Committee to Evaluate Drugs (CED)

Recommendations and Reasons

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Tobramycin inhalation powder

Product: tobramycin inhalation powder (TOBI Podhaler®)

Class of Drugs: antibiotic

Reason for Use: pulmonary infections in cystic fibrosis (CF)

Manufacturer: Novartis Pharmaceuticals Canada Inc.

Date of Review: October 12, 2011; March 14, 2012; and January 15, 2014

CED Recommendation

The CED noted that tobramycin inhalation powder (TOBI Podhaler®) appears to be as effective as tobramycin inhalation solution (a funded alternative). A clinical study comparing the two products reported a higher incidence of adverse events with tobramycin inhalation powder (TOBI Podhaler®); as such, the CED recommended that tobramycin inhalation powder (TOBI Podhaler®) not be funded.

Executive Officer Decision*

Based on the CED's recommendation, the Executive Officer decided not to fund tobramycin inhalation powder (TOBI Podhaler®).

Funding Status*

Not funded through the Ontario Public Drug Programs.

* *This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx.*

Ontario

Highlights of Recommendation:

- The EAGER study showed that tobramycin inhalation powder (TIP) was similar in effectiveness as tobramycin inhalation solution (TIS). The study reported a higher incidence of adverse events (e.g., cough, dyspnea) in patients treated with TIP compared with patients who received TIS.
- The CED also reviewed several studies based on real-world clinical practice and a meta-analysis comparing various drugs for the management of pulmonary infections in cystic fibrosis. The Committee noted that these studies were of poor quality and did not adequately address the potential for increased harm with the use of TIP.
- TIP costs the same as TIS per day.
- The Committee recognized that TIP requires less administration time than TIS, representing a significant benefit for patients with cystic fibrosis.

Background:

Cystic fibrosis (CF) is a genetic disease caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. CF causes thick, sticky mucus to build up in the lungs, digestive tract, and other areas of the body.

The mucus clogs the lungs, causing breathing problems and making it easy for bacteria to grow. This can lead to problems such as repeated lung infections and lung damage. *Pseudomonas aeruginosa* is a ubiquitous organism in the environment, and the majority of people with CF will acquire *P. aeruginosa* infection during the course of their disease. When *P. aeruginosa* is first acquired, the strain is more susceptible to antibiotics, but as chronic infection is established it becomes difficult to eradicate. Inhaled tobramycin is the standard treatment for both first-time and chronic *P. aeruginosa* infections.

Drugs funded through the Ontario Public Drug Programs for the treatment *P. aeruginosa* infection in CF patients include tobramycin inhalation solution (TIS, TOBI® inhalation solution) and aztreonam. Also, some patients use the injectable tobramycin product for administration via inhalation.

Detailed Discussions:

- The CED reviewed tobramycin inhalation powder (TIP) on three occasions, most recently in January 2014 following a manufacturer request for reconsideration.
- For the evaluations, the CED considered:
    - Information in the manufacturer's submissions;
    - Submission from one patient group.
- There are two randomized controlled studies that assessed the efficacy and safety of TIP, the EVOLVE study (placebo-controlled) and the EAGER study (active-controlled).
- The focus of the CED's reviews in 2011 and 2012 was the EAGER study, which compared TIP to tobramycin inhalation solution (TIS). The study demonstrated similar efficacy in

terms of FEV_1 (forced expiratory volume in 1 second) improvements and *P. aeruginosa* reduction between the TIP and TIS treatment groups. The number of patients hospitalized for respiratory-related events was also similar between the two treatment arms. The use of antipseudomonal antibiotics and the incidence of adverse events were higher in TIP treated patients, suggesting a potential for increased harm with the use of TIP.

- The Committee noted that EAGER is the only clinical study comparing TIP to TIS, and the study had a short (3-month) follow-up and a high withdrawal rate. All these factors severely limit the ability to make comparisons between the two products.
- At its January 2014 review, the CED considered additional data submitted by the manufacturer, including three real-world studies from the Régie de l'assurance maladie du Québec (RAMQ), Cork University Hospital (Ireland), and Sainte-Justine hospital (Montreal).
- The RAMQ data analysis was an unpublished retrospective cohort study of CF patients who used TIP, TIS or other tobramycin formulations on at least one occasion from January 2011 to June 2012. The results of the study demonstrated that medication costs were higher in patients using TIP compared to TIS, possibly due to increased compliance with TIP and therefore, an increase in the number of filled TIP prescriptions. The CED noted the lack of transparency in the study's methodology and questioned the validity of some of the outcome variables.
- The clinical experiences with TIP from Sainte-Justine and Cork hospitals were presented as posters. The Montreal study demonstrated that approximately 6% of patients discontinued therapy for reasons potentially related to the medication. The discontinuation rate was lower than that seen in clinical trials. The Cork study reported no significant difference in cough, lung function, or adverse events between TIS and TIP if patients who were intolerant to TIP or who discontinued TIP were excluded from the analysis. The CED noted that these are observational studies with small patient numbers that relied on historical controls, and the data were biased in favour of TIP.
- The manufacturer also submitted a network meta-analysis (Littlewood *et al.*) which concluded that all studied antibiotics (i.e., tobramycin, colistin, aztreonam) had comparable efficacy. The CED noted that this conclusion was based on a comparison of a surrogate efficacy outcome (i.e., FEV_1) for a period of up to 4 weeks only. Hospitalizations, acute exacerbations, and adverse events, such as cough, were not included in the analysis.
- TIP costs the same as TIS per day. The manufacturer submitted an economic analysis comparing TIP to TIS. There were several limitations in the analysis, including the assumption that TIP and TIS have similar efficacy and safety.
- The CED reviewed one patient group submission. The submission highlighted the impact of CF on patients and their families. Because a large part of their day is spent on the various therapies required to manage CF, patients highly valued the reduction in administration time with TIP (5 minutes versus 20 minutes for TIS).
- Overall, the CED noted that TIP has not been shown to be more effective than TIS. While the reduced administration time represents a significant benefit, the CED was concerned about the potential for increased harm with the use of TIP.

Committee to Evaluate Drugs (CED)

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

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

www.health.gov.on.ca/en/pro/programs/drugs/