

CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

SILDENAFIL CITRATE (Revatio™ – Pfizer Canada Inc.)

Description:

Sildenafil is a selective inhibitor of cyclic GMP specific phosphodiesterase type-5 and is approved for the treatment of erectile dysfunction (Viagra™) and pulmonary hypertension (Revatio™). The submission to the Common Drug Review was solely for the approved indication for the treatment of primary pulmonary arterial hypertension or pulmonary hypertension secondary to connective tissue disease, in patients with World Health Organization (WHO) functional class II or III who have not responded to conventional therapy.

Dosage Forms:

20 mg tablets. The recommended dose is 20 mg given three times daily.

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that sildenafil be listed in the same manner that drug plans list bosentan for patients with WHO class III pulmonary artery hypertension (PAH) of either primary origin or secondary to connective tissue disease, who have had an inadequate response to conventional therapy (e.g. diuretics, digoxin, warfarin and calcium channel blockers). The dose of sildenafil should be limited to 20 mg given three times daily.

Reasons for the Recommendation:

1. Compared to placebo in patients with WHO class II and III PAH, sildenafil use is associated with statistically significant improvements in exercise capacity and quality of life.
2. In WHO class III PAH, sildenafil provides an alternative treatment option to bosentan and is less expensive than bosentan, an oral medication already funded by some drug plans. The cost of sildenafil (as Revatio™) 20 mg given three times daily is \$31 per day versus \$128 per day for bosentan at a dose of 62.5 or 125 mg given twice daily.
3. In WHO class II PAH (defined as mild limitation of physical activity), the economic evaluation submitted by the manufacturer reported that sildenafil was associated with an incremental cost-effectiveness ratio of approximately \$46,000 per life year saved when compared to no PAH-specific treatment. However, the evaluation assumed a 100% rate of survival after one year of therapy with sildenafil compared to a 75% survival rate for patients not on therapy. As there are no data from randomized controlled trials (RCTs) that report improved survival with sildenafil for any class of

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PAH, the Committee felt that the true incremental cost-effectiveness of sildenafil for WHO class II PAH would be significantly less attractive than reported in the evaluation submitted by the manufacturer. As such, the Committee does not recommend that sildenafil be listed for patients with WHO class II PAH.

4. Since the RCT reviewed by the Committee found no difference in the efficacy of higher doses of sildenafil when compared to 20 mg given three times daily, the dose of sildenafil should be limited to 20 mg given three times daily.

Summary of Committee Considerations:

The Committee considered a systematic review of randomized controlled trials (RCTs) of adult patients with primary PAH or PAH secondary to connective tissue disease who had not responded to conventional therapy. One RCT of 12 weeks duration in 278 patients which compared sildenafil 20, 40 and 80 mg (each given three times daily) with placebo met the inclusion criteria for the systematic review.

Compared to placebo, sildenafil 20 mg given three times daily was associated with statistically significant improvements in the six minute walk test (mean difference of 45 m versus placebo), the percentage of patients with an improvement of at least one WHO functional class (28% for sildenafil versus 7% for placebo) and in measures of quality of life. There was no statistically significant difference between groups on the mean change in dyspnea score.

There were no statistically significant differences in the incidence of adverse events between sildenafil and placebo, although sildenafil use was associated with numerically higher rates of some specific adverse events, including epistaxis. Although not noted at the approved dose (20mg three times daily) the use of higher doses of sildenafil was associated with numerically higher rates of some eye disorders compared with placebo.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. Consideration should be given to limiting prescribing of sildenafil to physicians with expertise in the management of PAH.
3. There is insufficient evidence on the effectiveness of sildenafil in patients with PAH secondary to congenital heart disease.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.