CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

MEPOLIZUMAB (NUCALA — GLAXOSMITHKLINE INC.)
Indication: Severe eosinophilic asthma

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that mepolizumab 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 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. Mepolizumab 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 mepolizumab 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 mepolizumab should not exceed the drug plan cost of other IL-5 inhibitors

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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

MEPOLIZUMAB (NUCALA — GLAXOSMITHKLINE INC.)

Indication: severe eosinophilic asthma

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated June 16, 2016.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that mepolizumab 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 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. Mepolizumab 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 mepolizumab 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. Reimbursemet 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, 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 mepolizumab should not exceed the drug plan cost of other IL-5 inhibitors.

Reasons for the Recommendation

1. Evidence from two phase III, double-blind, randomized placebo-controlled trials supports the safety and efficacy of mepolizumab. In MENSA (N = 576), mepolizumab was associated with a statistically significant reduction in the rate of clinically significant asthma exacerbations compared with placebo at 32 weeks in patients currently on high-dose ICS and one or more additional asthma controller(s). In SIRIUS, (N = 135) mepolizumab was associated with a greater likelihood of a reduction in daily OCS dose at 24 weeks compared with placebo in patients currently on high-dose ICS and one or more additional asthma controller(s), and who were taking OCS at a dose of 5 mg/day to 35 mg/day.
2. At the submitted price of $[redacted], the CADTH Common Drug Review (CDR) estimated that mepolizumab plus standard of care (SOC) is associated with an incremental cost-effectiveness ratio (ICER) of $521,000 per quality-adjusted life-year (QALY) compared with SOC alone in the treatment of adults with severe eosinophilic asthma; therefore, mepolizumab 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; 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 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 in the ACT.
- Maintenance OCS treatment is defined as receiving greater than the equivalent of prednisone 5 mg per day.
- The manufacturer submitted an indirect treatment comparison (ITC) to evaluate the relative efficacy of mepolizumab and omalizumab in patients with severe eosinophilic asthma who would be eligible for both therapies. The CADTH CDEC identified some serious limitations in this ITC and noted a high degree of uncertainty associated with its findings. Therefore, no firm conclusion could be drawn regarding the comparative effectiveness, safety, and cost-effectiveness of mepolizumab versus omalizumab in the treatment of severe eosinophilic asthma.
- CDEC could not provide a recommendation for sequencing of mepolizumab 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 mepolizumab, 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 mepolizumab compared with other biologic drugs used to treat severe eosinophilic asthma.
- For the comparison of mepolizumab plus SOC with SOC alone, CDEC noted that a price reduction for mepolizumab of 89% is required to achieve an ICER of $50,000 per QALY, or 80% to achieve an ICER of $100,000 per QALY.

Discussion Points

- CDEC noted that the mepolizumab trial eligibility criteria related to peripheral eosinophil counts are notably different from those for reslizumab, but relatively similar to those for 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 mepolizumab and benralizumab was considered reasonable, but not between mepolizumab and reslizumab.
- MENSA and SIRIUS 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 mepolizumab 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-5) was a secondary outcome in MENSA and labelled as an "other" outcome in SIRIUS. 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 while patients as young as 12 were included in the trials for mepolizumab, the Health Canada indication limits the treating population to adults.

Background

Mepolizumab has a Health Canada indication for the add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with high-dose inhaled ICS and one or more additional asthma controller(s), and have a blood eosinophil count of ≥ 150 cells/µL at initiation of treatment or ≥ 300 cells/µL in the past 12 months. Mepolizumab is a humanized monoclonal antibody that targets IL-5, a cytokine responsible for regulating eosinophil development. Eosinophils are involved in the pathogenesis of asthma through the release of proinflammatory mediators at the airways, which contribute to epithelial cell damage, airway hyperresponsiveness, mucus hypersecretion, and airway remodelling. Mepolizumab is available as a lyophilized powder for subcutaneous injection in single-use vials at 100 mg/mL after reconstitution. The Health Canada-recommended dose is 100 mg administered subcutaneously once every four weeks.

Submission History

In June 2016, CDEC recommended that mepolizumab be reimbursed for add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with high-dose ICS and one or more additional asthma controller(s) (e.g., a LABA), and have a blood eosinophil count of ≥ 150 cells/µL at initiation of treatment with mepolizumab or ≥ 300 cells/µL in the past 12 months, if one of the following clinical criteria and both conditions are met:

Clinical Criteria

- Patients who have experienced two or more clinically significant asthma exacerbations in the past 12 months and who show reversibility (at least 12% and 200 mL) on pulmonary function tests (i.e., spirometry)
- Are treated with daily OCS.

Conditions

- Patients should be treated by a physician with expertise in treating asthma
- Substantial reduction in price

The CADTH CDR-participating drug plans submitted a request for advice to ask CDEC if the recommendation for mepolizumab should be updated to align with the CDEC recommendations for the other available IL-5 inhibitors, benralizumab 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 CDR review of mepolizumab.
- Input from two patient groups that described the impact of severe eosinophilic asthma and expectations from therapies.
- The 2016 CDEC recommendation for mepolizumab.
- The CDEC recommendations for reslizumab (Cinqair) 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

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 has a great impact on their physical and leisure activities, and to a lesser extent, their work, ability to travel, and 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 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 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 that patients needed be 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 to 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 treated by physicians with expertise in managing asthma.

Comparison of IL-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 controlled trials (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/day to 35 mg/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 MENSA (mepolizumab) trial in the following: age, the number of documented asthma exacerbations in the previous 12 months, pre-bronchodilator FEV_1, and post-bronchodilator reversibility in FEV_1. The three trials were similar in excluding patients who had clinically important pulmonary disease other than asthma, current smokers or former smokers with a smoking history of at least 10 pack years, receipt of any marketed (e.g., omalizumab) or investigational biologic drugs within four months (SIROCCO and CALIMA trials) or 130 days (MENSA trial), and 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 by excluding 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 by requiring 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 the 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 before visit 1 in SIRIUS), pre-bronchodilator FEV_1 of < 80% predicted, evidence of asthma as documented by either airway reversibility, documented reversibility, airway hyperresponsiveness, 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, current smokers or former smokers with a smoking history of at least 10 pack years, receipt of 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 in 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, except that ZONDA included patients with higher mean eosinophil counts at baseline compared with SIRIUS (583 cells/μL versus 380 cells/μL, respectively) and 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

The committee considered the following information prepared by the CADTH CDR: a systematic review of RCTs of mepolizumab, a manufacturer-provided ITC, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients who had severe eosinophilic asthma, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups, the Ontario Lung Association (OLA) and the Asthma Society of Canada (ASC)/National Asthma Patient Alliance (NAPA), responded to the CDR call for patient input. The OLA obtained information from a small number of online surveys, while the ASC/NAPA obtained information from personal interviews and an online quantitative survey. 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 impact the day-to-day lives of patients. Specifically, patients reported decreased physical activity, reduced performance at work or school, and social isolation due to stigma associated with the disease. Patients also reported frequent emergency room visits in the last 12 months.
- Patients reported that current therapies provide some relief from symptoms for some patients, and that side effects and less actual control of asthma than patients think there is may result in suboptimal adherence to current therapies. The use of

systemic corticosteroids is associated with adverse short-term and long-term effects. Patients also reported losses in productivity as a result of illness, medical appointments, and associated travel time.

- Patients are looking for drugs that can reduce asthma symptoms, reduce emergency department visits and hospitalizations, improve the ability to fight infections, and allow for higher energy levels.
- Patients expressed frustration that therapies (like omalizumab) used to treat other forms of severe asthma are ineffective for most patients with severe eosinophilic asthma, and no other comparable alternatives exist.

Clinical Trials

The CDR systematic review included two phase III, multi-centre, double-blind, placebo-controlled RCTs of patients with severe eosinophilic asthma. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab subcutaneous (SC) administration at 100 mg once every 4 weeks as adjunctive therapy in patients with severe eosinophilic asthma. SIRIUS (N = 135) was a 24-week corticosteroid sparing study that evaluated the effect of mepolizumab SC 100 mg once every four weeks in reducing OCS use in patients with severe eosinophilic asthma. Both studies enrolled patients at least 12 years of age with documented asthma who met specific peripheral blood eosinophil counts (≥ 150 cells/mcL at visit 1 or ≥ 300 cells/mcL in the past 12 months) and who were treated with high-dose ICS and an additional controller medication. In SIRIUS, eligible patients were to be using OCS at a dose between 5 mg/day and 35 mg/day.

Outcomes

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

- Asthma exacerbations — defined as a worsening of asthma symptoms that require either treatment with systemic corticosteroids for ≥ three days, hospitalization, or an emergency department (ED) visit.
- OCS use.
- FEV_1 — in adult asthma patients, a minimal patient perceivable improvement in FEV_1 of 230 mL has been reported.
- St. George's Respiratory Questionnaire (SGRQ) — a self-administered 50-item instrument used to assess impaired health and perceived well-being in respiratory disease. The minimal clinically important difference (MCID) has been reported to be an improvement of at least four units in SGRQ total score.
- ACQ — 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 per cent of predicted normal. The estimated MCID for all versions of the ACQ has been reported to be 0.5 points.
- Serious adverse events, total adverse events, and withdrawal due to adverse events.

The primary end point in MENSA was the rate of clinically significant exacerbations at week 32. Secondary end points in MENSA included the change from baseline in pre-bronchodilator FEV_1 and the change from baseline in SGRQ at week 32. The primary end point in SIRIUS was the percentage reduction of OCS dose during weeks 20 to 24 compared with baseline dose, while maintaining asthma control. In SIRIUS, secondary end points included the proportion of patients achieving specific OCS dose reductions (≥ 50% reduction; reduction to ≤ 5.0 mg/day; total reduction) and median percentage reduction in OCS dose from baseline.

Efficacy

In MENSA, the rate of clinically significant exacerbations was statistically significantly lower in the mepolizumab group than the placebo group (rate ratio 0.47; 95% CI, 0.35 to 0.64, $P < 0.001$). The rate of exacerbations requiring hospitalization or ED visit was statistically significantly lower in the mepolizumab group compared with the placebo group (rate ratio 0.39; 95% CI, 0.18 to 0.83, $P = 0.015$). The rate of exacerbations requiring hospitalization was lower in the mepolizumab group compared with the placebo group (rate ratio 0.31; 95% CI, 0.11 to 0.91, $P = 0.034$); however, this outcome was analyzed as exploratory based on the analysis hierarchy for control of multiplicity.

In SIRIUS, the odds ratio (OR) of mepolizumab compared with placebo of achieving a percentage reduction from baseline in OCS dose was statistically significant (OR 2.39; 95% CI, 1.25 to 4.56, $P = 0.008$). A statistically significantly greater proportion of patients

achieved a ≥ 50% reduction in daily OCS dose in the mepolizumab group compared with the placebo group (OR 2.26, 95% CI, 1.10 to 4.65, *P* = 0.027). A statistically significantly greater proportion of patients achieved a reduction in daily OCS dose to ≤ 5 mg in the mepolizumab group compared with the placebo group (OR 2.45; 95% CI, 1.12 to 5.37, *P* = 0.025). More patients in the mepolizumab group achieved a total reduction in OCS dose compared with the placebo group, but this difference was not statistically significant (OR 1.67; 95% CI, 0.49 to 5.75, *P* = 0.414). There was a statistically significant median percentage reduction from baseline in daily OCS dose in the mepolizumab group compared with the placebo group (median difference –30.0; 95% CI, –66.7 to 0.0, *P* = 0.007).

In MENSA, the mean change from baseline pre-bronchodilator FEV_1 at week 32 was statistically significantly greater in the mepolizumab group than in the placebo group (mean difference 98 mL; 95% CI, 11 to 184, *P* = 0.028). In SIRIUS, there was no clear improvement from baseline at week 24 in pre-bronchodilator FEV_1 (mean difference 114 mL; 95% CI, –42 to 271). In both trials, the statistical analyses of these outcomes were considered exploratory.

In MENSA, there was a statistically significantly greater improvement in SGRQ total score at week 32 in the mepolizumab group compared with the placebo group (mean difference –7.0; 95% CI, –10.2 to –3.8, *P* < 0.001). In SIRIUS, there was a greater improvement in SGRQ total score at week 24 in the mepolizumab group compared with the placebo group (mean difference –5.8; 95% CI, –10.6 to –1.0). In both studies, a greater proportion of patients in the mepolizumab group achieved a ≥ four-point improvement in SGRQ total score at the end of the double-blind period compared with baseline placebo (MENSA: 71% versus 55%; SIRIUS: 58% versus 41%). Statistical analyses of health-related quality of life outcomes were considered exploratory.

In MENSA and SIRIUS, there was a greater improvement from baseline in the ACQ-5 total score at week 32 in the mepolizumab group compared with the placebo group (MENSA: mean difference –0.44; 95% CI, –0.63 to –0.25; SIRIUS: mean difference –0.52; 9 5% CI, –0.87 to –0.17).

Harms (Safety)

In MENSA, a total of 78% of patients in the mepolizumab group and 83% of patients in the placebo group reported an adverse event during the 32-week, double-blind treatment period. In SIRIUS, a total of 83% of patients in the mepolizumab group and 92% of patients in the placebo group reported an adverse event during the 24-week, double-blind, OCS dose-reduction treatment period. Common adverse events included nasopharyngitis, headache, upper respiratory tract infections, asthma, sinusitis, bronchitis, and fatigue.

In both trials, the proportion of patients reporting a serious adverse event was higher in the placebo groups compared with the mepolizumab groups (MENSA, 14% versus 8%; SIRIUS, 18% versus 1%).

In MENSA, one patient (< 1%) in the mepolizumab group and four patients (2%) in the placebo group withdrew due to an adverse event. In SIRIUS, three patients in each group withdrew due to an adverse event.

Injection site reactions occurred infrequently, but were numerically more common in the mepolizumab group compared with the placebo group (MENSA, 9% versus 3%; SIRIUS, 6% versus 3%). All injection site reactions were reported as mild or moderate in intensity. Systemic allergic reactions were infrequent and balanced across the mepolizumab and placebo groups in both trials (MENSA, 2% for both groups; SIRIUS, 6% versus 5% respectively).

Indirect Treatment Comparisons

The manufacturer provided an ITC based on a systematic review of RCTs to compare the efficacy and safety of mepolizumab with omalizumab in the treatment of patients with severe asthma. Although the ITC results suggested that mepolizumab had similar efficacy compared with omalizumab in terms of clinically significant exacerbation, hospitalization, change in FEV_1, and with a similar safety profile, there are very serious limitations with the analysis — in part stemming from the limited number of source trials for the analysis — and a high degree of uncertainty associated with the ITC findings. Therefore, no conclusion can be drawn regarding the comparative effectiveness and safety of mepolizumab with omalizumab in the treatment of severe asthma.

Cost and Cost-Effectiveness

At the submitted confidential price of $[redacted], the annual cost of mepolizumab is $[redacted].

The manufacturer submitted a cost-utility analysis comparing mepolizumab plus SOC with SOC alone, as well as a cost-minimization analysis (CMA) comparing mepolizumab plus SOC with omalizumab plus SOC in adult patients with severe eosinophilic asthma. The perspective was that of a Canadian public payer. SOC was defined as high-dose ICS plus an additional controller medication (e.g., LABA, leukotriene receptor antagonist, or theophylline), with or without maintenance therapy with an OCS. The manufacturer's model used clinical data from the DREAM, MENSA, and SIRIUS trials to inform the comparison of mepolizumab plus SOC with SOC alone, and baseline characteristics for the model cohort were obtained from the MENSA trial. The results of an ITC were used to inform the comparative efficacy of mepolizumab plus SOC with omalizumab plus SOC. The analysis was performed over a lifetime time horizon; patients in the mepolizumab or omalizumab treatment groups were assumed to receive these treatments for a maximum of 10 years, at which point all patients received treatment with SOC alone.

According to the manufacturer's base-case analysis, the ICERs were $143,778 per QALY gained and $22,540 per exacerbation avoided for mepolizumab plus SOC versus SOC alone. In comparison with omalizumab plus SOC, mepolizumab plus SOC was associated with lower costs and greater benefits.

CDR identified several limitations with the manufacturer's pharmacoeconomic submission, including:

- Cost-effectiveness results varied considerably based on age at model entry. When either a younger or older age at model entry than the manufacturer's base-case analysis was used, the ICER increased. Use of an age distribution reflective of Canadian patients expected to receive mepolizumab would have been more appropriate.
- The model predicts a mortality benefit for mepolizumab over the 10 years of treatment, and the incremental benefit with mepolizumab compared with SOC from treatment discontinuation until death is due almost entirely to additional life-years accrued during these 10 years. However, these results are of uncertain validity as there are no trial data demonstrating a mortality benefit with mepolizumab over SOC.
- The model results were sensitive to utility values. The model employed health-state utility values derived using a mapping algorithm, rather than directly measured utility values collected in one of the mepolizumab trials. Directly measured values are preferred.
- Based on utilization data available to CADTH's CDR, the manufacturer may have overestimated the assumed average dose of omalizumab in their analysis.
- The CMA of mepolizumab versus omalizumab was of uncertain validity due to important shortcomings of the manufacturer-submitted ITC.

The CDR base-case analysis incorporated directly measured utility values, a reduced time horizon of 10 years, an assumption of equal efficacy for omalizumab and mepolizumab, and omalizumab utilization based on claims data. The resulting ICER for mepolizumab plus SOC versus SOC alone was $521,000 per QALY. For the comparison of omalizumab with mepolizumab, CDR reanalysis suggested that mepolizumab is less costly than omalizumab. A price reduction of 80% and 89% would be required for mepolizumab plus SOC to achieve willingness-to-pay thresholds of $100,000 per QALY and $50,000 per QALY, respectively, versus SOC alone. For jurisdictions that list omalizumab, mepolizumab is less costly than omalizumab (based on publicly available prices) for the subgroup of patients with severe asthma who are eligible for either of the two treatments, if more than [redacted] vials of omalizumab are used per administration. However, there is considerable uncertainty regarding the comparative efficacy and safety of the two products.

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 mepolizumab. 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 (Clarification)

Regrets

None

Conflicts of Interest

None