CADTH

CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**RESLIZUMAB (CINQAIR — TEVA CANADA INNOVATION)**
Indication: Severe eosinophilic asthma

**RECOMMENDATION**
The CADTH Canadian Drug Expert Committee recommends that reslizumab 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 a blood eosinophil count of ≥ 400 cells/μL in the past 12 months.
4. Patient has experienced two or more clinically significant asthma exacerbations in the past 12 months.

**Administration Criteria**
1. Reslizumab 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 reslizumab 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 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.

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


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# RESLIZUMAB (CINQAIR — TEVA CANADA INNOVATION)

Indication: Severe eosinophilic asthma.

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated March 22, 2017.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that reslizumab 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 (ICSs), 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 a blood eosinophil count of ≥ 400 cells/µL in the past 12 months.
4. Patient has experienced two or more clinically significant asthma exacerbations in the past 12 months.

**Administration Criteria**

1. Reslizumab 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 reslizumab 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 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.

**Pricing Conditions**

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

## Reasons for the Recommendation

1. Four phase III, double-blind, randomized placebo-controlled trials provided evidence for the efficacy and safety of reslizumab: two identical 52-week pivotal trials (studies 3082 [N = 489] and 3083 [N = 464]) and two supporting 16-week trials (studies 3081 [N = 315] and 3084 [N = 492]). In studies 3082 and 3083, reslizumab was associated with a statistically significant reduction in the rate of clinically significant asthma exacerbations compared with placebo at 52 weeks in patients currently on medium- to high-dose ICS with or without additional asthma controller(s) along with an elevated blood eosinophil level (i.e., ≥ 400 cells/µL). The adjusted rate ratios were 0.50 (95% confidence interval [CI], 0.37 to 0.67) in Study 3082 and 0.41 (95% CI, 0.28 to 0.59) in

Study 3083 for reslizumab versus placebo. However, the clinical significance was unclear for the differences observed in health-related quality of life, asthma symptoms, and pulmonary function in the pivotal trials.

2. The manufacturer submitted a network meta-analysis (NMA) to evaluate the relative efficacy of reslizumab [redacted]

3. At the submitted price of $640.00 per 10 mg/mL vial, the CADTH Common Drug Review (CDR) estimated that reslizumab plus standard of care (SOC) is associated with an incremental cost-effectiveness ratio (ICER) of $888,000 to $1,200,000 per quality-adjusted life-year (QALY) compared with SOC alone in the treatment of adults with severe eosinophilic asthma; therefore, reslizumab is not considered to be cost-effective at the submitted price.

## 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 the worsening of asthma symptoms resulting in administration of systemic corticosteroids for at least three days, or hospitalization due to uncontrolled asthma.
- A validated asthma control questionnaire includes the Asthma Control Questionnaire (ACQ) or the Asthma Control Test (ACT). The same questionnaire must be used at the time of assessment for reimbursement renewal as was used at the start of treatment. Scores demonstrating a benefit of treatment for renewal of reimbursement after the initial 12 months of use are:
  - a decrease of 0.5 points or more on the ACQ, or
  - an increase of three or more points on the ACT.
- CDEC could not provide a recommendation for sequencing of reslizumab 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 reslizumab, due to a lack of evidence regarding the effectiveness in this type of population.
- There is no evidence available that would justify a price premium for reslizumab compared with other biologic drugs used to treat severe eosinophilic asthma.
- For the comparison of reslizumab plus SOC with SOC alone, CDEC noted that a price reduction of 95% is required to achieve an ICER of $50,000 per QALY, and 89% to achieve an ICER of $100,000 per QALY.
- CDEC noted there may be a subset of patients with difficult-to-treat asthma for whom reslizumab may be more favourable from a cost-effectiveness perspective, but the clinical evidence did not identify this potential subgroup.

## Discussion Points

- The Health Canada indication for reslizumab includes patients with moderate disease. CDEC noted that in Canadian clinical practice, reslizumab, like other available biologics for the treatment of eosinophilic asthma, would be reserved for patients with difficult-to-treat disease (i.e., severe asthma requiring high-dose ICS and an additional controller[s]). Mean ICS total daily doses for the reslizumab randomized controlled trials (RCTs) were greater than 640 mcg fluticasone propionate equivalent, indicating most patients received high-dose ICS. Patients enrolled in the RCTs for mepolizumab and benralizumab were receiving high-dose ICS at baseline.
- The improvement in pulmonary function and patient-reported outcomes (e.g., ACQ-7 ≥ 2.5 points) from baseline in the placebo groups in the two reslizumab pivotal trials suggests that these patients may have been under-treated with conventional ICS and a second controller.
- CDEC noted that the reslizumab trial eligibility criteria related to peripheral eosinophil counts are notably different from those for mepolizumab and benralizumab; 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 reslizumab and the other two currently available IL-5 inhibitors (mepolizumab and benralizumab) is not recommended.

- The inclusion criteria for studies 3082 and 3083 stated that patients needed at least one asthma exacerbation that required systemic corticosteroids (for three days or more) in the past 12 months to be eligible. The median number of exacerbations at baseline for both studies was one; however, the number of exacerbations ranged from one to 12 exacerbations at baseline in the treatment groups, except Study 3082 which had a range of 1 to 20 exacerbations at baseline in the placebo group. Baseline exacerbation numbers were not reported for Study 3081 and Study 3084. CDEC heard clinician expert input that a single exacerbation in 12 months may not in itself confirm diminished asthma control as events are influenced by seasonal effects and environmental exposures that put patients at risk for an exacerbation. Moreover, the Canadian Thoracic Society includes frequent severe exacerbations (defined as two or more courses of systemic corticosteroids in the previous year) as part of its definition of uncontrolled severe asthma. The Global Initiative for Asthma guidelines present similar definitions for severe and uncontrolled asthma.
- All four reslizumab 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.
- CDEC noted that, unlike for mepolizumab and benralizumab, no corticosteroid sparing studies were conducted for reslizumab. Approximately 15% of patients were OCS dependent in Study 3082 and Study 3083. Subgroup analyses conducted on these patients were not defined in the individual study protocols; instead, these were post-hoc subgroup analyses that were unplanned and performed after data were collected. Results from such analyses should be interpreted with caution. Therefore, there remains very limited evidence and considerable uncertainty with respect to the efficacy and safety of reslizumab in patients who are treated chronically with daily OCS.
- Current smokers were excluded from the reslizumab 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 these 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-7) was a secondary outcome in all four reslizumab 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 reslizumab and that the Health Canada indication limits the treating population to adults.

## Background

Reslizumab is a humanized immunoglobulin 4 monoclonal antibody that binds to human IL-5, thereby reducing the production and survival of eosinophils. Reslizumab was approved by Health Canada as add-on maintenance treatment for adult patients with severe eosinophilic asthma who are inadequately controlled with medium- to high-dose ICS and an additional asthma controller(s) (e.g., LABA) and have a blood eosinophil count of ≥ 400 cells/μL at initiation of treatment. The recommended dose is 3 mg/kg, administered by intravenous (IV) infusion every four weeks.

## Submission History

In March 2017, CDEC recommended that reslizumab be reimbursed for add-on maintenance treatment for adult patients with severe eosinophilic asthma who are inadequately controlled with medium- to high-dose ICS and an additional asthma controller(s) (e.g., a LABA), and have a blood eosinophil count of ≥ 400 cells/μL at initiation of the treatment, if the following clinical criteria and both conditions are met:

Clinical Criteria

- Patients who have experienced one or more clinically significant asthma exacerbations in the past 12 months, who have an ACQ-7 score ≥ 1.5 points, and who show reversibility (at least 12% and 200 mL) on pulmonary function tests (i.e., spirometry).
- Reslizumab is not to be used in combination with other biologics for the treatment of asthma.

Conditions

- Patients should be managed by a physician with expertise in treating asthma.
- Reduction in price of 90%.

The CADTH CDR-participating drug plans submitted a request for advice to ask CDEC if the recommendation for reslizumab should be updated to align with the CDEC recommendations for the other available IL-5 inhibitors, mepolizumab and benralizumab. 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 CDR review of reslizumab
- input from two patient groups that described the impact of severe eosinophilic asthma and expectations from therapies
- the 2017 CDEC recommendation for reslizumab
- the CDEC recommendations for mepolizumab (Nucala) and benralizumab (Fasenra)
- 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 for the Request for Advice

Two patient groups, the Ontario Lung Association and Asthma Canada, provided input for the request for advice for reslizumab. 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 current treatments do provide some relief for fatigue, shortness of breath, cough, low energy, poor appetite, and the inability to fight infection, but patients indicated they want to experience greater assistance with managing all of these symptoms.

- Patients also indicated that they want treatments that would reduce shortness of breath, reduce coughing, reduce fatigue, and improve appetite. They would like an increased ability to fight infections and to have a higher energy level. Ideally, patients would experience an improved quality of life and improved lung function.
- One of the patient groups indicated supporting alignment of CDEC's recommendation conditions for mepolizumab, reslizumab, and benralizumab, and views this as an opportunity to address problematic issues, such as 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 ICSs 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 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 randomized, placebo-controlled trials (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 randomized, placebo-controlled trials (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 OCSs at a dose of 5 mg per day to 35 mg per day.

Four double-blind randomized, placebo-controlled trials 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 forced expiratory volume in one second ($FEV_1$) 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 current smokers and those who had clinically important pulmonary disease other than asthma. 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 RCTs of reslizumab, a manufacturer-provided NMA, 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.

### Summary of Patient Input

Two patient groups — the Asthma Society of Canada/National Asthma Patient Alliance (ASC) and the British Columbia Lung Groups/British Columbia Lung Association (BCLG) — provided input for this submission. Patient perspectives were obtained by the ASC in 2014 based on a mixed methods study involving 24 patient interviews and an online quantitative survey of 200 individuals with severe asthma. The BCLG did not specify the methods used to gather patient input. The following is a summary of key input from the perspective of the patient groups:

- Asthma symptoms, including shortness of breath, coughing, wheezing, difficulty fighting infections, and fatigue, negatively affect the day-to-day lives of patients. Specifically, patients reported decreased physical activity, reduced performance at work or school, and social isolation as a result of stigma associated with the disease. Patients also reported frequent emergency room visits in the last 12 months.
- Patients reported that barriers to optimal asthma control included the real or perceived lack of efficacy, unpleasant side effects, and financial constraints in accessing medication. Particular concern was raised regarding the use of oral (systemic) corticosteroids in patients who do not achieve adequate asthma control with an ICS drug. Systemic corticosteroids are associated with short- and long-term adverse effects. Patients also reported losses in productivity as a result of illness, medical appointments, and associated travel time.
- There are unmet treatment needs for patients with severe asthma who are unable to adequately control their symptoms and exacerbations with the use of currently available therapies. Additional therapies are needed that go beyond symptomatic relief and will improve overall lung function.

Although having a medication administered by infusion at the doctor's office is concerning for some patients, this concern is offset by only needing to receive one dose monthly.

### Clinical Trials

The systematic review included four double-blind RCTs: two identical 52-week pivotal trials (studies 3082 and 3083) and two supporting 16-week trials (studies 3081 and 3084), which compared reslizumab 3 mg/kg IV every four weeks with placebo. All trials enrolled patients with inadequately controlled asthma despite therapy with medium-to-high doses of ICS with or without other controller medication(s), which they maintained during the double-blind treatment period. Studies 3082, 3084, and 3081 enrolled patients with elevated blood eosinophil levels (≥ 400 cells/μL at screening). In total, 489, 464, 315 (only 211 included in the CDR systematic review, excluding those randomized to an unapproved dose), and 496 (492 included in the CDR systematic review) patients were randomized in studies 3082, 3083, 3081, and 3084, respectively.

## Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- Asthma exacerbations — defined as worsening signs or symptoms of asthma plus use of systemic corticosteroids or an increase in the use of ICS treatment for three days or more, or asthma-related emergency treatment, including at least one unscheduled visit to the physician's office for treatment, visit to the emergency room for asthma-related treatment, or asthma-related hospitalization.
- $FEV_1$ — in adult asthma patients, a minimal patient-perceivable improvement in $FEV_1$ of 230 mL has been reported.
- ACQ-7 — a patient-reported instrument that measures the adequacy of asthma treatment in the past week. It consists of seven items, including five items on symptoms, one item on rescue bronchodilator use, and one item on $FEV_1$ percentage of predicted normal. A score of 0 indicates well-controlled asthma and 6 indicates extremely poorly controlled asthma. The estimated minimal clinically important difference (MCID) for all versions of the ACQ has been reported to be 0.5 points.
- Asthma Quality of Life Questionnaire (AQLQ) — a 32-question quality-of-life instrument that includes four domains (symptoms, activity limitation, emotional function, and environmental stimuli). Patients respond using a seven-point scale from 7 (no impairment) to 1 (severe impairment) based on their recall of their experience over the previous two weeks. The MCID has been estimated to be 0.5 points.
- Asthma Symptom Utility Index (ASUI) — a patient-reported 11-item instrument designed to assess the frequency and severity of asthma symptoms and the side effects of asthma treatment, weighted by patient preferences. It is scored from 0 to 1, with lower scores indicating worse asthma symptoms. The MCID has been estimated to be 0.09 points.
- Serious adverse events (AEs), total AEs, and withdrawals due to AEs.

The primary outcome in studies 3082 and 3083 was the frequency of asthma exacerbations over the 52-week study period. Secondary end points included change from baseline in $FEV_1$, ACQ, AQLQ, and ASUI, and time to first exacerbation. In Study 3081, the primary outcome was the change from baseline in $FEV_1$ over 16 weeks, and in Study 3084, the primary outcome was the change from baseline in $FEV_1$ to week 16, relative to baseline eosinophil levels.

## Efficacy

In the 52-week pivotal trials, the patients who received reslizumab were less likely than those who received placebo to report a clinically important asthma exacerbation (Study 3082: adjusted rate ratio 0.50; 95% CI, 0.37 to 0.67; $P < 0.0001$; Study 3083: adjusted rate ratio 0.41; 95% CI, 0.28 to 0.59; $P < 0.0001$).

Reslizumab statistically significantly delayed the first asthma exacerbation, compared with placebo, with adjusted hazard ratios of 0.58 (95% CI, 0.44 to 0.75) in Study 3082 and 0.49 (95% CI, 0.35 to 0.67) in Study 3083.

In studies 3082 and 3083, the between-group differences in the change from baseline to week 16 in the AQLQ, ACQ-7, and ASUI were statistically significant, favouring reslizumab over placebo, but did not exceed the MCIDs.

Modest between-treatment differences in the change from baseline in $FEV_1$ were reported in the supporting trials (adjusted mean differences: 0.07 L to 0.17 L), and in the pivotal trials (adjusted mean differences: 0.07 L to 0.10 L) at 16 weeks for reslizumab versus placebo.

## Harms (Safety)

The majority of patients reported one or more AEs during the trials (52-week pivotal trials: 76% to 87%; 16-week trials: 55% to 74%). Asthma, nasopharyngitis, upper respiratory tract infections, and headache were the most commonly reported AEs.

In the 52-week pivotal trials, serious AEs were reported more frequently in the placebo groups (10% to 14%) than in the reslizumab groups (8% to 10%), and in the 16-week supporting trials, 1% to 4% of placebo patients and 4% of reslizumab patients reported a serious AE.

The frequency of withdrawals due to AEs ranged from 2% to 7% in reslizumab groups and from 3% to 12% in the placebo groups.

Five patients experienced an anaphylactic reaction, all of whom had been randomized to reslizumab. Three of these events occurred during or shortly after a reslizumab dose and these patients were withdrawn from reslizumab treatment.

## Indirect Treatment Comparisons

The efficacy and safety of reslizumab 3.0 mg/kg was indirectly compared with [redacted]

## Cost and Cost-Effectiveness

Reslizumab solution for IV infusion is available at a manufacturer-submitted price of $640 per 10 mg/mL vial. The annual cost ranges from $8,349 to $33,394 for patients weighing between 30 kg (one vial per 28 days) and 120 kg (four vials per 28 days).

The manufacturer's primary economic analysis was a cost-utility analysis comparing reslizumab plus SOC (LABAs, OCSs, and leukotriene modifiers) with SOC alone in the Health Canada–approved population. The model consisted of a decision tree for treatment response, followed by Markov cycles with three health states: day-to-day asthma, asthma exacerbations, and death. If patients responded to reslizumab at the end of the initial 16 weeks of treatment, they were assumed to continue treatment for 10 years before switching to SOC alone for the remaining duration of the model lifetime time horizon (50 years). The manufacturer reported an incremental cost-utility ratio (ICUR) of $256,000 per QALY for reslizumab plus SOC compared with SOC alone. CDR identified several limitations with the manufacturer's cost-utility analysis: overestimated treatment benefit with reslizumab based on an assumption of improved survival compared with SOC alone, which was not supported by the available clinical data; the asthma mortality rate appears to have been overestimated; an additional utility benefit was applied to reslizumab patients; utility values were derived from a scale of uncertain validity; and there were concerns that the definition of treatment response applied was not generalizable to Canadian clinical practice.

CDR undertook reanalyses to address the limitations, by removing the assumed survival benefit for reslizumab versus SOC and the assumed utility benefit for patients receiving reslizumab, assuming a lower asthma mortality rate, a revised cost of SOC, and a revised patient weight distribution. These revised assumptions resulted in a CDR base case of $888,000 per QALY for reslizumab plus SOC compared with SOC alone. A price reduction of 95% would be required for the ICUR of reslizumab plus SOC compared with SOC alone to fall below $50,000 per QALY, while an 89% price reduction would be required to achieve an ICUR of $100,000 per QALY.

The manufacturer also presented a supplemental cost-minimization analysis (CMA) comparing reslizumab with two biologic drugs assuming equal safety and efficacy based on a manufacturer-funded NMA, resulting in a lower annual drug cost for reslizumab compared with mepolizumab and omalizumab. CDR identified limitations with the CMA, including substantial uncertainty regarding the comparative efficacy of reslizumab and omalizumab, the potential overestimation of treatment use for omalizumab, and the potential that the costs associated with reslizumab were underestimated. As CDR was unable to validate the conclusion of the manufacturer's NMA reporting that the compared biologics had similar efficacy, the choice of a CMA to compare these treatments may not have been appropriate.

## Request for Clarification

The drug plans that participate in the CDR process filed a request for clarification during the embargo period for the CDEC recommendation of reslizumab. 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, Ms. Heather Neville, Mr. Allen Lefebvre, 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