CEDAC FINAL RECOMMENDATION

TADALAFIL
(Adcirca – Eli Lilly Canada Inc.)
Indication: Pulmonary Arterial Hypertension

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that tadalafil be listed in a similar manner to sildenafil if the cost of tadalafil does not exceed the cost of sildenafil.

Reasons for the Recommendation:
1. The daily cost of tadalafil is currently less than the daily cost of sildenafil and considerably less than other agents used to treat patients with pulmonary arterial hypertension who have not responded to conventional therapy.

2. In one double-blind randomized controlled trial, tadalafil was associated with statistically significant improvements in the six-minute walk distance and in quality of life compared with placebo.

Of Note:
1. The Committee noted that the availability of generic sildenafil could eliminate cost savings associated with listing tadalafil.
2. It was noted that in the randomized placebo-controlled trial of tadalafil, improvements in the six-minute walk distance (6MWD) were greater in the pre-specified subgroup of bosentan-naive patients compared with those already receiving bosentan. Thus, the Committee considered that addition of tadalafil to bosentan was not supported by these clinical trial results.

Background:
Tadalafil (Adcirca) has a Health Canada indication for the treatment of idiopathic ("primary") pulmonary arterial hypertension or pulmonary arterial hypertension associated with connective tissue disease, congenital heart disease, or anorexigen use in patients with World Health Organization (WHO) functional class II or III who have not responded to conventional therapy. Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil (Cialis) also has a Health Canada indication for the treatment of erectile dysfunction in men.

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The recommended dose of tadalafil for pulmonary arterial hypertension is 40 mg once daily; dividing the dose is not recommended. Tadalafil (Adcirca) is available as a 20 mg tablet.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind randomized controlled trials of tadalafil and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials
The CDR systematic review included one double-blind randomized controlled trial, Study LVGY (N = 405), that compared four doses of tadalafil (2.5 mg, 10 mg, 20 mg, and 40 mg daily) with placebo over 16 weeks. The Committee focused on patients receiving the Health Canada approved dose of 40 mg daily (n = 79).

Most patients had WHO functional class II or III (97%). Approximately half of the patients had been diagnosed with pulmonary arterial hypertension for more than two years. Not all patients included in the study were diagnosed using right heart catheterization, which may have allowed some patients to enter the trial who did not meet the standard criteria for pulmonary arterial hypertension. The etiology of pulmonary arterial hypertension was predominantly idiopathic (61%) or related to collagen vascular disease (24%).

The mean baseline 6MWD was 344 metres across all treatment groups. Approximately 53% of patients received bosentan during the study; the mean duration of prior bosentan use at baseline was approximately two months.

Eighty-four per cent of patients completed the study.

Outcomes
The primary outcome of Study LVGY was the change from baseline in 6MWD. The minimum clinically important change in the 6MWD is uncertain.

Other outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality, Borg dyspnea score, quality of life as measured by the SF-36, WHO functional class improvement, and time to clinical worsening.

Results

Efficacy or Effectiveness
- Based on Study LVGY's pre-specified primary statistical analysis, statistically significant improvements in the 6MWD were observed for tadalafil 40 mg compared with placebo (mean difference: 26 metres, $P < 0.01$).
- According to the manufacturer's pre-specified statistical analysis plan, no statistically significant benefit could be claimed for tadalafil compared with placebo for WHO functional class improvement, Borg dyspnea score, or mean time to clinical worsening.

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- Tadalafil 40 mg compared with placebo resulted in statistically significant improvements in SF-36 scores in six of eight domains (physical-functioning, role-physical, bodily pain, general health, vitality, and social functioning) and in EuroQol scores.
- Based on a manufacturer pre-specified subgroup analysis of patients receiving tadalafil 40 mg, the placebo-adjusted change in 6MWD for patients (n = 37) not taking bosentan was higher than for patients (n = 42) receiving background bosentan (44 metres versus 23 metres respectively).

Harms (Safety and Tolerability)

- The proportion of patients reporting a serious adverse event was low and similar across treatment groups. The most common serious adverse events were right ventricular failure, anemia, and dyspnea.
- The proportion of patients reporting an adverse event was greater in the tadalafil 40 mg group compared with placebo (95% versus 79%, P = 0.003). The most common adverse events included headache, flushing, and myalgia.

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis comparing tadalafil plus supportive care with placebo plus supportive care during a 50-year time horizon in patients naive to bosentan. The manufacturer estimated that the incremental cost per life-year gained for tadalafil compared with placebo was $43,813 and the incremental cost per quality-adjusted life-year was $70,753. The clinical inputs were based on a post-hoc analysis of Study LVGY. The treatment benefits with tadalafil that were predicted by the model appeared to be driven by patients who improve from WHO functional class III to II, which is consistent with the results of Study LVGY.

The daily cost of tadalafil (40 mg daily; $26) is less than the daily cost of sildenafil (20 mg three times daily; $34), ambrisentan (5 mg daily; $121), bosentan (125 mg twice daily; $130), and sitaxsentan (100 mg daily; $126). The recent patent expiry of sildenafil and the future availability of generic sildenafil could eliminate the cost savings associated with tadalafil compared with sildenafil.

Other Discussion Points:

- It was discussed that bosentan induces cytochrome P450 3A4. This drug interaction reduces tadalafil levels when the two agents are used in combination and was observed in the randomized placebo-controlled trial of tadalafil.
- The Committee discussed that the improvements in 6MWD observed in patients not taking bosentan and receiving tadalafil 40 mg appeared similar in magnitude to improvements observed in patients receiving sildenafil in placebo-controlled trials of sildenafil.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:

None.

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Conflicts of Interest:
One CEDAC member reported receiving institutional funding through Eli Lilly, but no direct payments were received and funding was not related to tadalafil; therefore, this did not preclude participation in the discussion and voting.

One CEDAC member reported a conflict of interest and did not participate in the vote.

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation 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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