CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

MEPOLIZUMAB
(Nucala — GlaxoSmithKline Inc.)
Indication: Severe eosinophilic asthma

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that mepolizumab be reimbursed for add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with high-dose inhaled corticosteroids (ICS) and one or more additional asthma controller(s) (e.g., a long-acting beta-agonist [LABA]), and have a blood eosinophil count of ≥ 150 cells/mcL at initiation of treatment with mepolizumab or ≥ 300 cells/mcL in the past 12 months, if one of the following clinical criteria and both conditions are met:

Clinical Criteria:
1. 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)
2. Are treated with daily oral corticosteroids (OCS).

Conditions:
1. Patients should be managed by a physician with expertise in treating asthma.
2. Substantial reduction in price.

Reasons for the Recommendation:
1. Evidence from two phase 3, 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] per vial, 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.

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Of Note:

1. 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.
2. 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.

Background:

Mepolizumab is a humanized monoclonal antibody that targets interleukin-5 (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 indicated 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/mcL at initiation of treatment or ≥ 300 cells/mcL in the past 12 months. 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 4 weeks.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CADTH CDR: a systematic review of randomized controlled trials (RCTs) of mepolizumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

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 information provided by 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.

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- 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 3, multi-centre, double-blind, placebo-controlled RCTs. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab subcutaneous (SC) administration at 100 mg and mepolizumab intravenous (IV) administration at 75 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 4 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 ≥ 3 days, hospitalization, or an emergency department (ED) visit.
- OCS use.
- 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.
- 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 4 units in SGRQ total score.
- Asthma Control Questionnaire (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 withdrawals 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.

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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 ≥ 4 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 Asthma Control Questionnaire (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; 95% CI, –0.87 to –0.17).

Harms (Safety and Tolerability)

- 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.

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- 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).

Cost and Cost-Effectiveness

At the submitted confidential price of $[redacted] per 100 mg/mL vial, the annual cost of mepolizumab is $[redacted].

The manufacturer submitted a cost-utility analysis (CUA) comparing mepolizumab plus SOC with SOC alone, and 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 over 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.

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- Based on utilization data available to CADTH's CDR, the manufacturer may have overestimated the assumed average dose of omalizumab in their analysis.
- The CUA 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.

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.

May 18, 2016 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing 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 requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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