

MEDICATIONS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

The Ontario Public Drug Programs (OPDP) and its expert advisory committee, the Committee to Evaluate Drugs (CED), recently re-evaluated the funding of medications for the treatment of pulmonary arterial hypertension (PAH), with a focus on combination therapy. As a result, the funding criteria for both monotherapy and combination therapy have been revised.

Key Findings

- ◆ Very few randomized controlled trials (RCTs) have been completed that provide good quality evidence for combination therapy. However, there are ongoing trials that may provide useful information about combination therapy in the future.
- ◆ There is RCT evidence from smaller trials suggesting that some combination regimens may cause harm. Most of the RCT data available are for combinations using parenteral therapy (i.e. epoprostenol) or iloprost which is not available in Canada. RCT data on combination treatment with two oral agents from different classes are not yet available.
- ◆ Extending funding of individual drugs for PAH to combination therapy, based on the current level of evidence, is inconsistent with previous recommendations for other drugs and diseases that have not been funded due to insufficient evidence. The lack of good quality evidence for combination therapy was noted in previous reviews of the individual drugs; as such, combination therapy for PAH was previously not funded.
- ◆ Combination therapy is expensive, ranging from approximately \$160 per day (sildenafil plus bosentan) to more than \$300 per day (epoprostenol plus bosentan). Additional equipment and healthcare costs are incurred for patients on parenteral (i.e. intravenous, subcutaneous) therapy.
- ◆ In view of the increasing number of funding requests for combination therapy, input was sought from specialists who treat PAH, drug manufacturers and patient groups.

New Funding Criteria

Primarily in consideration of limited alternatives for patients who progress on single-agent treatment, the EAP funding criteria has been modified to consider funding combination therapy for patients who have not achieved therapeutic targets after at least 3 months of monotherapy. In addition to providing funding for combination therapy, there have been some revisions to the EAP criteria for monotherapy which can be found at

http://www.health.gov.on.ca/english/providers/program/drugs/eap_criteria.html

and

http://www.health.gov.on.ca/english/providers/program/drugs/pdf/frequently_requested_drugs.pdf

SUMMARY OF REVISIONS:

- ◆ Requests must be from a recognized PAH referral centre: Toronto General Hospital/University Health Network, Kingston General Hospital, London Health Sciences Centre, Hamilton Health Sciences, Ottawa Civic Hospital/Ottawa Heart Institute. This approach to care is strongly supported by clinicians, patient groups, publications and PAH treatment guidelines to improve the diagnosis and management of PAH patients while also promoting appropriate prescribing of PAH drugs, especially when combination therapy is considered.
- ◆ Patient must have proven PAH defined as ≥ 25 mmHg mean pulmonary artery pressure (mPAP) on right heart catheterization (RHC) with normal pulmonary capillary wedge pressure (≤ 15 mmHg) and without interstitial lung disease, COPD or left ventricular failure either systolic or diastolic.
- ◆ Combination therapy may be considered for patients who have not achieved treatment targets after at least **three** months of single agent therapy (monotherapy) with a PAH-specific drug. Drugs used in combination must be from different classes (i.e., ERA, PDE-5 inhibitor, prostanoid).
- ◆ Triple therapy will not be funded except to allow an overlap period of 6 months with weaning of one drug.

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Background

Pulmonary arterial hypertension (PAH) is a severe and disabling 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 or as a complication of congenital heart disease, HIV or connective tissue diseases such as scleroderma. The diagnosis is complicated, requiring a specialist, and a right heart catheterization is required for a definitive diagnosis. 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 sicker patients

Disease specific medications have become available in the last several years. There are several classes of disease specific medications: prostanoids, endothelin receptor antagonists and phosphodiesterase inhibitors.

Prostanoids include epoprostenol, treprostinil and iloprost. Prostanoids work by acting as prostacyclin in the body to dilate the blood vessels and prevent blood clots. Epoprostenol is given as an intravenous infusion and treprostinil can be given by intravenous or subcutaneous infusion. Iloprost is not available in Canada.

Endothelin receptor antagonists (ERA) are a class of oral medications that include bosentan, ambrisentan, and sitaxsentan. ERAs help by decreasing the blood pressure in the lungs by blocking the effect of endothelin-1, a natural substance that causes blood vessels in the lungs to constrict.

Sildenafil is a phosphodiesterase (PDE-5) inhibitor. Sildenafil is taken three times a day. Phosphodiesterase inhibitors improve blood vessel dilation in the lungs, thereby reducing pressure in the lungs.

Detailed Discussion

- ◆ The CED expressed concern about the lack of good quality evidence to support combination therapy and about evidence from smaller randomized, controlled trials that suggest some combination regimens may cause harm. In addition, to extend funding of PAH drugs to combination therapy based on the current level of evidence would be inconsistent with previous recommendations for other drugs and diseases where funding is not provided because of insufficient evidence.
- ◆ The PACES trial (Simonneau et al. *Ann Intern Med* 2008;149(8):521-30) is the only good quality RCT available evaluating the combination of epoprostenol with sildenafil. This trial demonstrated improvements in six-minute walk duration (an accepted surrogate marker), SF-36 (quality of life assessment) and an improvement in time to clinical worsening. These results may serve as a paradigm for combination therapy because combination of drugs with different mechanisms of action may have additional beneficial effects.
- ◆ PAH specialists provided an unpublished systematic review of the literature, which added results from 26 observational studies. Overall the majority of the studies demonstrated benefit for combination therapy.
- ◆ A report from the Canadian Agency for Drugs and Technology in Health (CADTH) was also considered. (This report is available at http://www.cadth.ca/media/pdf/M0004_Drugs_for_Pulmonary_Arterial_Hypertension_tr_e.pdf)
- ◆ Since the CED's interim review in May 2009, there was no new RCT evidence for combination therapy. There is no good data directly studying the combination dual oral therapy (e.g., bosentan plus sildenafil). One ongoing RCT directly evaluating the efficacy of dual oral therapy (sildenafil plus bosentan versus bosentan alone) is expected to be completed in March 2011.
- ◆ Most PAH guidelines and published trials encourage clinicians and patients to enroll in trials of combination therapy, but no Canadian centres are participating in the ongoing trials.

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- ◆ This review considered input from a patient advocacy group and from individual patients:
 - ◆ The severity of illness may be underestimated because most patients using ODB-funded drugs are very ill;
 - ◆ Patients have very limited activities of daily living, poor functional status, and live with the awareness of their shortened lifespan;
 - ◆ PAH drugs are very expensive and many patients depend on government funding.
- ◆ No cost-effectiveness analyses for combination therapy are available. Combination therapy is expensive, ranging from approximately \$160 per day (sildenafil plus bosentan) to more than \$300 per day (epoprostenol plus bosentan). Drugs such as epoprostenol and treprostinil have additional hidden costs, including equipment, monitoring and nursing. There is also a risk of line infections that need to be treated.
- ◆ PAH is a progressive disease. Patients are morbidly ill with no suitable treatment alternatives other than lung transplant. There are a limited number of PAH patients living with advanced disease and all are followed closely by specialists. There is agreement that specialists should treat PAH. Most specialists treating PAH are respirologists, but only a very few subspecialize in treating PAH.
- ◆ Looking only at the ODB data, the CED noted a higher than expected prevalence and PAH drug utilization in Ontario which may be reflective of inappropriate diagnoses and prescribing outside of PAH referral centres. Prevalence data in patients >65 years of age was much higher than expected. Concerns over inappropriate prescribing may be mitigated by restricting funding to PAH referral centres. This approach is likely to improve the diagnosis and management of PAH patients while also providing appropriate prescribing of PAH drugs.
- ◆ Overall, there are limited RCT data for combination therapy. The CED recommended that combination therapy be funded for patients who progress on monotherapy and that the current EAP criteria be revised primarily in consideration of the limited options for patients who progress on monotherapy. Diagnostic criteria and a treatment algorithm for monotherapy and combination therapy, were used to develop EAP criteria for funding.
- ◆ Noting that there will be new data forthcoming, there is an opportunity to revisit funding of combination therapy in the future.

Committee to Evaluate Drugs

The Committee to Evaluate Drugs (CED) is an expert advisory group that makes recommendations to the Executive Officer of the Ontario Public Drug Programs. The CED's recommendations are based on an evaluation of the therapeutic value and cost-effectiveness of the drug relative to available alternatives. Membership on the CED includes practicing physicians, pharmacists, health economics experts, and patients.

A subcommittee with CED physician members, a health economics expert, a CED patient member and PAH physician specialists was convened to review the available evidence for combination therapy in the treatment of PAH.

For more information about the Ontario Public Drug Programs and the Committee to Evaluate Drugs, please visit:
http://www.health.gov.on.ca/english/providers/program/drugs/drugs_program_mn.html