostinil has not been proven to be cost-effective in any group of patients but, recognizing the need for treatment alternatives in patients with severe pulmonary hypertension, recommends the following restrictive formulary listing criteria.

It is recommended that treprostinil be listed for patients with primary pulmonary hypertension or pulmonary hypertension secondary to collagen vascular disease, with New York Heart Association class III or IV disease who have both:
1. failed to respond to non-prostanoid therapies and;
2. who are not candidates for epoprostenol therapy because of:
   - prior recurrent complications with central line access (eg. infection, thrombosis) or,
   - inability to operate the complicated delivery system of epoprostenol or,
   - they reside in an area without ready access to medical care, which could complicate problems associated with an abrupt interruption of epoprostenol therapy.

**Reasons for the Recommendation:**
1. The Committee considered four RCTs which compared treprostinil and placebo. In the two largest RCTs, the use of treprostinil was associated with statistically significant improvements in the six-minute walk test although this positive treatment effect was confined to patients with NYHA class III and IV. Treprostinil use was also associated with

statistically significant improvements in measures of dyspnea and quality of life. There is no definitive evidence that treprostinil improves survival.

2. In addition to the three RCTs reviewed in the original treprostinil submission, the Committee also reviewed a more recent trial conducted in 22 patients, who were stabilized and responding to epoprostenol. In this study, patients were randomized to transition from epoprostenol to either treprostinil or placebo. This trial was terminated prematurely due to the high number of treatment failures in placebo patients (7/8 placebo patients versus 1/14 treprostinil patients). The mean dose of treprostinil in this study was 32.2 ng/kg/min, which is significantly higher than in the other RCTs (mean dose ~10 ng/kg/min). The Committee felt that these results confirmed that treprostinil was superior to placebo.

3. There have been no head-to-head comparisons between treprostinil and either epoprostenol or bosentan. Because of its subcutaneous administration, treprostinil offers an advantage over epoprostenol, which requires continuous IV infusion through a permanent central venous catheter. However, most recipients experience pain at the injection site with subcutaneous treprostinil, which may limit the dose that can be utilized.

4. Treprostinil is a very expensive medication, with drug cost varying from $18,000 to more than $70,000 per year, depending upon the dose used. While the comparator drugs, epoprostenol and bosentan, are also expensive, the annual cost per patient of treprostinil is approximately $22,000 higher than epoprostenol at doses of 30 ng/kg/min, assuming dose equivalency between treprostinil and epoprostenol. The cost savings reported for treprostinil compared to epoprostenol in the economic model provided by the manufacturer assumed a substantially lower duration of hospitalization for treprostinil treated patients. However, given current practice patterns in managing patients with epoprostenol and questions regarding dose equivalency between epoprostenol and treprostinil, it is uncertain whether this purported cost advantage actually exists. Therefore, at the current price of treprostinil, the Committee did not feel that there was sufficient evidence to support the use of treprostinil before epoprostenol.

**Of Note:**

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.