Canada's Drug and Health Technology Agency

DRAFT Reimbursement Recommendation

Mepolizumab

Reimbursement request: For the treatment of eosinophilic granulomatosis with polyangiitis (EGPA), with or without oral corticosteroids and/or immunosuppressive therapy

Draft Recommendation: Reimburse with Conditions

Summary of Recommendation

The Formulary Management Expert Committee (FMEC) conditionally recommends that mepolizumab should be reimbursed for individuals diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) if the conditions in Table 2 are met.

FMEC concluded that mepolizumab meets unmet medical need and achieves important outcomes for persons with eosinophilic granulomatosis with polyangiitis (EGPA), specifically improved remission rates and reductions in oral corticosteroid (OCS) exposure.

FMEC reviewed two Phase III, randomized, double-blind trials. The MIRRA trial was a placebo-controlled study evaluating mepolizumab 300 mg subcutaneously every 4 weeks over 52 weeks in patients 18 years or older with relapsing or refractory EGPA. The MANDARA trial was a non-inferiority study assessing benralizumab 30 mg subcutaneously every 4 weeks as compared to 300 mg mepolizumab. Positive outcomes with mepolizumab treatment on the total weeks of remission and proportion of persons in remission were reported in the trials, although certain limitations were also raised including lack of long-term data to inform mepolizumab's long-term effectiveness and ability to prevent end organ damage.

In comparison with current treatment options, mepolizumab poses incremental costs to the health care system, and the cost-effectiveness is presently unknown.

Therapeutic Landscape

What is eosinophilic granulomatosis with polyangiitis (EGPA)?

EGPA is an antineutrophil cytoplasm antibody vasculitis characterized by tissue and blood eosinophilia, small to medium-size vessel vasculitis, extravascular granulomas, asthma, and sinonasal symptoms. It is a rare disease, affecting 12 to 59 people per 1 million. Persons with EGPA experience acute relapses with periods of remission, and relapses increase the likelihood of developing organ damage including cardiomyopathy and chronic kidney disease. As a result, treatment goals are focused on induction and maintenance of remission, prevention of relapses, prevention of organ damage, and minimizing the harms associated with treatments used in individuals with EGPA.

Why Did We Conduct This Review?

This review was driven by the clinical need to provide an effective treatment option for patients with EGPA. Mepolizumab is later in the drug development lifecycle with data protection on the innovator version having expired (2024-06-03). Given the manufacturer has previously declined to file through the reimbursement review process, publicly funded drug programs have requested a reimbursement review and recommendation.

Person With Lived Experience

A person with Lived experience from urban Ontario, was diagnosed with Eosinophilic Granulomatosis with Polyangiitis (EGPA) in April 2022, shortly after retiring. He described his symptoms initially manifesting with respiratory issues and progressed to severe joint pain, acid reflux, weight loss, and nerve damage affecting mobility. Treatment began with high-dose intravenous prednisone followed by cyclophosphamide and later azathioprine. He highlighted concerns about the long-term toxicity, potential risks, and expressed apprehension about the potential dependency on these drugs to maintain remission. Despite initial challenges, including severe nerve pain and mobility issues, he has responded well to treatment and is currently in remission. Recently, he started mepolizumab at the lower dose of 100 mg in March to ensure coverage, to manage respiratory symptoms, noting a benefit in stabilizing his condition without observable adverse effects. He views mepolizumab as a promising alternative to traditional treatments emphasizing its potential for long-term use and reduced toxicity risks for patients living with EGPA.

Input from Community Partners

What Did We Hear from Persons Living with EGPA?

Vasculitis Foundation Canada submitted input, noting that patients with EGPA frequently experience lengthy hospitalizations and require high-dose intravenous steroids and immune-suppressing treatments to induce remission. Most patients remain on maintenance therapy, often azathioprine and oral prednisone. Patients wish to reduce the need for repeated steroid treatments to mitigate toxicity and long-term side effects and they wish to have equitable access to coverage.

What Did We Hear from Clinicians?

Clinicians emphasized the lack of approved treatments for EGPA in Canada, and that current treatments are often insufficient particularly for many individuals with refractory eosinophilic symptoms requiring high dose glucocorticoids to control symptoms. Glucocorticoids are also associated with both short- and long-term complications such as infection, osteoporosis, diabetes, cardiovascular risk, weight gain, and neuropsychiatric effects. Clinicians also emphasized that individuals with EGPA often continue to experience sinopulmonary symptoms that have a negative impact on health-related quality of life (HRQoL).

What Did We Hear from the Pharmaceutical Industry?

Industry (GlaxoSmithKline Inc) noted that treatment for EGPA is tailored based on the severity of symptoms; individuals with more severe disease usually receive more intense immunosuppressive agents. OCS and systemic glucocorticoids are the foundation in the standard of care for EGPA, and the industry highlighted the same concerns with currently available therapies for EGPA as persons living with EGPA and treating clinicians.

What Did We Hear from Public Drug Programs?

Public drug plans inquired about considerations for initiation, continuation, and duration of therapy. Questions were asked about at the stage in the EGPA disease process where mepolizumab should be initiated, and defining loss of response to mepolizumab.

Refer to Stakeholder Input section of the report.

Deliberation

With a unanimous, 6 to 0 vote, Formulary Management Expert Committee (FMEC) concluded that mepolizumab at the dose of 300 mg every 4 weeks addresses several unmet needs and achieves important outcomes for persons with eosinophilic granulomatosis with polyangiitis (EGPA), specifically improved remission rates and reductions in OCS (oral corticosteroid) exposure. Mepolizumab represents incremental costs to the health care system and the cost-effectiveness of this intervention is presently unknown.

FMEC deliberated on the following domains as illustrated in the Deliberative Framework (Figure 1):

- Clinical Value: whether the drug under review provides clinical value.
- Unmet Clinical Need: whether there is an unmet clinical need that available treatment(s) is/are not currently addressing.
- Comparable Efficacy: whether the drug under review shows at least similar efficacy to other available treatment(s) for the condition.
- Patient Perspective: whether the drug under review addresses patients' specific unmet needs and values.
- Economic Implications: the economic implications of reimbursing the drug under review based on public list prices.
- Health System & Social Considerations: whether there are health system or social considerations (e.g., administration, testing, equity, access, ethical) for the drug under review.

Figure 1: Deliberative Framework

Alt Text: The committee deliberated on 6 domains: clinical value, unmet clinical need, comparable efficacy, patient values, health system& social considerations, and economic implications.

Decision Summary

Table 1: Why Did FMEC Make This Recommendation?

Domains	Reason
Patient Values: whether the drug under review addresses patients' specific unmet needs and values.	• FMEC agreed that mepolizumab meets some of the unmet needs and achieves important outcomes identified by persons with EGPA such as providing an effective treatment for management of acute symptoms of EGPA and reducing the risks associated with oral corticosteroids (OCS) and immunosuppressive therapies. • The Committee also expressed a desire to reduce the risks of end-organ damage which was identified as an important patient need. However, the clinical trials for mepolizumab, namely the MIRRA and MANDARA trials which were considered during the deliberative process, did not address this outcome, nor did they include long-term evaluations (past 52 weeks) required for assessing chronic complications. • Clinical experts and patients shared that from their experience, persons with EGPA under their treatment particularly value the reduction in steroid use which can be associated with serious adverse events.
Clinical Value: whether the drug under review provides clinical value.	• Based on the MIRRA and MANDARA trials, FMEC concluded that mepolizumab improves remission rates while also reducing steroid exposure compared to placebo. • FMEC also highlighted the exclusion organ-threatening or life-threatening EGPA within 3 months prior to screening in both the MIRRA and MANDARA trials and the lack of long-term data to inform mepolizumab's long-term effectiveness and ability to prevent end organ damage. • The committee noted that some included patients did not benefit from the treatment. It is important to identify the characteristics of these patients and understand how they differ in terms of eligibility for treatment as well as their response or lack of response to treatment with mepolizumab. • Given the rarity of the disease, FMEC concluded that there should be greater allowance for uncertainty with the clinical evidence.

Domains	Reason
Unmet Clinical Need: whether there is an unmet clinical need that available treatment(s) is/are not currently addressing.	• FMEC discussed that the severe condition of EGPA with life-threatening implications and available treatments including standard of care (SoC) and Immunosuppressive therapies are inadequate. • FMEC also highlighted that mepolizumab has a different harm profile than current therapy and might lead to better tolerance for patients • Current treatments are not effective for all patients in inducing or sustaining remission and may often require prolonged treatment, which presents with a range of adverse effects. • Although rare, EGPA presents with disease heterogeneity, manifesting a spectrum of adverse effects. Asthma and respiratory issues are of primary concern that often drive treatment decisions. However, issues with the heart, kidneys, and nervous system, may bear more long-term effects and consequence to the health and quality of life.
Comparable Efficacy: whether the drug under review shows at least similar efficacy to other available treatment(s) for the condition.	• FMEC agreed that mepolizumab demonstrates an improved effect on outcomes of EGPA compared to available therapies, including effects on total accrued weeks of remission, proportion of patients in remission, OCS dosing considerations and time to first relapse.
Health System & Social Considerations: whether there are health system or social considerations for the drug under review.	• FMEC discussed that the clinician input received highlighted that some patients in Canada that receive mepolizumab receive reimbursement from private drug insurance, which reflects inequity in access across Canada.
Economic Implications: what are the economic implications of reimbursing the drug under review based on public list price.	• The Committee noted that using publicly available pricing information, mepolizumab is more costly than OCS and immunosuppressive therapies. Consequently, mepolizumab results in incremental costs relative to all relevant comparators. • The Committee observed that a comprehensive economic assessment would need to consider potential cost savings and impact on health-related quality of life (HRQoL) over a lifetime, taking into account efficacy and the prevention of adverse events associated with standard of care (SoC) treatments. However, the lack of robust clinical evidence reduces the feasibility of conducting a cost-effectiveness analysis. The absence of evidence for long-term treatment benefits of mepolizumab beyond 52 weeks limits the availability of data needed to assess its cost-effectiveness.

Full Recommendation

With a unanimous, 6 to 0 vote, the Formulary Management Expert Committee (FMEC) recommends that mepolizumab be conditionally reimbursed for the treatment of adult persons with eosinophilic granulomatosis with polyangiitis (EGPA) if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
Mepolizumab should be reimbursed in persons with a diagnosis of EGPA and who meet the following condition(s): • have relapsing or refractory EGPA and are at least 6 months since the last flare • receiving prednisone at a dose 7.5mg/day or above, with or without additional immunosuppressive therapies (i.e.: azathioprine or methotrexate).	Treatment with mepolizumab should be reimbursed for persons with EGPA whose disease characteristics are consistent with those of patients included in the MIRRA clinical trial. The initiation criteria reflect current practice.	
Discontinuation criteria		
Mepolizumab should be discontinued after a trial of at least 26 weeks therapy if there is no clinical improvement as demonstrated by one of the following: - inability to reduce the daily dosage of prednisone by 50% *or* - inability to reduce the daily dosage of prednisone below 7.5 mg/day *or* - if there is a consistent recurrent need to increase or resume oral corticosteroid therapy	Treatment should be continued for at least 26 weeks, at which time effectiveness should be assessed. Expert opinion suggests that mepolizumab therapy must demonstrate a benefit and/or a reduction in the dosing of concomitant OCS administration to qualify for renewal. The recurrent need to increase or resume oral corticosteroid therapy constitutes a treatment failure according to the clinical experts.	The intent of mepolizumab therapy may further include reducing the dose of prednisone and immunosuppressive therapy
Prescribing		
Mepolizumab must be initiated by a clinician with expertise in the management of EGPA.	Persons with EGPA are expected to be under the care of an experienced clinical team to address the complexity of treatment, maximize potential benefits, and mitigate adverse events.	

Reimbursement condition	Reason	Implementation guidance
Cost		
A price reduction may be required.	Based on publicly available pricing information, mepolizumab is more costly than OCS and immunosuppressive therapies, leading to incremental costs to the health care system. The cost-effectiveness of mepolizumab relative to SoC is currently unknown. Given the degree of uncertainty and price of mepolizumab relative to SoC, a price reduction may be required.	

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Feedback on Draft Recommendation

<to be updated after the stakeholder feedback period.>

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and our two guest clinical immunology, rheumatology and internal medicine expert specialists from Ontario and Alberta.

Meeting date: July 4, 2024

Conflicts of interest: None

Special thanks: Canada's Drug Agency extends our special thanks to the individuals who presented directly to FMEC on behalf of people with lived experience and to the patient organizations representing the community of those living with eosinophilic granulomatosis with polyangiitis (EGPA), notably Vasculitis Foundation Canada, which includes Jon Stewart and Craig Taylor.

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