



COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

ROFLUMILAST

(Daxas — Nycomed Canada Inc.)

Indication: Chronic Obstructive Pulmonary Disease

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that roflumilast not be listed.

Reasons for the Recommendation:

1. In the two double-blind randomized controlled trials (RCTs), in the patient population for which roflumilast is approved, there were no statistically significant differences between roflumilast and placebo in the clinical outcomes of: severe chronic obstructive pulmonary disease (COPD) exacerbations, quality of life, or mortality.
2. In the two double-blind RCTs, differences between roflumilast and placebo for the co-primary outcomes (pre-bronchodilator forced expiratory volume in one second [FEV₁] and the rate of moderate or severe COPD exacerbations) were small.

Of Note:

Neither RCT included an active comparator, therefore the trials were considered to have limited clinical relevance for patients with severe COPD because they disallowed concomitant treatment with long-acting anticholinergics and/or inhaled corticosteroids.

Background:

Roflumilast has a Health Canada indication for add-on therapy to bronchodilator treatment for the maintenance treatment of severe COPD associated with chronic bronchitis (i.e., patients with a history of chronic cough and sputum) in adult patients with a history of frequent exacerbations. Roflumilast is a selective inhibitor of the enzyme phosphodiesterase 4. It is available as a 500 mcg tablet and the Health Canada-approved dose is 500 mcg daily.

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of roflumilast, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Common Drug Review

CEDAC Meeting — May 18, 2011; CEDAC Reconsideration – July 20, 2011

Notice of CEDAC Final Recommendation – July 27, 2011

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Clinical Trials

Two double-blind multinational RCTs of patients with severe or very severe COPD met the inclusion criteria for the CDR systematic review protocol. Studies M2-124 (N = 1,523) and M2-125 (N = 1,568) compared roflumilast 500 mcg daily with placebo; study durations were 56 weeks (composed of a four-week single-blind placebo run-in period and a 52-week treatment period). Enrolled patients were 40 years of age or greater with severe or very severe COPD ($FEV_1 \leq 50\%$ of predicted) associated with chronic bronchitis and a history of exacerbation. Randomization was stratified by concomitant treatment with long-acting beta agonists (LABA) and by smoking status; approximately 50% of patients in both trials received concomitant LABA. The use of long-acting anticholinergics and/or inhaled corticosteroids was disallowed during the treatment periods of both trials. There was a high withdrawal rate; approximately 30% of patients from both trials withdrew, and post-withdrawal outcome data were not made available.

The reviewed studies are limited by their lack of an active comparator. Due to the restrictions on concomitant therapy in the reviewed trials, there is insufficient evidence of efficacy when added to current standard therapy, such as long-acting anticholinergics and/or LABA plus inhaled corticosteroids.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these the Committee discussed the following: COPD exacerbations, quality of life, exercise tolerance, hospitalization, mortality, FEV_1 , total adverse events, and serious adverse events.

The co-primary outcomes in the reviewed trials were: (i) the mean change from baseline to end of treatment in pre-bronchodilator FEV_1 , and (ii) the mean rate of COPD exacerbations that required oral or parenteral corticosteroids and/or hospitalization, or that led to death. In supplemental analyses the manufacturer examined the incidence of moderate and severe COPD exacerbations separately; a moderate COPD exacerbation was defined as the requirement for oral or parenteral corticosteroids and a severe COPD exacerbation as resulting in hospitalization and/or leading to death.

Results

Efficacy or Effectiveness

- The mean rate of moderate or severe COPD exacerbations was statistically significantly lower for roflumilast compared with placebo in both studies; the mean difference (MD) in combined moderate or severe COPD exacerbations per patient per year was -0.19 for study M2-124 and -0.28 for study M2-125. In both trials, the statistically significantly lower rate of COPD exacerbations for roflumilast compared with placebo was driven by differences in moderate exacerbations. Severe exacerbations were much less frequent and not statistically significantly different between roflumilast and placebo.
- Roflumilast groups had statistically significantly greater improvements from baseline to end of treatment in pre-bronchodilator FEV_1 (in mL) compared with placebo, independent of LABA use; MD (95% confidence interval): 39 mL (18 mL to 60 mL) and 58 mL (41 mL to 75 mL) in studies M2-124 and M2-125, respectively.

Common Drug Review

Common Drug Review

- Quality of life, as assessed by the EuroQol-5 Dimension questionnaire, demonstrated no statistically significant improvement in patients treated with roflumilast compared with placebo. No COPD-specific quality of life measures (e.g., St. George's Respiratory Questionnaire) were collected in the trials.
- Neither trial reported total hospitalizations, hospitalizations for COPD, or exercise tolerance.

Harms (Safety and Tolerability)

- The incidence of mortality and serious adverse events was similar between roflumilast and placebo in both trials. However, the long-term safety of roflumilast is uncertain, given that no data are currently available from studies longer than one year in duration, and post-marketing data are also of limited duration.
- In both trials, gastrointestinal and nervous system disorders were more frequently observed in roflumilast groups compared with placebo. Mean weight loss was 2.09 kg in the roflumilast group (based on pooled data from studies M2-124 and M2-125) compared with a weight gain of 0.08 kg for the placebo group.
- Two patients treated with roflumilast (compared with none treated with placebo) experienced suicide-related adverse events: one attempted in M2-124 and one completed in M2-125.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis in patients with severe COPD, in which they considered three comparisons: 1) roflumilast plus LABA versus LABA alone (based on a subgroup of M2-124 and M2-125 pooled); 2) roflumilast plus tiotropium versus tiotropium alone (based on M2-128, a trial with a mixed population of severe and moderate COPD that was not eligible for inclusion in the CDR systematic review); and 3) roflumilast plus tiotropium versus tiotropium plus inhaled corticosteroid/LABA (based on an indirect comparison of M2-128 and the OPTIMAL trial, which was also not eligible for the CDR systematic review). The model simulated the natural history of FEV₁ decline and treatment effects in FEV₁ and exacerbations over a five-year time frame.

The main limitation of the manufacturer's economic evaluation was its assumptions regarding the duration of clinical benefits. The manufacturer assumed that roflumilast would result in persistent clinical benefits over the five-year analysis period; however, the observed rate of exacerbations in the clinical trials was similar by week 44 for roflumilast plus LABA versus LABA alone. This assumption drives the improvements in quality-adjusted life-years (0.0622), despite the lack of observed differences in quality of life in the clinical trials.

At recommended doses, the daily cost of roflumilast (\$2.10) is the same as tiotropium. Roflumilast is more expensive compared with LABA (\$1.45 to \$1.87).

Patient Input Information:

The following is a summary of information provided by four patient groups that responded to the CDR Call for Patient Input:

- Shortness of breath and excess phlegm were reported as the most difficult and uncomfortable symptoms. Controlling symptoms and preventing exacerbations were suggested to be key in the management of COPD.

Common Drug Review

- Patients' inability to work or perform daily tasks were noted to result in considerable caregiver burden. Patient groups specifically wanted to draw CEDAC's attention to a qualitative study of the extent and nature of the burden experienced by caregivers in advanced COPD.
- Patients indicated that they are willing to experience adverse effects if the treatment allows them better quality of life.

Other Discussion Points:

- The Committee noted that none of the reviewed trials were conducted in a population of interest; specifically, patients with severe COPD treated with long-acting anticholinergics in combination with LABA and inhaled corticosteroids. The manufacturer has announced plans for the REACT study, a 52-week RCT to compare roflumilast with placebo in COPD patients concomitantly treated with fixed combination LABA plus inhaled corticosteroids, with or without long-acting anticholinergics.
- The Committee noted that the statistically significantly lower rate of moderate or severe COPD exacerbations, combined, for roflumilast compared with placebo, was driven by the difference in moderate rather than severe exacerbations. The Committee discussed an exploratory analysis of results from M2-124 and M2-125 by the FDA that suggested the lower rate of moderate or severe COPD exacerbations observed with roflumilast compared with placebo was attenuated between 28 and 36 weeks and disappeared by study end.
- The Committee considered the validity of study findings to be compromised by the high frequency of withdrawals and protocol violations.
- The Committee noted that the trials did not capture data on a number of outcomes important to patients, such as the ability to perform work or daily tasks, and COPD-specific changes in quality of life.
- Given the minimal clinical benefit demonstrated in the reviewed trials, the Committee expressed concern regarding the higher mean weight loss, and greater frequency of neuropsychiatric and suicide-related adverse events observed in patients treated with roflumilast.

CEDAC Members:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. James Silvius.

May 18, 2011 Meeting

Regrets:

None

Conflicts of Interest:

None

July 20, 2011 Meeting

Regrets:

None

Common Drug Review

Common Drug Review

Conflicts of Interest:

None

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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Common Drug Review