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 recommends that benralizumab be reimbursed as an add-on maintenance treatment for adult patients with severe eosinophilic asthma, if the following conditions are met:

Conditions for Reimbursement
Initiation Criteria
1. Patient must have a documented diagnosis of asthma.
2. Patient is inadequately controlled with high-dose inhaled corticosteroids, defined as greater or equal to 500 mcg of fluticasone propionate or equivalent daily, and one or more additional asthma controller(s) (e.g., long-acting beta agonists).
3. Patient has one of the following:
    3.1. blood eosinophil count of ≥ 300 cells/μL within the past 12 months AND has experienced two or more clinically significant asthma exacerbations in the past 12 months, or
    3.2. blood eosinophil count of ≥ 150 cells/μL AND is receiving maintenance treatment with oral corticosteroids (OCS).

Administration Criteria
1. Benralizumab should not be used in combination with other biologics used to treat asthma.
2. A baseline assessment of asthma symptom control using a validated asthma control questionnaire must be completed prior to initiation of benralizumab treatment.
3. Patients should be managed by a physician with expertise in treating asthma.

Renewal Criteria
1. The effects of treatment should be assessed every12 months to determine whether reimbursement should continue.
2. Reimbursement of treatment should be discontinued if:
    2.1. the 12 month asthma control questionnaire score has not improved from baseline, when baseline represents the initiation of treatment, or
    2.2. the asthma control questionnaire score achieved after the first 12 months of therapy has not been maintained subsequently, or
    2.3. the number of clinically significant exacerbations has increased within the previous 12 months, or
    2.4. in patients on maintenance treatment with OCS, there has been no decrease in the OCS dose in the first 12 months of treatment, or
    2.5. in patients on maintenance treatment with OCS, the reduction in the dose of OCS achieved after the first 12 months of treatment is not maintained subsequently.

Pricing Conditions
1. Price reduction resulting in a drug plan cost that would be considered cost-effective.
2. The cost of benralizumab should not exceed the drug plan cost of other interleukin-5 inhibitors.

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Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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CADTH

BENRALIZUMAB (FASENRA — ASTRAZENECA CANADA INC.)

Indication: Severe eosinophilic asthma.

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated August 21, 2018.

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 conditions are met:

Conditions for Reimbursement

Initiation Criteria

1. Patient must have a documented diagnosis of asthma.
2. Patient is inadequately controlled with high-dose inhaled corticosteroids (ICS), defined as greater or equal to 500 mcg of fluticasone propionate or equivalent daily, and one or more additional asthma controller(s) (e.g., long-acting beta agonists [LABAs]).
3. Patient has one of the following:
   - 3.1. blood eosinophil count of ≥ 300 cells/μL within the past 12 months AND has experienced two or more clinically significant asthma exacerbations in the past 12 months, or
   - 3.2. blood eosinophil count of ≥ 150 cells/μL AND is receiving maintenance treatment with oral corticosteroids (OCS).

Administration Criteria

1. Benralizumab should not be used in combination with other biologics used to treat asthma.
2. A baseline assessment of asthma symptom control using a validated asthma control questionnaire must be completed prior to initiation of benralizumab treatment.
3. Patients should be managed by a physician with expertise in treating asthma.

Renewal Criteria

1. The effects of treatment should be assessed every 12 months to determine whether reimbursement should continue.
2. Reimbursement of treatment should be assessed using the same asthma control questionnaire used at baseline and should be discontinued if:
   - 2.1. the 12 month asthma control questionnaire score has not improved from baseline, when baseline represents the initiation of treatment, or
   - 2.2. the asthma control questionnaire score achieved after the first 12 months of therapy has not been maintained subsequently, or
   - 2.3. the number of clinically significant asthma exacerbations has increased within the previous 12 months, or
   - 2.4. in patients on maintenance treatment with OCS, there has been no decrease in the OCS dose in the first 12 months of treatment, or
   - 2.5. in patients on maintenance treatment with OCS, the reduction in the dose of OCS achieved after the first 12 months of treatment is not maintained or improved subsequently.

Pricing Conditions

1. Price reduction resulting in a drug plan cost that would be considered cost-effective.
2. The cost of benralizumab should not exceed the drug plan cost of other interleukin-5 (IL-5) inhibitors.

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 plus LABA. One double-blind RCT, ZONDA (N = 220; 28 weeks), which enrolled patients with severe eosinophilic 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 eosinophilic asthma. An indirect treatment comparison (ITC) submitted by the manufacturer suggested that benralizumab is as effective and as safe as mepolizumab [redacted], but the comparative efficacy of benralizumab versus reslizumab is unknown.
3. At the submitted price of $3,876.92 per syringe, the incremental cost-utility ratio (ICUR) for benralizumab plus 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 drugs used to treat severe eosinophilic asthma.

Implementation Considerations

- A diagnosis of asthma may be defined by the following: spirometry showing excessive variability in lung function and airflow limitation or spirometry showing reversible airway obstruction. Alternatives include peak expiratory flow variability or a positive challenge test (such as a methacholine or exercise challenge).
- Clinically significant asthma exacerbations are defined as worsening of asthma resulting in administration of systemic corticosteroids for at least three days, or hospitalization.
- A validated asthma control questionnaire includes the Asthma Control Questionnaire (ACQ) or the Asthma Control Test (ACT). The same questionnaire must be used at each assessment for reimbursement renewal as was used at the start of treatment. Scores demonstrating a benefit of treatment for renewal of reimbursement are:
  - a decrease of 0.5 points or more on the ACQ, or
  - an increase of three or more points in the ACT.
- Maintenance OCS treatment is defined as receiving greater than the equivalent of prednisone 5 mg per day.
- CDEC could not provide a recommendation for sequencing of benralizumab relative to other IL-5 inhibitors because of limited evidence regarding the comparative efficacy of the various IL-5 inhibitors and the effectiveness of different sequencing options. Similarly, CDEC cannot recommend that a different IL-5 inhibitor be used to treat patients who have failed treatment with benralizumab due to a lack of evidence regarding the effectiveness in this type of population.

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.
- CDEC noted that the benralizumab trial eligibility criteria related to peripheral eosinophil counts are notably different from those for reslizumab, but relatively similar to those for mepolizumab; the differences in eosinophil counts are also reflected in the Health Canada indications for the IL-5 inhibitors. Therefore, alignment of the eosinophil count condition between benralizumab and mepolizumab was considered reasonable, but not between benralizumab and reslizumab.
- All three benralizumab studies required evidence of reversibility on spirometry as an inclusion criterion, similar to the pivotal studies for other IL-5 inhibitors. CDEC heard clinician expert input that the reversibility criterion is a historical trial requirement. The expert also indicated that while reversibility is still used in Canadian practice to initially diagnose patients with asthma, reversibility is not necessarily sensitive enough to be used as a routine assessment of response to asthma therapies, and the

degree to which a patient's asthma is controlled. Some chronic patients also have irreversible airway obstruction that limits the effectiveness of the aforementioned investigation.

- Current smokers were excluded from the benralizumab studies, which is consistent with the pivotal studies for other IL-5 inhibitors. However, CDEC heard clinician expert input that current practice would not exclude treatments from patients with asthma who smoke and who require additional therapies to gain control of their disease.
- CDEC discussed and heard clinician expert input that assessment of asthma control has evolved and that several instruments, such as the ACQ and ACT, are valid, reliable, and practical means of assessing control. Change from baseline in the ACQ (specifically the ACQ-6) was a secondary outcome in all three benralizumab pivotal studies; ACT was not a pre-specified outcome measure in the studies but has been demonstrated to be well correlated with the ACQ. CDEC noted that the Canadian Thoracic Society recommends that poorly controlled asthma symptoms may be defined using standardized questionnaires, such as the ACQ and ACT.
- CDEC noted that no sub-adult patients were included in any of the included trials of benralizumab and that the Health Canada indication limits the treating population to adults.

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.

Submission History

In August 2018, CDEC recommended 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 ICSs and one or more additional asthma controller(s) (e.g., 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 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 should not to exceed the drug plan cost of the least expensive IL-5 inhibitor reimbursed for the treatment of severe eosinophilic asthma.

The CADTH CDR-participating drug plans submitted a request for advice to ask CDEC if the recommendation for benralizumab should be updated to align with the CDEC recommendations for the other available IL-5 inhibitors, mepolizumab and reslizumab. The drug plans asked the following three questions:

- Should the clinical criteria in the CDEC recommendations for mepolizumab and/or reslizumab be updated to align with those that were specified in the more recent CDEC recommendation for benralizumab?
- If the clinical criteria in the benralizumab recommendation should not be applied to the recommendations for mepolizumab and reslizumab, would it be appropriate for CDEC to establish new clinical criteria that are aligned for all three products?
- If aligned criteria would not be appropriate for benralizumab, mepolizumab, and reslizumab, could CDEC provide the rationale why different criteria are required for these drugs? Specifically, for mepolizumab and reslizumab, is it appropriate to have to demonstrate reversibility (at least 12% and 200 mL) on pulmonary function tests (i.e., spirometry) as a clinical criterion for eligibility?

Summary of Evidence Considered by CDEC for the Request for Advice

CDEC considered the following to address the request for advice:

- materials included in the CDEC brief for the 2017 CADTH Common Drug Review (CDR) review of benralizumab
- input from two patient groups that described the impact of severe eosinophilic asthma and expectations from therapies
- the 2017 CDEC recommendation for benralizumab
- the CDEC recommendations for mepolizumab (Nucala) and reslizumab (Cinqair)
- the CDR request for advice review report, which included a detailed comparison of the studies included in each of the CDR reviews for mepolizumab, reslizumab, and benralizumab with respect to eligibility criteria and patient baseline characteristics, as well as a comparison of the place in therapy section for each drug.

Summary of Patient Input

Two patient groups, the Ontario Lung Association and Asthma Canada, provided input for this submission. Patient perspectives were obtained from phone interviews, online surveys, and through consultation with a Medical Advisory Committee. The following is a summary of key input from the perspective of the patient groups:

- The symptoms and challenges that patients experience as a result of asthma are shortness of breath, fatigue, coughing (with or without mucus), wheezing, difficulty fighting infections, and weight loss.
- Patients indicated that asthma greatly impacts their physical and leisure activities, and to a lesser extent, their work, ability to travel, and ability to socialize.
- Patients indicated that while current treatments do provide some relief for fatigue, shortness of breath, cough, low energy, poor appetite, and the inability to fight infection for many patients, a significant number of patients fail to achieve an optimum response and are continuing to seek more effective options that would provide an improved quality of life and improved lung function.
- One of the patient groups support the alignment of CDEC recommendation conditions for mepolizumab, reslizumab, and benralizumab, and views this as an opportunity to address problematic issues such the reversibility criteria (to be removed from the clinical criteria), the age indication (to include as broad an age range as possible), and patchwork access across the provinces.

Comparison of CDEC Recommendations

The CDEC recommendations for mepolizumab, reslizumab, and benralizumab similarly specified reimbursement of each drug as add-on maintenance treatment for adult patients with severe eosinophilic asthma inadequately controlled with ICS and one or more additional asthma controller(s). The recommendation for reslizumab indicated that patients had to be inadequately controlled with medium- to high-dose ICS, whereas the recommendations for mepolizumab and benralizumab specified inadequately controlled with high-dose ICS.

Blood eosinophil count was one of the more heterogeneous criteria across the CDEC recommendations for mepolizumab, reslizumab, and benralizumab because different blood eosinophil count levels were used in the pivotal studies for the three IL-5 inhibitors. Patients had to have blood eosinophil counts equal to or greater than 400 cells/µL at treatment initiation in the recommendation for reslizumab. Patients had to have blood eosinophil counts equal to or greater than 300 cells/µL and had experienced two or more clinically significant asthma exacerbations in the past 12 months, or have eosinophil counts equal to or greater than 150 cells/µL at initiation and receiving chronic OCS treatment in the recommendation for benralizumab. In the recommendation for mepolizumab, patients were required to have a blood eosinophil count of equal to or greater than 150 cells/µL at initiation of treatment with mepolizumab, or a count equal to or greater than 300 cells/µL in the past 12 months. Daily OCS treatment was required for treatment initiation in the mepolizumab recommendation; no condition regarding OCS use was specified in the reslizumab recommendation.

The CDEC recommendations for mepolizumab and benralizumab were also similar with respect to the number of clinically significant asthma exacerbations occurring in the 12 months before treatment initiation (two or more) and neither required that asthma control

be assessed using a questionnaire such as the ACQ. The reslizumab recommendation indicated one or more exacerbations in the 12 months before starting treatment was required, as well as the need to have an ACQ-7 score greater than or equal to 1.5 points.

Post-bronchodilator reversibility (12% or 200 mL) on spirometry was required for reimbursement in the mepolizumab and reslizumab CDEC recommendations, but not in the one for benralizumab.

Patients could not be current smokers at the time of initiating treatment with benralizumab, but this was not a condition in the mepolizumab and reslizumab recommendations. In addition, CDEC specified that reslizumab and benralizumab could not be used in combination with other biologics for the treatment of asthma, but did not include this condition in the recommendation for mepolizumab, which was the first IL-5 inhibitor for the treatment of severe eosinophilic asthma reviewed by CDR and issued a CDEC recommendation.

All three CDEC recommendations included a condition that patients be managed by physicians with expertise in treating asthma.

Comparison of Interleukin-5 Inhibitor Study Characteristics

The CDR request for advice report compared the eligibility criteria, patient baseline characteristics and the magnitude of benefits and risks of the included studies in each of the CDR reviews for mepolizumab, reslizumab, and benralizumab. This information was instrumental in understanding the evidence base and identifying the clinical similarities between mepolizumab, reslizumab, and benralizumab.

Three double-blind RCTs (CALIMA, SIROCCO, and ZONDA) were included in the CDR clinical review for benralizumab. CALIMA and SIROCCO enrolled patients with severe eosinophilic asthma who were not controlled on high-dose ICS/LABA combinations. ZONDA enrolled patients with severe eosinophilic asthma who required chronic use (for at least six months) of an OCS to maintain asthma control.

Two double-blind RCTs (MENSA and SIRIUS) were included in the CDR clinical review for mepolizumab. MENSA enrolled patients with severe eosinophilic asthma who were on high-dose ICS and one or more additional asthma controller(s). SIRIUS enrolled patients who were on high-dose ICS and one or more additional asthma controller(s), and who were taking OCS at a dose of 5 mg per day to 35 mg per day.

Four double-blind RCTs were included in the CDR clinical review for reslizumab: two identical pivotal trials (Study 3082 and Study 3083) and two supporting trials (Study 3081 and Study 3084). Studies 3082 and 3083 enrolled patients who were on medium- to high-dose ICS with or without additional asthma controller(s) and had an elevated blood eosinophil level (i.e., ≥ 400 cells/μL).

The inclusion criteria were similar between the SIROCCO and CALIMA (benralizumab) trials and the MENSA (mepolizumab) trial in the following criteria: age, the number of documented asthma exacerbations in the previous 12 months, pre-bronchodilator FEV_1 criteria, and post-bronchodilator reversibility in FEV_1 criteria. The three trials were similar in that they excluded patients who had clinically important pulmonary disease other than asthma, were current smokers or former smokers with a smoking history of at least 10 pack years, had received any marketed (e.g., omalizumab) or investigational biologic drugs within four months (SIROCCO and CALIMA trials) or 130 days (MENSA trial), and had a previous history of cancer in remission for less than 12 months. Studies included in the CDR clinical review for reslizumab were similar in their inclusion criteria to the MENSA, SIROCCO, and CALIMA trials in terms of age and airway reversibility of at least 12%. The reslizumab trials were similar to the others in that they excluded patients who had clinically important pulmonary disease other than asthma and current smokers. Trials included in the CDR clinical review for reslizumab were also similar in their inclusion criteria to the SIROCCO and CALIMA trials as they required patients to have an ACQ score of at least 1.5 (ACQ-7 was used in trials included in the CDR clinical review for reslizumab, while ACQ-6 was used in SIROCCO and CALIMA).

The inclusion criteria were similar between ZONDA (benralizumab) and SIRIUS (mepolizumab) for the following criteria: peripheral blood eosinophil count of ≥ 150 cells/μL at visit 1; OCS use (chronic OCS therapy for at least six continuous months directly preceding visit 1 in ZONDA versus patients with maintenance systemic corticosteroids in the six months prior to visit 1 in SIRIUS), pre-bronchodilator FEV_1 of < 80% predicted; evidence of asthma as documented by either airway reversibility, documented reversibility, airway hyper-responsiveness, or airflow variability. As for the exclusion criteria, the three trials were similar in excluding

patients who had clinically important pulmonary disease other than asthma, were current smokers or former smokers with a smoking history of at least 10 pack years, and had received any marketed (e.g., omalizumab) or investigational biologic within four months (ZONDA trial) or 130 days (SIRIUS trial).

Patients enrolled in the studies for benralizumab and reslizumab appeared to be receiving high-dose ICS (mean ICS total daily dose > 500 mcg fluticasone propionate equivalent) at baseline, although based on the distributions of daily doses, a certain proportion of patients included into the reslizumab studies were receiving medium doses of ICS. The mepolizumab study, MENSA, did not report the distribution of daily ICS doses at baseline, only that 100% of patients were receiving high-dose ICS based on the inclusion criteria.

Baseline mean eosinophil levels ranged from 590 cells/μL to 710 cells/μL in three of the four reslizumab studies (280 cells/μL in Study 3084) and from 480 cells/μL to 490 cells/μL in the benralizumab CALIMA and SIROCCO studies. The mean baseline eosinophil levels were not reported for MENSA.

Baseline exacerbation history within the previous 12 months varied across the studies for mepolizumab, reslizumab, and benralizumab; however, the mean number of exacerbations in two of the four reslizumab studies (data were not reported for Study 3081 and Study 3084) and SIROCCO and CALIMA (benralizumab trials) was approximately two or greater. The mean number of exacerbations before randomization was not reported in MENSA (mepolizumab), but more than half of patients randomized had had three or more asthma exacerbations in the previous 12 months.

More patients in MENSA (mepolizumab) were taking OCS at baseline in comparison with patients in CALIMA and SIROCCO (benralizumab; 30% versus 13%, respectively). Patients in MENSA were identified as taking OCS at baseline as maintenance therapy, but it is unclear whether patients in CALIMA and SIROCCO were receiving OCS on a persistent basis when baseline assessments were performed. Approximately 15% of patients in reslizumab studies 3082 and 3083 were OCS dependent. Systemic corticosteroid use within 30 days before enrolment was an exclusion criterion for the other two reslizumab studies.

The OCS-sparing studies for benralizumab (ZONDA) and mepolizumab (SIRIUS) were generally similar with respect to baseline characteristics; differences were that ZONDA included patients with higher mean eosinophil counts at baseline compared with SIRIUS (583 cells/μL versus 380 cells/μL, respectively) and the proportion of never smokers (80.4% versus 60.5%, respectively). No OCS-sparing studies were conducted for reslizumab.

Summary of Evidence Considered by CDEC for the Original Recommendation

CDEC considered the following information prepared by CDR: a systematic review of three double-blind RCTs 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. They also 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 described 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 "
  - "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 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 per cent reduction in OCS dose, and benralizumab was superior to placebo for this outcome after 28 weeks, with an estimate for 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 (LSMD of −0.25; 95% CI, −0.45 to −0.06; *P* = 0.012). The six-question 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 (AE) was 14% in each group after 48 weeks in SIROCCO, 10% of patients receiving benralizumab and 14% of patients receiving placebo after 56 weeks in CALIMA, and 10% of patients receiving benralizumab and 19% of patients receiving placebo in ZONDA after 28 weeks had a serious AE.

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

Upper respiratory tract infections occurred in patients receiving benralizumab and placebo 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 ITC that was reviewed and critically appraised by CDR. The objective of the ITC 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] Overall the ITC did not find statistically significant differences in efficacy between benralizumab and mepolizumab for annual rate of clinically significant exacerbations, annual rate of exacerbations resulting in ER visits or hospitalizations, and change from baseline in FEV_1. [redacted] A comparison versus reslizumab could not be performed.

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 plus 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 plus SOC compared individually with mepolizumab plus SOC, omalizumab plus SOC, and SOC alone in the mixed population, and the fourth analysis assessed benralizumab plus 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 plus 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 plus 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 plus SOC were: $201,172 per QALY compared with SOC alone; $19,865 per QALY compared with mepolizumab plus SOC; and $40,241 per QALY compared with omalizumab plus SOC. For the chronic OCS use population, the ICUR for benralizumab plus 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 plus 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 chronic OCS use population, 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 ITC. 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.

Request for Clarification

The drug plans that participate in the CDR process filed a request for clarification during the embargo period for the CDEC revised recommendation of benralizumab. The drug plans asked CDEC to consider all options for the potential alignment of the recommendations for mepolizumab, reslizumab, and benralizumab. The CDEC Recommendation report outlines the various comparisons that were made and for which criteria the committee was able to align the recommendations for the three IL-5 inhibitors.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 16, 2019 Meeting (Initial)

Regrets

None

Conflicts of Interest

None

March 20, 2019 Meeting (Reconsideration and Clarification)

Regrets

None

Conflicts of Interest

None