CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

BENRALIZUMAB (FASENRA — ASTRAZENECA CANADA INC.)
Indication: Severe Eosinophilic Asthma

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that benralizumab be reimbursed as an add-on maintenance treatment for adult patients with severe eosinophilic asthma, if the following criteria and conditions are met:

Criteria

- Patient is inadequately controlled with high-dose inhaled corticosteroids (ICSs) and one or more additional asthma controller(s) (e.g., long-acting beta agonists [LABAs]), if one of the following two clinical criteria is met:
  - Blood eosinophil count of ≥ 300 cells/μL AND has experienced two or more clinically significant asthma exacerbations in the past 12 months
    OR
  - Blood eosinophil count of ≥ 150 cells/μL AND is treated chronically with oral corticosteroids (OCSs).
- Benralizumab should not be prescribed to patients who smoke.
- Benralizumab should not be used in combination with other biologics used to treat asthma.

Conditions

- Patients should be managed by a physician with expertise in treating asthma.
- Drug plan cost of treatment not to exceed the drug plan cost of the least expensive IL-5 inhibitor reimbursed for the treatment of severe eosinophilic asthma.

Service Line: CADTH Drug Reimbursement Recommendation
Version: Final
Publication Date: August 2018
Report Length: 7 Pages

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

BENRALIZUMAB (FASENRA — ASTRAZENECA CANADA INC.)

Indication: Severe Eosinophilic Asthma

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that benralizumab be reimbursed as an add-on maintenance treatment for adult patients with severe eosinophilic asthma, if the following criteria and conditions are met:

Criteria

- Patient is inadequately controlled with high-dose inhaled corticosteroids (ICSs) and one or more additional asthma controller(s) (e.g., long-acting beta agonists [LABAs]), if one of the following two clinical criteria is met:
    - Blood eosinophil count of ≥ 300 cells/μL AND has experienced two or more clinically significant asthma exacerbations in the past 12 months
      OR
    - Blood eosinophil count of ≥ 150 cells/μL AND is treated chronically with oral corticosteroids (OCSs).
- Benralizumab should not be prescribed to patients who smoke.
- Benralizumab should not be used in combination with other biologics used to treat asthma.

Conditions

- Patients should be managed by a physician with expertise in treating asthma.
- Drug plan cost of treatment not to exceed the drug plan cost of the least expensive interleukin-5 (IL-5) inhibitor reimbursed for the treatment of severe eosinophilic asthma.

Reasons for the Recommendation

1. Two multinational double-blind randomized controlled trials (RCTs), CALIMA (N = 1,306, 56 weeks) and SIROCCO (N = 1,206, 48 weeks) demonstrated that, compared with placebo, benralizumab treatment reduced the annualized exacerbation rate in patients with severe eosinophilic asthma who were not controlled on high-dose ICS + LABA. One double-blind RCT, ZONDA (N = 220; 28 weeks), which enrolled patients with severe asthma who required chronic use (at least six months) of an OCS to maintain asthma control, demonstrated that patients receiving benralizumab experienced a greater reduction in OCS dose than with placebo.
2. No head-to-head trials have been conducted comparing benralizumab with other IL-5 inhibitors in patients with asthma. An indirect comparison (IDC) submitted by the manufacturer suggested that [redacted]
3. At the submitted price of $3,876.92 per syringe, the incremental cost-utility ratio (ICUR) for benralizumab + standard of care (SOC) was $1,534,803 per quality-adjusted life-year (QALY) compared with SOC alone. At this ICUR, it is highly unlikely that benralizumab will be cost-effective at the submitted price for all patients with severe uncontrolled eosinophilic asthma. There is no evidence available that would justify a price premium for benralizumab compared with other biologic agents used to treat severe eosinophilic asthma.

Of Note

- Although CDEC considered developing potential discontinuation criteria, there was no clinical evidence available to inform such criteria.

- CDEC noted that mepolizumab and reslizumab were reviewed previously by CADTH for severe eosinophilic asthma, and that both of these drugs had received CDEC recommendations to reimburse with clinical criteria and/or conditions.

Discussion Points

CDEC discussed the impact of benralizumab on pulmonary function, noting that patients in both CALIMA and SIROCCO experienced statistically significant improvements in forced expiratory volume in one second (FEV_1) with benralizumab versus placebo. FEV_1 was a key, multiplicity-controlled secondary outcome in both studies. The clinical significance of these findings is unclear as there is limited published evidence relating to a minimal clinically important difference for FEV_1 among adult patients with asthma.

Background

Benralizumab is an IL-5 inhibitor, targeting the IL-5 alpha receptor, specifically, and has a Health Canada–approved indication as an add-on maintenance treatment for adult patients with severe eosinophilic asthma. Benralizumab is administered by subcutaneous injection, 30 mg once every four weeks for the first three doses, then once every eight weeks thereafter.

Summary of CDEC Considerations

CDEC considered the following information prepared by CADTH Common Drug Review (CDR): a systematic review of three double-blind randomized controlled trials of benralizumab and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with severe eosinophilic asthma, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

Two patient groups, Asthma Canada and the British Columbia Lung Groups, provided input for this submission. Patient perspectives were obtained from online surveys and patient interviews, as well as a previous study of patient experiences with asthma conducted in Canada. The following is a summary of key input from the perspective of the patient groups:

- Patients with severe eosinophilic asthma described significant impacts on their quality of life, including limitations on almost all daily activities, an inability to sleep, and reduced performance at work or school, and felt stigmatized as a result of their condition.
- In their input to CDR, 38% of patients described inadequate control with their current therapy. The most common side effects noted were weight gain, increased heart rate, and hoarseness. Patients also described the need for multiple daily doses as a limitation of current therapy that affects compliance, as well as the continued need for hospitalizations and physician visits. Patients also cited cost as a barrier to current therapies.
- Patients who had experience with benralizumab describe improved efficacy and reduced side effects with this new therapy. Patients specifically noted enhanced symptom control, reduced exacerbations, and the subsequent reduction in hospitalizations as advantages of benralizumab.

Clinical Trials

The systematic review included three multinational double-blind randomized placebo-controlled trials of patients with poor asthma control (CALIMA, N = 1,306 over 56 weeks, and SIROCCO, N = 1,206, over 48 weeks) or patients with poor asthma control despite chronic OCS use (ZONDA, N = 220 over 28 weeks). Patients in CALIMA were required to be on at least a medium dose of an ICS (≥ 500 mcg fluticasone propionate dry powder equivalent) plus a LABA. In SIROCCO, all patients had to be on a high-dose ICS (> 500 mcg fluticasone propionate dry powder equivalent) plus a LABA. In ZONDA, patients had to have continuous treatment with an oral corticosteroid (between 7.5 mg and 40 mg of prednisone daily) as well as documented treatment with a high-dose ICS for at least six continuous months preceding visit 1.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following: annualized asthma exacerbation rate, exacerbations resulting in hospitalization or emergency room (ER) visits, asthma symptom scores, per cent reduction in oral corticosteroid dose, and change in FEV_1.

- The annualized exacerbation rate was calculated as 365.25 multiplied by the total number of exacerbations divided by total number of days of follow-up. An asthma exacerbation was defined as a worsening of asthma requiring:
    - "Use of systemic corticosteroids (or a temporary increase in a stable OCS background dose) for at least three days (a single depo-injectable dose of corticosteroids was considered equivalent to a three-day course of systemic corticosteroids)"
    - "An emergency department/urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per above)"
    - "An inpatient hospitalization due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a health care facility for ≥ 24 hours)."
- Asthma symptom scores were assessed using an asthma daily diary, which was filled out twice daily. This is a four-point response scale, from zero ("no symptoms") to 3 ("unable to sleep/perform normal activities") due to asthma. No minimum clinically important difference could be found for the total asthma symptom score.
- Per cent reduction in oral corticosteroid dose was the percentage reduction in final OCS dose compared with baseline while asthma is under control.
- FEV_1 is the amount of air that can be forcibly exhaled from the lungs in one second. The minimal patient perceivable improvement for FEV_1 is 230 mL.

The primary outcome in CALIMA and SIROCCO was the annualized exacerbation rate while the primary outcome in ZONDA was per cent reduction in OCS dose.

Efficacy

The primary analysis in CALIMA and SIROCCO focused on the population with eosinophils ≥ 300 cells/µL and on a high-dose ICS.

The primary outcome of both CALIMA and SIROCCO was the annualized relapse rate, and benralizumab was superior to placebo for this outcome after 56 weeks in CALIMA (rate ratio of 0.72; 95% confidence interval [CI], 0.54 to 0.95; *P* = 0.019) and after 48 weeks in SIROCCO (rate ratio of 0.49; 95% CI, 0.37 to 0.64; *P* < 0.001). The rate ratio was also lower for benralizumab than placebo in ZONDA, but this analysis was not adjusted for multiple comparisons (rate ratio over 28 weeks in ZONDA was 0.30 (95% CI, 0.17 to 0.53; *P* <0.001).

The primary outcome in ZONDA was the median per cent reduction in OCS dose, and benralizumab was superior to placebo for this outcome after 28 weeks, with an estimate for median treatment difference between groups of 37.5% (95% CI, 20.8% to 50.0%; *P* <0.001). The percentage of patients able to reduce their dose by different percentages (25%, 50%, 75%, and 100%) was also reported. A total of 30% of patients treated with benralizumab and 11% of patients treated with placebo were able to reduce their dose by 100%.

Pre-bronchodilator change from baseline in FEV_1 was an outcome that was controlled for multiplicity in CALIMA and SIROCCO. In both studies FEV_1 was improved versus placebo, and these differences were statistically significant in CALIMA (least squares mean difference [LSMD] of 0.116 litres; 95% CI, 0.028 to 0.204; *P* = 0.010) and in SIROCCO (0.159 litres; 95% CI, 0.068 to 0.249; *P* = 0.001).

The change from baseline in total asthma symptom score was a key secondary outcome in both CALIMA and SIROCCO, and it was controlled for multiple comparisons. The score was reduced (improved) for benralizumab versus placebo in both studies and these differences were statistically significant in both CALIMA (LSMD of −0.23; 95% CI, −0.43 to −0.04; *P* = 0.019) and SIROCCO (−0.25; 95% CI, −0.45 to −0.06; *P* = 0.012). The six-question Asthma Control Questionnaire (ACQ-6) was also used to assess symptoms in

both CALIMA and SIROCCO. Total ACQ-6 results decreased (improved) from baseline for benralizumab versus placebo in both CALIMA (LSMD of −0.25; 95% CI, −0.44 to −0.07; *P* = 0.008) and SIROCCO (LSMD of −0.29; 95% CI, −0.48 to −0.10; *P* = 0.003).

Harms (Safety and Tolerability)

The percentage of patients with a serious adverse event was 14% in each group after 48 weeks in SIROCCO, 10% of benralizumab and 14% of placebo patients after 56 weeks in CALIMA, and 10% of benralizumab patients and 19% of placebo patients in ZONDA after 28 weeks had a serious adverse event.

Withdrawals due to an adverse event occurred in 2% of benralizumab patients versus 1% of placebo patients in CALIMA and in SIROCCO, and in 4% of benralizumab versus 3% of placebo patients in ZONDA.

Upper respiratory tract infections occurred in benralizumab and placebo patients in each of the three studies (CALIMA: 9% benralizumab versus 10% placebo; SIROCCO: 8% benralizumab versus 9% placebo; ZONDA: 7% in each group).

Indirect Treatment Comparisons

The manufacturer submitted an IDC that was reviewed and critically appraised by CDR. The objective of the IDC was to compare benralizumab with other monoclonal antibodies in patients with severe uncontrolled asthma. The network meta-analysis included [redacted] studies; however, only [redacted] were included in the matched-adjusted indirect comparison: [redacted]

Cost and Cost-Effectiveness

Benralizumab is available as a solution for subcutaneous injection in a 30 mg/mL syringe. The submitted price of benralizumab is $3,876.92 per syringe. At the recommended dose of 30 mg administered once every four weeks for the first three doses, and then once every eight weeks thereafter, the annual cost is $31,015 in year 1 and $25,200 in subsequent years.

The manufacturer submitted a cost-utility analysis that assessed benralizumab in addition to SOC: high-dose ICS + LABA ± OCS) in adult patients with severe uncontrolled eosinophilic asthma over a 50-year (lifetime) time horizon from the perspective of the Canadian health care payer. The manufacturer presented four base-case analyses based on two distinct severe uncontrolled eosinophilic asthma patient populations: one looked at a mix of patients with chronic or no chronic OCS use based on the SIROCCO and CALIMA trials, and the other looked at patients receiving OCS chronically (based on the ZONDA trial). Three pairwise analyses were presented assessing benralizumab + SOC compared individually with mepolizumab + SOC, omalizumab + SOC, and SOC alone in the mixed population, and the fourth analysis assessed benralizumab + SOC compared with SOC alone in a chronic OCS-user population. The Markov model included four health states: day-to-day asthma receiving a biologic + SOC, day-to-day asthma receiving SOC alone, a general exacerbation health state (incorporating OCS burst treatment, ER visit, or hospital admission), and mortality (including increased mortality for exacerbations requiring ER or hospital visit). Data from three clinical trials of benralizumab were used to inform the efficacy and safety of benralizumab + SOC compared with SOC alone. Data from two separate matched-adjusted indirect comparisons were used to inform the comparison of benralizumab with mepolizumab, and with omalizumab. Health state utility values were derived from the clinical trials. The manufacturer reported that for the combined chronic/non-chronic OCS use population, the ICURs for benralizumab + SOC were: $201,172 per QALY compared with SOC alone; $19,865 per QALY compared with mepolizumab + SOC; and $40,241 per QALY compared with omalizumab + SOC. For the chronic OCS use population, the ICUR for benralizumab + SOC compared with SOC alone was $42,223 per QALY.

CDR identified several key limitations with the submitted analysis:

- The proportion of patients with chronic OCS in the mixed population was assumed to be higher in the model (21%) than expected in Canadian practice. Additionally, the manufacturer assumed patients requiring acute OCS therapy had the same response to therapy as patients on chronic daily OCS treatment.

- The manufacturer assumed a survival benefit with benralizumab based on a reduction in exacerbations necessitating an ER visit or hospital admission. This survival benefit has not been demonstrated in clinical trials and is likely to overestimate the benefit of benralizumab.
- The definition of response used in the economic model may not be aligned with the definition in CDR-participating drug plans. Further, it is not clear that all patients who do not achieve response (i.e., “non-response”) would stop treatment with benralizumab.
- The utility values for the day-to-day asthma health states in the model were assumed to differ between treatments. Increased utility for responders to biologic treatment may overestimate treatment benefit.
- The relative safety and efficacy of benralizumab compared with other biologics is uncertain.

The lack of comparative clinical information to allow a sequential analysis that compared benralizumab, SOC, mepolizumab, and omalizumab, in addition to the limitations of the submitted model structure, limited the reanalyses that CDR was able to undertake. CDR reanalyses considered the following revisions: 5% chronic OCS use in the mixed analysis (based on clinical expert feedback); the same baseline utility values between treatment groups in the day-to-day asthma health states; and no difference in mortality between comparators.

In the CDR base case, the ICUR for benralizumab + SOC was $1,534,803 per QALY compared with SOC alone. A price reduction of more than 95% for benralizumab is required to reduce the ICUR to $50,000 per QALY. When considering the population on chronic OCS use, CDR reanalysis indicated an ICUR of $62,209 per QALY; a 15% price reduction is required to achieve an ICUR of $50,000 per QALY. The comparison of benralizumab with other biologics used in asthma was hindered by differences in indication (particularly versus omalizumab) and by the lack of head-to-head trials. CDR clinical reviewers identified several limitations with the submitted IDC. When assuming similar safety and efficacy, benralizumab was more costly than mepolizumab and omalizumab, as the drug acquisition cost of benralizumab is higher than the other two biologics. The price of benralizumab would need to be reduced by 4% to be less costly than mepolizumab and 7% to be less costly than omalizumab (or 1 to 3% with administration costs) based on the modelled treatment costs and current public prices for these comparators.

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

July 18, 2018 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None