Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

ROFLUMILAST
(Daxas – Nycomed Canada Inc.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Daxas, which is also called roflumilast, not be listed by Canada's publicly funded drug plans for the treatment of chronic obstructive pulmonary disease (COPD).

Reasons for the Recommendation:

1. In the two studies that CEDAC reviewed, which included the type of patients for whom Health Canada approved Daxas, there was no real difference between Daxas and placebo (a tablet containing no active medication) in terms of severe COPD exacerbations (worsenings), quality of life, or mortality (death).
2. In the two reviewed studies, differences between Daxas and placebo for the two main outcomes (pre-bronchodilator forced expiratory volume in one second [FEV_1] and the rate of moderate or severe COPD exacerbations) were small.

Of Note:
Neither study compared Daxas with another treatment for COPD, or allowed patients to use long-acting anticholinergics and/or inhaled corticosteroids during the study. Therefore, the results of the studies may not apply to patients with severe COPD.

Background:
Daxas belongs to a class of drugs called phosphodiesterase 4 inhibitors, a type of anti-inflammatory. It works by reducing the activity of phosphodiesterase 4, which results in less inflammation in the lungs. This helps to stop the narrowing of airways that occurs in COPD. Health Canada has approved Daxas to be used in addition 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. It is available as a 500 mcg tablet and the Health Canada-approved dose is 500 mcg daily.

Summary of CEDAC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Daxas and a review of economic information prepared by the manufacturer of Daxas. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated, or who might use the drug.

Clinical Trials
Two studies were included in the review. Studies M2-124 (with 1,523 patients) and M2-125 (with 1,568 patients) compared Daxas 500 mcg daily with placebo; the studies lasted 56 weeks. For the first four weeks, all patients were given placebo. For the next 52 weeks, patients received treatment with Daxas or placebo. Patients in the studies were 40 years of age or older, with severe or very severe COPD (FEV_1 of 50% or less of predicted) associated with chronic bronchitis and a history of exacerbation. Approximately 50% of patients in both studies received long-acting beta agonists (LABA) at the same time. The number of smokers in each treatment group was similar. The use of long-acting anticholinergics and/or inhaled corticosteroids was not allowed during the treatment periods of either study. For the approximately 30% of patients who stopped taking part during the study, any data collected once they left the study were not made available.

There were some problems with the studies; for example, Daxas was not compared with another treatment for COPD. In addition, because the use of long-acting anticholinergics and/or inhaled corticosteroids was not allowed, the studies don't provide evidence about the effectiveness of Daxas when used in combination with these other treatments.

Outcomes
Outcomes of interest were defined in advance 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 side effects, and serious side effects.

Both studies had the same two main purposes: to compare the following between patients taking Daxas and patients taking placebo:
- The average change in FEV_1 (measured before bronchodilator medication), from the start of the study to the end of the study
- The average rate of COPD exacerbations that required patients to take corticosteroids (by either mouth or injection) and/or be hospitalized, or that led to death.

In addition to the above, the manufacturer also looked at the occurrence of moderate and severe exacerbations separately. A moderate COPD exacerbation was one that required corticosteroids (by either mouth or injection). A severe COPD exacerbation was one that resulted in hospitalization and/or led to death.

Results

Efficacy or Effectiveness
- Compared with placebo, Daxas-treated patients had a lower rate of moderate or severe COPD exacerbations in both M2-124 and M2-125; 0.19 and 0.28 fewer COPD exacerbations per patient per year, respectively. In both studies, this was mostly due to fewer moderate COPD exacerbations with Daxas compared with placebo. Severe COPD

exacerbations occurred much less often than moderate exacerbations, and the occurrence of severe COPD exacerbations was about the same for Daxas as for placebo.
- Compared with placebo, Daxas-treated patients had greater increases (improvements) in pre-bronchodilator FEV_1 (in mL), from study start to end of treatment, regardless of whether patients were also using LABA; average differences were 39 mL and 58 mL in studies M2-124 and M2-125, respectively.
- Quality of life, as assessed by the European Quality of Life – 5 Dimension questionnaire (EQ-5D), did not show any significant improvement in patients treated with Daxas compared with placebo. No quality of life measures specific to COPD (e.g., the St. George's Respiratory Questionnaire) were collected in the studies.
- Neither study reported results for total hospitalizations, hospitalizations for COPD, or exercise tolerance.

Harms (Safety and Tolerability)
- There were about the same number of deaths and serious side effects for Daxas and placebo in both studies. However, the long-term safety of Daxas is not certain because no data are currently available from studies lasting longer than one year, and Daxas has not been on the market for very long.
- In both studies, gastrointestinal (bowel) and nervous system disorders were more frequently seen in patients treated with Daxas compared with placebo. The average weight loss was 2.09 kg for Daxas compared with an average weight gain of 0.08 kg for placebo (when data from studies M2-124 and M2-125 were combined).
- Two patients treated with Daxas (compared with none of the patients treated with placebo) had suicide-related side effects; one tried to commit suicide in M2-124 and one did commit suicide in M2-125.

Cost and Cost-Effectiveness
The manufacturer submitted economic information for three comparisons to evaluate the health benefit over five years for patients with severe COPD:
- Daxas plus LABA, versus LABA alone (based on selected patients from studies M2-124 and M2-125, combined)
- Daxas plus tiotropium (also called Spiriva), versus tiotropium alone (based on study M2-128, which included patients with both moderate and severe COPD and which did not meet the criteria to be included in the CDR systematic review)
- Daxas plus tiotropium, versus tiotropium plus the combination of an inhaled corticosteroid and LABA (based on a comparison of study M2-128 and the OPTIMAL study, which also did not meet the criteria to be included in the CDR systematic review).

There were a few problems with the economic information provided by the manufacturer. The manufacturer assumed that Daxas would result in ongoing benefit over the five-year analysis period; however, the observed rate of exacerbations in the studies was similar by week 44 for Daxas plus LABA, versus LABA alone. In addition, no important differences in quality of life were seen in the studies.

At recommended doses, the daily cost of Daxas ($2.10) is the same as tiotropium (Spiriva). Daxas is more expensive than 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.
- Patients' inability to work or perform daily tasks was noted to result in considerable caregiver burden. Patient groups specifically wanted to draw CEDAC's attention to a study of the extent and nature of the burden experienced by caregivers to patients with advanced COPD.
- Patients indicated that they are willing to experience side effects if the treatment allows them better quality of life.

Other Discussion Points:

- The Committee noted that none of the reviewed studies included 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 study to compare Daxas with placebo in COPD patients who are also treated with fixed combination LABA plus inhaled corticosteroids, with or without long-acting anticholinergics.
- The Committee noted that the lower rate of moderate or severe COPD exacerbations with Daxas compared with the rate with placebo was mostly due to fewer moderate rather than severe exacerbations. The Committee discussed a Food and Drug Administration analysis of results from M2-124 and M2-125 that suggested that the difference between Daxas and placebo, in terms of the rate of moderate or severe COPD exacerbations, had grown smaller by weeks 28 to 36, and had disappeared by the end of the study.
- The Committee considered the soundness of the results of the studies to be questionable, given the large amount of patients who stopped participating in the studies and who did not follow the study rules.
- The Committee noted that the studies did not collect 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 improvement for patients in these studies, the Committee expressed concern regarding the higher average weight loss, and more frequent psychiatric side effects and suicide-related side effects seen in patients treated with Daxas.

CEDAC Members Participating:
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

Conflicts of Interest:
None

About this Document
The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC
CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The Committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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The manufacturer has reviewed this document and has not requested the deletion of any confidential information.