CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

RESLIZUMAB
(Cinqair — Teva Canada Innovation)
Indication: Severe eosinophilic asthma

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that reslizumab be reimbursed for add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with medium- to high-dose inhaled corticosteroids (ICSs) and an additional asthma controller(s) (e.g., a long-acting beta-agonist [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:
1. Patients who have experienced one or more clinically significant asthma exacerbations in the past 12 months, who have an Asthma Control Questionnaire 7 (ACQ-7) score ≥ 1.5 points, and who show reversibility (at least 12% and 200 mL) on pulmonary function tests (i.e., spirometry).
2. Reslizumab is not to be used in combination with other biologics for the treatment of asthma.

Conditions:
1. Patients should be managed by a physician with expertise in treating asthma.
2. Reduction in price of 90%.

Reasons for the Recommendation:
1. A total of 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 ICSs with or without additional asthma controller(s) and 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 with mepolizumab and omalizumab in patients with severe eosinophilic asthma who would be eligible for all three therapies. CDEC identified some serious limitations in the NMA with respect to the comparison between reslizumab, mepolizumab, and omalizumab and noted a high degree of uncertainty associated with its findings. Therefore, no firm conclusion could be drawn regarding the comparative effectiveness and safety of reslizumab versus other biologics in the treatment of severe eosinophilic asthma.
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.

Of Note:

- CDEC considered potential discontinuation criteria, including criteria based upon those used in the manufacturer-submitted pharmacoeconomic model; however, there was no clinical evidence available to inform such criteria.
- For the comparison of reslizumab plus SOC versus 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 the drug may be more favourable from a cost-effectiveness perspective, but the clinical evidence did not identify this potential subgroup.

Other Discussion Points:

CDEC also discussed the following:

- 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).
- 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 pivotal trials suggests that these patients were under-treated with conventional ICSs and a second controller.

Background:

Reslizumab is a humanized immunoglobulin 4 (IgG4κ) monoclonal antibody that binds to human interleukin-5 (IL-5), thereby reducing the production and survival of eosinophils. Reslizumab was approved by Health Canada as add-on maintenance treatment of 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 the treatment. The recommended dose is 3 mg/kg, administered by intravenous (IV) infusion every four weeks.

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials (RCTs) and pivotal studies of reslizumab in the treatment of severe eosinophilic asthma, a critique of the manufacturer's pharmacoeconomic evaluation, and information submitted by patient groups about outcomes and issues that are important to individuals living with asthma.

Patient Input Information:

Two patient groups submitted input: the Asthma Society of Canada/National Asthma Patient Alliance (ASC) and the British Columbia Lung Groups/British Columbia Lung Association (BCLG). Information provided by the ASC was based on a mixed-methods study involving 24 patient interviews and an online quantitative survey of 200 individuals with severe asthma, conducted by ASC in 2014. The BCLG did not specify the methods used to gather patient input.

- 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-term 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

Four double-blind RCTs met the inclusion criteria: 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 to 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, CDEC 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.

- Forced expiratory volume in one second (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 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, total adverse events, and withdrawals due to adverse events.

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 [MDs] 0.07 L to 0.17 L), and in the pivotal trials (adjusted MDs 0.07 L to 0.10 L) at 16 weeks for reslizumab versus placebo.

Harms (Safety and Tolerability)

- The majority of patients reported one or more adverse events 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 adverse events.
- In the 52-week pivotal trials, serious adverse events 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 adverse event.
- The frequency of withdrawals due to adverse events 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.

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 (CUA) comparing reslizumab plus SOC (LABAs, oral corticosteroids, 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 CUA: 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.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

Regrets:

January 18, 2017 Meeting: None
March 15, 2017 Meeting: None

Conflicts of Interest:

None

About This Document:

CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient, nor is it intended to replace professional advice.

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