Summary

Roflumilast is an inhibitor of phosphodiesterase-IV (PDE4), a cellular enzyme that is linked to airway inflammation in asthma and chronic obstructive pulmonary disease (COPD).

In clinical trials, roflumilast produced significant improvements in FEV1 (forced expiratory volume in one second) and PEF (peak expiratory flow) compared with low-dose inhaled beclomethasone in asthma patients, and compared with placebo in COPD patients. Roflumilast reduced the use of rescue medication in both populations. COPD patients on roflumilast experienced fewer exacerbations.

The most common adverse effects reported in roflumilast trials were diarrhea, nausea, headache, and abdominal pain.

Evidence is only available in non-peer-reviewed format abstracts. Most of the measures used are markers of clinical effects as opposed to clinical outcomes. More studies are needed to determine the role of roflumilast in the treatment of asthma and COPD.

The Technology

Roflumilast is a selective inhibitor of PDE4 for oral use. PDE4 is the main type of phosphodiesterase located in airway structural and inflammatory cells. The inhibition of PDE4 suppresses the inflammatory activity in many airway cells that are implicated in the pathogenesis of asthma and COPD, and that contribute to the clinical manifestations.

Regulatory Status

Roflumilast (Daxas™, ALTANA Pharma Inc.) has not been approved for use in Canada. In the US, ALTANA has delayed its application to the Food and Drug Administration (FDA) because of ongoing phase III trials. Regulatory approval for roflumilast (ALTANA Pharma AG, Germany) is pending in Europe after submission to the European Medicines Agency in February 2004.

Patient Groups

Asthma is a chronic inflammatory disease of the airways. It is characterized by intermittent or persistent symptoms including shortness of breath (dyspnea), chest tightness, sputum production, wheezing, and coughing. In the last 20 years, asthma has become increasingly prevalent in young children. It affects an estimated 2.5 million Canadians (12% of children and 8% of adults).

COPD is a progressive, partially reversible respiratory disease that typically occurs in older patients with a history of smoking. Patients with COPD may present with increased sputum production (bronchitis), chronic airflow obstruction, impaired gas exchange (emphysema), and cardiovascular and other systemic changes. Acute exacerbations of COPD are a frequent cause of morbidity and contribute to mortality. An estimated 3.7% of Canadians who are older than 35 years have probable COPD. In 1999, COPD was the fourth leading cause of death among men and the fifth among women.

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is funded by Canadian federal, provincial and territorial governments. (www.ccohta.ca)
**Current Practice**

Drugs that are used in the outpatient treatment of asthma are categorized as relievers or controllers. Relievers, which have bronchodilating effects, are used to treat acute symptoms. They are best represented by the short-acting beta-2 agonists (SABAs) for inhalation. Controllers have anti-inflammatory effects. Inhaled corticosteroids (ICS) are the controller of choice and are indicated in all but the mildest cases of asthma. When the use of one drug cannot ensure adequate symptom control, there is evidence supporting the use of a long-acting beta-2 agonist (LABA) in addition to an ICS. Other add-on therapies include leukotriene receptor antagonists, methylxanthines (e.g., theophylline), and infrequently, cromoglycate and nedocromil.

Bronchodilators (beta-2 agonists, anticholinergics, and methylxanthines) form the mainstay of COPD treatment. The first-line treatment for regularly symptomatic patients is the combination of an inhaled short-acting anticholinergic (ipratropium) and a SABA as needed. If a SABA is regularly used more than twice a day, a long-acting bronchodilator for inhalation, such as a LABA or tiotropium, should be considered. ICS are not recommended as first-line therapy in COPD, but may be used in moderate to severe disease to reduce the frequency of exacerbations. Paramount in the management of COPD is smoking cessation, the only intervention that is known to slow the progression of the disease.

**The Evidence**

**Asthma**

One double-blind, double-dummy, parallel group study compared daily roflumilast 500 µg with low-dose (200 µg twice daily), inhaled beclomethasone dipropionate (BDP). The 12-week study involved 499 symptomatic asthma patients. Both roflumilast and BDP produced significant (p<0.001) improvements in FEV1, FVC (forced vital capacity), and morning PEF versus baseline. Both treatments also significantly (p≤0.001) reduced asthma symptom scores and the use of rescue medication. Roflumilast produced less favourable results on all outcome measures compared with BDP, although the differences between treatments were not statistically significant.

**COPD**

A double-blind, randomized controlled trial was conducted in 516 patients with moderate to severe COPD during a 26-week period. At baseline, patients were randomized to receive daily placebo (n=172), 250 µg roflumilast (n=175), or 500 µg roflumilast (n=169). Results showed statistically significant improvements in FEV1 (p<0.001) and morning PEF (p<0.012) when roflumilast was compared with placebo.

### Table 1: Outcome measures from RECORD study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Roflumilast 250 µg</th>
<th>Roflumilast 500 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>280</td>
<td>576</td>
<td>555</td>
</tr>
<tr>
<td>Change in FEV1 (mL)</td>
<td>NR</td>
<td>74±18 (39, 108)†</td>
<td>97±18 (62, 131)†</td>
</tr>
<tr>
<td>Change in FVC (mL)</td>
<td>NR</td>
<td>71±31 (12, 131)‡</td>
<td>114±31 (53, 174) **</td>
</tr>
<tr>
<td>Patients with an exacerbation, n (%)</td>
<td>98 (35)</td>
<td>207 (36)</td>
<td>155 (28)</td>
</tr>
<tr>
<td>Mean exacerbations per patient</td>
<td>1.13§</td>
<td>1.03§</td>
<td>0.75§</td>
</tr>
<tr>
<td>SGRQ total score</td>
<td>-1.71ª</td>
<td>-3.35ª</td>
<td>-3.51ª</td>
</tr>
</tbody>
</table>

FEV1=forced expiratory volume in one second, FVC=forced vital capacity, NR=not reported, SGRQ=St. George’s Respiratory Questionnaire

Changes in FEV1 and FVC are reported as least squares mean increases versus placebo: LSMean±Std Err
Mean (95% CI); †p<0.0001, ‡p=0.0193, **p=0.0002 for change versus placebo; all exacerbations: mild, moderate, and severe; †p=0.0029, ªp<0.025, §p<0.0001 for change versus baseline.
The exacerbation rate per patient was lower in the 500 µg roflumilast group versus the placebo group (0.09 exacerbations per patient versus 0.15 exacerbations per patient respectively). The statistical significance was unreported.14

The RECORD study, a double-blind randomized controlled trial, compared roflumilast with placebo in 1,411 patients with moderate to severe COPD. After 24 weeks of treatment, roflumilast produced significant dose-dependent improvements in FEV₁ and FVC compared with baseline values (Table 1).15

Compared with placebo, 500 µg roflumilast daily significantly reduced the number of patients experiencing an exacerbation (relative risk: 0.80; 95% CI: 0.65, 0.98; number needed to treat: 14; 95% CI: 7, 335) and the average number of exacerbations per patient (Table 1).16 This effect was mainly based on a reduction in mild exacerbations; neither dose of roflumilast significantly reduced moderate or severe exacerbations.16 The health-related quality of life was evaluated using the St. George’s Respiratory Questionnaire (SGRQ). Roflumilast improved quality of life to a greater degree than did placebo (Table 1). None of the treatment groups reached the minimal criteria for clinical improvement (i.e., -4.0 units).16

### Adverse Effects

Limited data from available roflumilast trials suggest that the drug is well tolerated in most patients.14,17-19 PDE inhibitor adverse events (e.g., nausea, emesis, headache, and dyspepsia) that limit the early development of other PDE4 inhibitors remain a concern.5 The most common adverse events reported with roflumilast in clinical trials are headache, diarrhea, nausea, insomnia, and abdominal pain.14,17-19 Most adverse events are mild to moderate in intensity and are reported to occur more frequently with roflumilast than placebo. Roflumilast does not produce clinically relevant changes in vital signs, electrocardiogram measures, or laboratory results.14,17-19 It is reported from study extensions of ≤1 year’s duration for both asthma and COPD that the incidence of adverse events decreases with continued treatment.17,18

### Administration and Cost

The manufacturer’s recommended dosages have not been disclosed. In clinical trials, roflumilast is administered orally, once daily, as tablets containing 250 µg or 500 µg (100 µg tablets are used in one study). The cost is unavailable.

### Concurrent Developments

Two other PDE4 inhibitors are in the late stages of development: cilomilast (Ariflo®, GSK), and BAY 19-8004 (Bayer).20 Ariflo® is undergoing phase III studies for COPD after an approvable letter from the FDA appeared in October 2003. The clinical development of Ariflo® for asthma has been discontinued because of poor efficacy.20,21

As PDE4 is located in a variety of inflammatory cells, PDE4 inhibitors are being investigated for the management of inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, osteoporosis, allergic rhinitis, and skin diseases.22-24

### Rate of Technology Diffusion

As roflumilast is in clinical development, it is difficult to determine how this emerging drug will diffuse in clinical practice. Its convenient once-daily oral administration may be attractive, because most first-line therapies for asthma and COPD require multiple inhalations daily. The systemic absorption of roflumilast could lead to a higher incidence of adverse events. If roflumilast proves to be effective and safe, it could have an impact on the clinical management of patients with asthma and COPD. Whether roflumilast provides significant clinical benefits compared with established therapies is undetermined.
Implementation Issues

The findings from clinical trials are based on the markers of clinical effects. There is a need to better evaluate how roflumilast compares with existing therapies for asthma and COPD in terms of clinical benefits (patients’ functional capacity, emergency visits, hospitalization, mortality) and the potential for harm. Long-term safety data are also lacking. From clinical practice and policy-making perspectives, it would be important to determine whether specific populations of asthma and COPD patients would benefit from roflumilast or would be more at risk for adverse events.

References


Cite as: Cowan C. Roflumilast for asthma and chronic obstructive pulmonary disease [Issues in emerging health technologies issue 74]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2005.

***************

CCOHTA takes sole responsibility for this bulletin and appreciates comments from its reviewers.

Reviewers: Manuel G. Cosio MD, McGill University, Montréal QC; Malcolm King PhD FCCP, University of Alberta, Edmonton AB.

Production of this report is made possible by a financial contribution from Health Canada's Health Care Strategies and Policy, federal, provincial and territorial partnership grant program.

CCOHTA takes sole responsibility for the final form and content of this report. The statements, conclusions and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is funded by Canadian federal, provincial and territorial governments. (www.ccohta.ca)