Sildenafil (for pulmonary arterial hypertension)

Product:
SILDENAFIL (Revatio®) 20mg tablet

Class of drugs:
Phosphodiesterase inhibitor

Indication:
Treatment of pulmonary arterial hypertension

Manufacturer: Pfizer Canada Inc.

CED Recommendation-

The CED recommended that sildenafil (Revatio®) be funded through the Exceptional Access Program (EAP), according to specific criteria, on the basis that the drug has demonstrated short-term clinical benefits and value for money in selected patients with pulmonary arterial hypertension.

Executive Officer Decision

Based on the CED's recommendation, the Executive Officer decided to fund sildenafil (Revatio®) through the EAP for the treatment of pulmonary arterial hypertension, according to specific criteria.

Status

Funding available through the Ontario Public Drug Programs via the Exceptional Access Program (EAP).

Highlights of Recommendation:

- Sildenafil is used to treat pulmonary arterial hypertension, a disease marked by an increase in blood pressure in the artery which takes blood from the heart to the lungs.
- In a key study that the Committee reviewed, sildenafil improved the patients' performance in the six-minute walk test when compared to patients taking a placebo. In this trial, the quality of life of patients who used sildenafil also improved.
- There are no long-term published studies for sildenafil in the treatment of pulmonary arterial hypertension; therefore, the long-term effectiveness of the drug is unknown. There is no evidence that sildenafil decreases mortality.
- **Overall, the Committee acknowledged that sildenafil appears to have short-term benefits in improving patients' exercise capacity and their quality of life. However, evidence on long-term benefit and safety is lacking.**

Background:

Pulmonary arterial hypertension (PAH) is a disabling and typically progressive disease that occurs when dangerously high blood pressure builds up in the blood vessels that lead from the heart to the lungs. The small blood vessels in the lungs narrow and their walls thicken, causing the pressure to build. The heart is unable to keep up with the extra work needed to pump blood through the lungs, resulting in right-sided heart failure. Symptoms include fatigue, dizziness, shortness of breath, chest pain and, eventually, heart failure and death.

PAH can occur on its own, due to unknown causes (idiopathic), or as a complication of congenital heart disease, HIV or connective tissue diseases such as scleroderma (a collagen vascular disease). A right heart catheterization is required for a definitive diagnosis by a specialist. PAH is classified according to clinical status and functional capacity.

The goals of treatment are to prevent disease progression, prevent blood clots, relieve symptoms, improve exercise capacity and prolong survival. Standard treatment for PAH includes lifestyle modifications, conventional non-specific medications (such as oral anticoagulants, digoxin, calcium channel blockers, diuretics) and supplemental oxygen therapy. Exercise can be an important part of treatment for some patients if used cautiously and with close monitoring; however, it is not an alternative for patients who have more severe disease.

Disease specific medications have become available in the last several years. There are several classes of disease specific medications: prostanoids (epoprostenol, treprostinil), endothelin type A receptor antagonists (bosentan, ambrisentan, sitaxsentan) and phosphodiesterase inhibitors (sildenafil, tadalafil).

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Detailed Discussion:

- The Committee reviewed one published randomized controlled trial of 12 weeks duration in 278 patients with pulmonary arterial hypertension (Galie et al., NEJM 2005). Compared to placebo, sildenafil 20mg three times daily was associated with statistically significant improvements in the six-minute walk test (mean difference of 45 meters vs. placebo), the percentage of patients with an improvement of at least one World Health Organization (WHO) functional class (28 percent for sildenafil vs. seven percent for placebo), and measures of quality of life.
- The clinical trial design and duration did not allow for the evaluation of time to death or time to transplantation. Because only short-term studies are available, the long-term safety and effectiveness of sildenafil in the treatment of pulmonary arterial hypertension is unknown.
- No significant dose response effect was observed for the three doses (20mg, 40mg, 80mg three times daily) of sildenafil.
- The pivotal study did not show any statistically significant difference in the incidence of serious adverse events between sildenafil and placebo. Sildenafil use was associated with higher rates of nose bleeds and eye disorders.
- The Committee evaluated the cost-effectiveness of sildenafil in patients with WHO class II and WHO class III pulmonary arterial hypertension. Value for money was not demonstrated in patients with WHO class II pulmonary arterial hypertension. In WHO class III patients, sildenafil appeared to provide reasonable cost-effectiveness.
- There are no direct head-to-head studies between sildenafil and bosentan to determine comparative efficacy and safety between the two agents. Sildenafil costs approximately $30 per day (at the 20mg three times daily dose), while bosentan costs approximately $130 per day (at a dose of 125mg twice daily). In the absence of evidence indicating one agent is clinically superior to another, the Committee felt that sildenafil is a cost-effective alternative to bosentan in patients with WHO class III pulmonary arterial hypertension of either primary origin or secondary to connective tissue disease.
- The Committee expressed concerns with combination use of sildenafil with other pulmonary arterial hypertension agents. There are no good quality randomized controlled trial evaluating combination therapy. Only one trial evaluated combination therapy of sildenafil and epoprostenol. There are ongoing trials evaluating combination oral therapy (sildenafil with bosentan).
- **Overall, the Committee acknowledged sildenafil appears to have short-term benefits in improving pulmonary hemodynamics and increasing the six-minute walk distance in the relevant population.** However, the supporting evidence stems from one randomized clinical trial of 12 weeks. The long-term effectiveness of this drug in patients with pulmonary arterial hypertension is unknown. Key outcomes such as time to death or transplantation have not been evaluated. Nevertheless, the Committee recognized this therapy offers short-term clinical benefit and value for money in patients with WHO Class III pulmonary arterial hypertension.

EAP Funding Criteria:

Criteria for drugs used to treat PAH change often in response to evolving clinical evidence and on-going reviews. Therefore, please check http://www.health.gov.on.ca/english/providers/program/drugs/eap_criteria.html for the most up-to-date funding criteria.

CEDAC Recommendation:

(http://www.cadth.ca/index.php/en/cdr/recommendations)

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that sildenafil (Revatio®) be listed in the same manner that drug plans list bosentan.

Ontario

Ministry of
Health and Long-Term Care
Ontario Public Drug Programs

For more information, please contact:

Ministry of Health and Long-Term Care
Ontario Public Drug Programs
Hepburn Block, 9th Floor
80 Grosvenor Street, Queen's Park
Toronto, Ontario M7A 1R3
or click: http://www.health.gov.on.ca/english/providers/program/drugs/ced_rec_table.html