CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

mepolizumab

Non-Sponsored

Indication: Eosinophilic Granulomatosis with Polyangiitis (EGPA)

February 20, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Mepolizumab
Indication: Eosinophilic Granulomatosis with Polyangiitis (EGPA)
Name of Patient Group: Vasculitis Foundation Canada
Author of Submission: Jon Stewart

1. About Your Patient Group

Vasculitis Foundation Canada's mission is to encourage and support research efforts for the cause and cure for all forms of Vasculitis. To establish a rapport with all known vasculitis patients and to try and alleviate the isolation of having an uncommon, life-threatening disease. We want to assist vasculitis patients and their families with clinical information and coping strategies, to help them develop a strong and positive outlook.

We hope to create greater awareness of vasculitis within the medical community, and the general public. We organize and administer periodic meetings, forums, and conventions for the sharing of information and ideas in the research, treatment, and diagnosis of vasculitis. Also see: www.vasculitis.ca

2. Information Gathering

In February 2024 we interviewed a small cross section of just 6 EGPA patients from five provinces. The age of patients ranged from 36 to 76, with disease onset of ~30 to 56 years of age. They were equally divided between male and female. Mepolizumab, the drug under review, has not been used by any of the patients interviewed at either the 100mgs 1x/month for asthma, or 300mgs 1x/month for EGPA. Up to three of the candidates interviewed indicated their interest in sharing their EGPA experience in a CADTH interview.

3. Disease Experience

EGPA is a life-threatening, and life-altering disease, within the family of ~26 vasculitic diseases. EGPA is a very rare disease for which there are no accurate record or registry of the exact number of patients in Canada. It is estimated that the prevalence of EGPA in Canada is in the range of 400 to 1600 with an annual incidence in the range of 40 to 80 cases per year.

For the patients we spoke to, EGPA has changed every single aspect of their lives, and not for the better! It is a chronic disease that requires powerful immune suppressive medications to induce and maintain remissions. There is a high burden of care with ongoing and repeated lab and diagnostic tests, and often lengthy hospital stays, and even repeat hospitalizations.

We asked patients to describe what their experience with EGPA has been. The responses were revealing, but not unexpected. EGPA is a very isolating disease, most patients have never met or spoken with another EGPA patient. Those who don't have close family members to care for them in hospital, and while recovering, will find there are few social supports.

Repeatedly, we hear about GI issues, lung and nerve damage (both physical and sensory), fatigue, osteoporosis, cataracts, and a broad spectrum of impacts on quality-of-life. For example, all patients we spoke with reported they were on short-term or long-term disability. All but one could not return to work, lost their jobs, or retired early. All

experienced negative impacts on their family life and relationships with huge disruptions in their day-to-day lives, including suffering from anxiety and depression. All patients experienced long periods of physical therapy to rebuild physical nerve damage, and none fully regained 100% of their lost motor skills.

The most important aspects of EGPA are to improve early diagnosis, to prevent organ involvement and tissue damage, to start treatment early, and to have new treatments available that are proven for EGPA. Patients can always benefit from proven modern treatments that are more precisely targeted, but they also need equal access and private or public coverage. Equally important would be a treatment that dramatically reduces the impact of high doses of steroids, which are often repeated, and avoid the need for toxic agents for immune suppression like cyclophosphamide.

4. Experiences With Currently Available Treatments

All patients interviewed shared similar stories of multiple hospitalizations measured in weeks or months, multiple courses of high dose IV steroids, and one of several immune suppressing treatments to induce a disease remission. All patients remain on some form of maintenance therapy, often a combination of oral azathioprine +/-125mg's/day and low dose oral prednisone +/-5mg's/day, as well as a variety of asthma inhalers. In most cases maintenance treatments have been, or will be, for years and perhaps lifelong. One patient has not achieved remission and has steroid induced osteoporosis in her spine, and is in a back brace. All patients suffer from asthma and some form of motor nerve damage, commonly foot and/or hand drop. All patients, except one, are no longer able to work, are on disability, or were forced into early retirement. All patients require ongoing physiotherapy. All but one patient tolerates current medications.

5. Improved Outcomes

We know that all vasculitis patients hate being treated with high dose steroids, and steroid reliant treatments for EGPA remain the mainstay of treatment. Glococorticoids save lives, but we also know the damage that is left behind. Steroid sparing agents are essential to progress in treating EGPA, but also other vasculitis conditions. Mepolizumab appears to be one such add-on therapy that can reduce the total amount of steroids patients are exposed to initially, and for maintenance. It also appears to reduce the need for repeat treatments with steroids. This reducing of steroid exposure represents significant progress in EGPA treatment.

6. Experience With Drug Under Review

Mepolizumab, the drug under review, has not been used by any of the patients interviewed at either the 100mgs 1x/month for asthma, or 300mgs 1x/month for EGPA. This may change as two or three patients are aware of Mepolizumab and one plans to start treatment in March 2024 as add-on therapy to assist in maintaining disease remission and to assist with steroid tapering to a zero daily dose.

One of the key values of mepolizumab is to reduce the overall dependance on steroids for EGPA induction treatment, but also to eliminate steroids in maintenance treatment.

As mentioned in point 5. We know patients hate steroids and Mepolizumab appears to be one such add-on therapy that can reduce the total amount of steroids patients are exposed to initially, and for maintenance. It also appears to reduce the need for repeat treatments with steroids. This represents significant progress in EGPA treatment.

7. Companion Diagnostic Test

We are unaware of a specific companion test for mepolizumab. However, EGPA patients are monitored on a frequent basis for a number of routine lab tests which will also be monitored while on mepolizumab. These tests all monitor disease status and whether treatments are progressing to a remission, or to maintain a remission. The most common tests performed will be the following three or four tests: eosinophil count, CRP, ESR and MPO ANCA.

8. Anything Else?

On behalf of the Vasculitis Foundation Canada community, I am a strong advocate of faster drug approvals, private and public coverage, and access to new and modern medications that target a specific need within the EGPA treatment sphere. We know that treatment with glococorticoids saves lives, but we also know the damage that is left behind. Steroid sparing agents like mepolizumab are essential to progress in treating EGPA.

Adopting new treatments, as with technology, brings forth new possibilities and can provide for a seismic shift forward in the treatment and care of Canadians with devastating diseases like EGPA. Until we can prevent diseases like EGPA, we can, and should, improve access to modern treatments as expeditiously as possible to reduce the negative impacts of such diseases.

Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Otsuka Canada Pharmaceutical Inc.,			X	
AstraZeneca Canada		X		

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Jon Stewart
Position: President
Patient Group: Vasculitis Foundation Canada
Date: 2024.02.20

CADTH Project Number - SX0839-000
Drug Name – mepolizumab
Indication – eosinophilic granulomatosis with polyangiitis
Clinician group – Vasculitis specialists of McMaster University and St Joseph's Healthcare
Author of submission – Mats Junek

Dear CADTH,

Further to your request for clinician input, please find below a letter in support of an approval of subcutaneous mepolizumab at a dose of 300 mg monthly for management of eosinophilic granulomatosis with polyangiitis (EGPA)

About Your Clinician Group

The vasculitis specialists of McMaster University and St. Joseph's Healthcare consist of an affiliated group of clinicians from rheumatology, nephrology, radiology, and respiratory medicine who provide care for patients with all forms of vasculitis and other rare, multisystemic autoimmune conditions. We are a network of both new and experienced clinicians, epidemiologists, and trialists who have both participated in and led trials and research in EGPA. We seek to better characterize patients with vasculitis, understand their care needs, and provide optimal therapy tailored to disease control and patient values and preferences.

2. Information Gathering

Information for this submission was based on several years of clinical experience caring for patients with EGPA across the spectrum of manifestations and severity, enrolling and caring for patients, and participating in other EGPA research initiatives.

3. Current Treatments and Treatment Goals

Clinicians who care for patients with EGPA have four main treatment goals: 1) induce remission of active EGPA; 2) prevent relapses of disease; 3) minimize medication burden required to maintain remission; and 4) minimize permanent damage from disease manifestations. This is done using a two-phase approach where induction treatment is provided to induce remission and then maintenance agents are used to maintain it. Induction therapies are directed by manifestations of disease and severity of these manifestations. EGPA may manifest with hypereosinophilic, allergic, and/or vasculitic symptoms (or, more often, a combination of the three) that may affect any organ. It is common for patients with EGPA to have worsening eosinophilic sinopulmonary disease that climaxes as overt vasculitis that leads to escalation in therapy for their originally sinopulmonary disease.

Trials for treatments of EGPA have expanded as collaboration has grown and have led to modern treatment guidelines (DOI: 10.1002/acr.24634). The presence of organ- or life-threatening disease manifestation (e.g. cardiomyopathy, mononeuritis multiplex) or having one or more manifestation on the five factor score (DOI: 10.1097/00005792-199601000-00003) necessitates aggressive immunosuppression with prednisone and a second

agent (typically rituximab or cyclophosphamide) followed by maintenance with rituximab, azathioprine, or other agents. For many patients, however, their crescendo of eosinophil-mediated symptoms drives disease, and these agents do not provide the same disease control, particularly for airway and sinus disease. These patients are treated with conventional agents as well as escalating doses of glucocorticoids (both oral and inhaled), which can control their disease but are associated with a large number of complications (infection risk, osteoporosis, diabetes, cardiovascular risk, weight gain, neuropsychiatric effects, etc), and patients often continue to suffer from sinopulmonary symptoms that have a dramatic impact on health-related quality of life.

These multiple treatment pathways present a complex picture that involves many different treatment agents, a coordinated team of specialists who can provide specialty care for each organ affected, and often trials of multiple therapeutic regimens to achieve control. In the Canadian context, this is complicated by a complex and heterogenous treatment landscape as there are no drugs with indication for treatment of EGPA, many generic agents (e.g. prednisone, cyclophosphamide) are used off label with variable efficacy, many medications are provided using

compassionate access (e.g. rituximab), and others are accessed through shared indication (mepolizumab/benralizumab for eosinophilic asthma). The approval of mepolizumab would allow for the first approved medication for the treatment of EGPA in Canada that directly targets the underlying pathology, improve lung and other affected organ function, improve health related quality of life, reduce medication, and improve patient independence and function. Indeed, the MIRRA and MANDARA trials (DOIs: 10.1056/NEJMoa1702079, 10.1016/j.jaci.2023.11.868) have already demonstrated these benefits.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

As highlighted above, there are currently many important treatment gaps for patients with EGPA in Canada:

- There is a lack of any approved agent for EGPA in Canada;
- There is accumulating evidence that several anti-IL5 agents are effective in treating EGPA which are not funded for this indication;
- there are no common methods of accessing off label treatments for EGPA leaving patients at the mercy of insurance and compassionate supply programs;
- Current agents are often insufficient for the large number of patients with refractory eosinophilic symptoms who require high dose glucocorticoids to manage their disease that is associated with its own complications highlighted in section 3;
- Effective treatment often requires a large number of agents to control symptoms;
- Refractory disease leads to ongoing symptoms, impaired quality of life, and organ damage; and
- Current doses of mepolizumab used to treat eosinophilic asthma are often insufficient for EGPA

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The approval of mepolizumab would provide a first-in-mechanism agent that directly controls a central pathogenic pathway in EGPA. As such, Mepolizumab is advocated to be the ideal front-line medication in EGPA without organ- or life-threatening manifestations of disease, as highlighted in the American College of Rheumatology/Vasculitis Foundation EGPA treatment guidelines where previous therapies for refractory eosinophilic asthma regularly fall without ongoing high dose glucocorticoids, which can also be insufficient. The approval of mepolizumab would bring the Canadian EGPA treatment landscape into the modern era by providing a standard access pathway to mepolizumab for patients with EPGA who have been refractory to less intensive treatment. This may slightly shift the treatment paradigm, however, as a significant fraction of patients with EGPA have symptoms that are only now treated by anti-IL-5 agents where availability is driven by private insurance, this approval would improve equity for patients who have this complex disease.

Balancing the multiple treatments for EGPA available, the cost of mepolizumab, and the improvement in patient outcomes it offers, it should be expected that patients with EGPA, especially those with sinopulmonary disease, get treatment with other therapies (inhaled corticosteroids, oral corticosteroids, rituximab, cyclophosphamide, azathioprine, or other agents as appropriate) before commencing mepolizumab. It should be recognized, however, that the diagnosis of EGPA is often made after a patient has been refractory to conventional treatments and mepolizumab may be the appropriate first therapy after a diagnosis of EGPA in this context.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients who are best suited to treatment with the drug under review are patients with active EGPA despite treatment with glucocorticoids and immunosuppressants or requiring high dose glucocorticoids (over 7.5 mg daily prednisone equivalent) to control their symptoms. It is likely that individuals with objective evidence that their disease is associated with hypereosinophilia (seen on blood tests, bronchoalveolar lavage, fraction of excreted nitrous oxide, tissue findings, or other indices) will most benefit, however, research suggests that mepolizumab may benefit individuals with any manifestation of EGPA, even those that have been previously attributed to vasculitis (a pathophysiologic process that may have a more loose association with inappropriate eosinophil activity). These patients are best identified by clinicians who care for them who have specialist knowledge of these tests and their appropriate interpretation.

It can be difficult in some patients to separate a diagnosis of EGPA from hypereosinophilic syndrome and severe eosinophilic sinopulmonary disease, however, all of these syndromes often manifest with symptoms refractory to the same therapy (glucocorticoids) and evidence has demonstrated that mepolizumab is therapeutic for all of these diagnoses. As such, it is important that individuals who are being treated undergo comprehensive assessment to confirm their diagnosis is EGPA, and, if there is equipoise, patients should undergo ongoing monitoring by their treating clinicians to observe for evolution in the diagnosis and/or needs for changes in treatment. Given the rarity of EGPA as a diagnosis, this process is already standard of care and would not be altered by the addition of mepolizumab, nor would new methods of assessing EGPA be needed for appropriate prescribing of mepolizumab to occur.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

A response to mepolizumab is best observed through improved control of symptoms of EGPA (reduced flares of sinopulmonary disease, reduced chronic sinopulmonary symptoms, and improved quality of life), lowering in need of oral glucocorticoids to maintain symptoms, or both. A clinically meaningful response is often through patient reported improvement or progressive de-escalation of oral glucocorticoids for symptom management, well documented in the MIRRA trial. As assessments of asthma and chronic rhinosinusitis have become standardized, demonstrating this benefit across patient populations and contexts is now a simple task. This response is often seen within the first 4-12 weeks of treatment and is assessed through both clinical encounters as well as improvements in blood test results, pulmonary function testing, and imaging.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

There are two contexts in which drug discontinuation of mepolizumab needs to be addressed: refractory disease and disease in persistent remission.

For patients with refractory disease with ongoing symptoms or damage despite multimodal therapy, mepolizumab is often used with escalating doses of oral and or inhaled glucocorticoids. If insufficient, other anti-IL5 agents such as benralizumab and reslizumab are demonstrating an emerging role in EGPA and will be important considerations for future drug approvals that are currently only available with insurance approval or trial participation, other trials in EGPA for refractory disease are also being started. In this context, mepolizumab is typically stopped for new agents rather than continued, however, there are cases where combination therapy with mepolizumab and non-IL-5 agents (e.g. dupilumab) may manage refractory symptoms.

For patients where remission has been induced and symptoms are effectively managed, there is a paucity of data on how long one should be treated or if treatment may be de-intensified. Treatment is typically continued as long as medications are available; it is possible that a trial of de-intensification to lower doses of mepolizumab or other agents may be able to take place however this is done on a case-by-case basis without data to guide such practices at this

time. Factors important to these decisions include duration of disease control, other therapies needed to control disease, patient values and preferences, adverse effects of treatment, damage from disease, and the risk of organ- or life-threatening events on relapse.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Mepolizumab is best prescribed by individuals with experience in treating patients with EGPA, namely respirologists and rheumatologists. It may be started in an inpatient or outpatient setting safely and does not need inpatient monitoring for its first dose. As long as patients are on drug they should be monitored by specialists both clinically as well as blood tests, relevant imaging, and assessment of pulmonary and physical function.

6. Additional Information

None

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Mats Junek

Position: Rheumatologist, Vasculitis Fellow, PhD candidate focusing on trials in vasculitis, co-founder McMaster Vasculitis Research Group

Date: 20 Feb 2024

CADTH Project Number - SX0839-000
Drug Name – mepolizumab
Indication – eosinophilic granulomatosis with polyangiitis
Clinician group – Vasculitis specialists of McMaster University and St Joseph's Healthcare
Author of submission – Mats Junek

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Roche			X	

* Place an X in the appropriate dollar range cells for each company.

Recipient of unrestricted educational funding from Roche to complete vasculitis fellowship.

Declaration for Clinician 2

Name: Nader Khalidi

Position: Rheumatologist and Professor of Medicine

Date: 20 February 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
BMS		X		
AbbVie			X	
Sanofi			X	
Astra Zeneca	X			
Kataka Medical	X			
Otsuka	X			
GSK	X			
Mallinckrodt	X			

* Place an X in the appropriate dollar range cells for each company

Funding from BMS, AbbVie, and Sanofi are for GCA clinical trials

Funds from Astra Zeneca, Kataka Medical, Otsuka, GSK, and Mallinckrodt are for ad board participation

[redacted]

[redacted]

Dr. Daniel Ennis
MD, FRCPC (MSP 82914)
Clinical Assistant Professor
UBC Division of Rheumatology
VCH-Mary Pack Arthritis Program Vasculitis Clinic

regarding patient

CADTH, Cadth

BC, CAN

date of birth :
home phone :
work phone :
other phone :

age :
sex : U
PHN :

February 20, 2024

To the CADTH,

This letter is in support of coverage for Mepolizumab for the indication of Eosinophilic Granulomatosis with Polyangiitis.

There have been significant research advances in this disease that consistently show benefit with Mepolizumab for this indication. The available literature is compelling that Mepo is effective not only for asthma or eosinophilic pneumonia, but also for vasculitic manifestations of the disease. I have included a powerpoint presentation in support of this.

Mepolizumab is also supported in multiple guidelines for use in refractory, glucocorticoid dependent, or relapsing EGPA.

It should be accessible to Rheumatologists for use. This is a rare disease and our treatment options are limited. It is a reasonable treatment option with low risk and high potential benefit as a steroid sparing agent.

Thank you for your consideration

Sincerely,

[redacted]

Daniel Ennis, MD, FRCPC
Internal Medicine and Rheumatology

Dr. Daniel Ennis, MD, FRCPC
Electronically Authenticated by PLEXIA EMR

Accepted By: Daniel Ennis - Feb 20, 2024
Entered By: Daniel Ennis - Feb 20, 2024

CADTH Reimbursement Review

Drug Program Input on Implementation Issues

Section 1: General Information

1.1 Drug Product Information:	
Drug name (generic): Mepolizumab	**Sponsor:** **Non-Sponsored**
Indication: Eosinophilic Granulomatosis with Polyangiitis Nucala is indicated as an add-on to corticosteroids for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).	
Reimbursement Request: As this is a non-sponsored review, the reimbursement request aligns with the indication for treatment of eosinophilic granulomatosis with polyangiitis.	

1.2 Lead Jurisdiction
Jurisdiction: Saskatchewan

Section 2: Jurisdictional Implementation Issues

Table 1: Jurisdictional Context

2.1 RELEVANT COMPARATORS Check (type "X") whether you have identified potential or current **issues** and provide brief details	
X	**a) Issues with the choice of comparator in the submitted trial(s)** Example text: Comparator drug is not funded in most provinces. Corticosteroids are full benefits in most provinces. Methotrexate, cyclophosphamide and azathioprine are full benefits. Access to rituximab varies across jurisdictions.
X	**b) Other implementation issues regarding relevant comparators (e.g., access/funding, covered population)** Nucala is the only IL-5 with the HC approved indication for treatment of EGPA. Question for Expert: Is there evidence to suggest other IL-5 inhibitors (Fasenra or Cinqair) are effective for the treatment of EGPA?

Table 2: Policy Considerations for Reimbursing the Drug

2.2 CONSIDERATIONS FOR INITIATION OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
X	**a) Disease diagnosis, scoring or staging for eligibility** Nucala is indicated as add-on therapy to corticosteroids. Question for clinical expert: When is it appropriate to add Nucala therapy to corticosteriods? At what stage in the disease process is should Nucala be added to the treatment regimen for EGPA?
X	**b) Other patient characteristics for eligibility (e.g., age restrictions, comorbidities)**

	Patients with EGPA and asthma may qualify for coverage of Nucala under public drug plans. However the dose is much higher for EGPA. Questions for Drug Plans: Do drug plans have quantity limits in place to limit dosing to those appropriate for asthma? What is the anticipated duration of therapy for Nucala for EGPA? Is this long-term therapy?
X	**c) Prior therapies required for eligibility** Are there other therapies that should be trialed (other than steroids) before Nucala for treatment of EGPA? Standard of care in the clinical trial was gluccocorticoids +/- immunosuppressive therapy.
☐	**d) Eligibility to re-treatment** Example: Can the drug be given again to patients who relapsed while off therapy? If so, what would be the appropriate timing of re-treatment?
☐	**e) Special subtypes (not explicitly mentioned in the indication) to consider separately for eligibility** Example: Would patients with CNS metastases equally benefit from this oncology drug and would they be considered eligible?
☐	**f) Consistency with initiation criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with reimbursement criteria for drug B.
2.3 CONSIDERATIONS FOR CONTINUATION OR RENEWAL OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Challenges related to assessment and monitoring of therapeutic response** Example: Need for regular brain MRI scans to monitor response to drug. There is limited access in some provinces.
☐	**b) Consistency with renewal criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with renewal criteria for drug B.
2.4 CONSIDERATIONS FOR DISCONTINUATION OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
X	**a) Definition of loss of response, absence of clinical benefit, or disease progression** How is loss of response to Nucala in EGPA defined?
☐	**b) Treatment interruptions** Example: If there is progression during a "drug holiday", can treatment be resumed? According to what timeframe?
X	**c) Definition of fixed-duration therapy** What is the anticipated duration of therapy? Are patients able to discontinue treatment with Nucala for EGPA? The trial was 52 weeks in duration, and the primary outcome was achievement of remission at week 36 or week 48.
☐	**d) Consistency with discontinuation criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with stopping criteria for drug B.
2.5 CONSIDERATIONS FOR PRESCRIBING OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
X	**a) Dosing, schedule/frequency, dose intensity** For EGPA the dose is 300 mg subcut every 4 weeks. Nucala is available in a 100 mg syringe, therefore the patient will need to deliver 3 separate injections for a dose. This dose is 3 times higher than that for asthmas or nasal polyps.
X	**b) Drug administration** Patients can be trained to self administer the drug. May be more prone to injection site reactions with EGPA due to the dose.
☐	**c) Concerns related to accessing clinical specialists and/or special settings** Example: There is limited access to specialists within some regions.
☐	**d) Concerns related to combination usage**

	Example: The combination includes an oral and an IV drug that would be reimbursed through different programs.
☐	**e) Consistency with prescribing criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with prescribing criteria for drug B.

Table 3: Special Implementation Issues

2.6 GENERALIZABILITY Check any category where you have identified potential or current **issues** and provide brief details	
X	**a) Populations of interest matching the indication but with insufficient data** Nucala for EGPA is indicated only for adult patients. In asthma, Nucala is indicated for treatment of patients as young as 6 years of age, and the drug is available in a pediatric format (40 mg prefilled syringe). Nucala is indicated as an add-on to steroids for EGPA. Can it also be used as monotherapy? The clinical trial excluded the following groups of patients: • Patients with granulomatosis with polyangiitis or microscopic polyangiitis; • Patients with organ or life-threatening EGPA
X	**b) Populations outside the indication or reimbursement request but of interest to jurisdictions** Nucala is also indicated for hypereosinophilic syndrome, but has not been reviewed for this indication by CADTH.
☐	**c) Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review** Example: Potential need to allow switching patients currently receiving a comparator, if the drug under review is recommended and deemed superior.
2.7 FUNDING ALGORITHM (ONCOLOGY ONLY) Check any aspect that may require the development of a provisional funding algorithm by CADTH	
☐	Drug may change place in therapy of comparator drugs
☐	Drug may change place in therapy of drugs reimbursed in previous lines
☐	Drug may change place in therapy of drugs reimbursed in subsequent lines
☐	Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products
☐	Other aspects:
2.8 CARE PROVISION ISSUES Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Drug preparation, storage, administration or dispensing** Example: Drug needs to be initiated in the hospital setting while maintenance therapy would be provided in the community setting.
☐X	**b) Management of adverse effects** **c) Is the higher dose associated with a higher risk of side effects?**
☐	**d) Additional supportive medication or other health interventions** Example: Immunosuppressive drug requires co-administration of prophylactic antimicrobials.
☐	**e) Companion diagnostics (e.g., access issues, timing of testing)** Example: Need advice on optimal timing of biomarker testing (e.g., at time of diagnosis, as part of eligibility assessment prior to initiation).
☐	**f) Other care provision issues** Example: To manage toxicity, can one drug of the pair be stopped and the other continued until loss of clinical benefit?
2.9 SYSTEM AND ECONOMIC ISSUES Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Concerns regarding the anticipated budget impact and sustainability**

	Example: Provision of this drug in the first line setting may translate into substantial budget impact. A prioritization scheme may be required.
☐	**b) Additional costs to be considered (other than related to care provision as detailed above)** Example: This therapy requires facilities that are not available in all provinces. Drug plans may need to cover travel expenses for eligible patients.
☐	**c) Involvement of additional payers** Example: The implantable device component of this therapy will need to be funded by medical services departments within jurisdictional health care systems.
X	**d) Presence of confidential negotiated prices for comparators** pCPA has successfully negotiated pricing for Nucala for eosoinophilic asthma. Nucala for nasal polyps is still under negotiation at pCPA.
☐	**e) Special programs or initiatives for the introduction and management of the drug(s) under review** Example: Due to their abuse potential, drugs of this class are usually subjected to a controlled distribution program.
X	**f) Other system or economic issues** Since Nucala is a biologic, biosimilars would be expected in the future.

GlaxoSmithKline Inc.
[redacted]
www.gsk.ca

February 20, 2024

Canadian Agency for Drugs and Technologies in Health (CADTH)
600-865 Carling Avenue
Ottawa, ON K1S 5S8

Dear CADTH Review Team,

Reference: Non-Sponsored Reimbursement Review of mepolizumab for EGPA

GlaxoSmithKline Canada (GSK) welcomes the opportunity to provide a written submission in response to the CADTH Non-Sponsored Reimbursement Review of mepolizumab for eosinophilic granulomatosis with polyangiitis (EGPA). It is also worth recognizing our appreciation for the inclusive nature of the stakeholder outreach.

The purpose of our submission is to provide CADTH a summary of the unmet need, diagnostic challenges, treatments and management, and quality of life in this rare disease. This submission also summarizes the clinical evidence for mepolizumab (NUCALA) in EGPA.

Unmet Medical Need for a Rare Disease

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare and complex disease presenting with heterogenous manifestations characterized by tissue eosinophilia, necrotizing vasculitis and eosinophil-rich granulomatous inflammation.[1] As such, EGPA is often unrecognised by physicians leading to delays in diagnosis[2-4] which can have a profound impact on patient prognosis.[2,5]

Patients with EGPA often experience significant co-morbidities and symptom burden involving frequent relapses, persistent severe asthma, and end-organ damage.[6] These poor outcomes contribute to increased psychological distress for the patient, including anxiety and depression[7,8], and significantly greater healthcare resource utilization.[9,10] Such disease burden is exemplified in a meta-analysis of 35 observation EGPA studies, where relapses were reported as high as 80% and the annual inpatient admission and emergency room visits were 17%–42% and 25–42% respectively.[9]

EGPA is also associated with chronic complications and damage involving possible multiple organs. Long-term lung complications such as chronic airway obstruction are commonly reported.[11,12] Cardiac involvement is considered to be the most life-threatening manifestation of EGPA as it can go undetected, negatively affecting prognosis and increasing mortality.[13,14]

Current immunosuppressive therapies available for EGPA (e.g. cyclophosphamide, rituximab, azathioprine, methotrexate) are associated with possible adverse effects (such as infection, cancer, infertility) and require dose monitoring/adjustments.[2] Patients with severe or non-severe EGPA are initially treated with systemic glucocorticoids (GCs)[15,16], however, many patients will either relapse and/or progress when tapering off GC.[16] Cumulative GC exposure can lead to significant toxicities such as diabetes mellitus, myopathy, osteoporosis, hypercortisolism, and vertebral fractures.[17-20] With these associated comorbidities and toxicities related to current therapies, there is a pressing need for effective and licensed treatment options for relapsing and remitting EGPA with an acceptable safety profile.

Diagnostic Challenges in EGPA

EGPA has been described in three successive phases: a prodromal phase, mainly characterized by late on-set asthma, that can also include chronic rhinosinusitis and nasal polyposis; an eosinophilic phase characterized by peripheral blood and tissue eosinophilia; and a vasculitic phase characterized by necrotizing vasculitis of the small to medium blood vessels often affecting the skin and nervous system, but any organ system may be involved.[21] Not all patients experience all phases, and these phases may overlap adding to the complexity of the diagnosis.[1]

In fact, this 3-phase concept has shifted towards a multistep disease with longer-term manifestations and complications and damage.[22] Formal diagnostic criteria for EGPA are lacking; classification criteria is used to classify a patient as having EGPA.[23] It can often be difficult to differentiate EGPA from Hypereosinophilic Syndrome (HES) – another rare condition which is marked by hypereosinophilia (blood eosinophil ≥ 1500 cells/µL) and which presents with symptoms that may overlap with EGPA. This differential diagnosis is important since these conditions require different clinical management.[24]

Amongst the variable symptomology, EGPA is considered a form of antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with myeloperoxidase-ANCA present in approximately 40% of patients, and all patients experience eosinophilia (blood eosinophil ≥ 1000 cells/µL) prior to treatment.[1,6,23,25-27] Asthma is the most common feature of EGPA, occurring in 96% to 100% of patients[28], with severe asthma reported in 65% of patients with EGPA.[9] Patients typically have an adult-onset asthma, which becomes more severe with time and is often refractory to the traditional inhalation treatment. Due to the heterogeneity of EGPA, it is possible for patients with the disease to also have severe asthma with an eosinophilic phenotype (SA-EP) symptoms.[22,28,29] For patients with EGPA and SA-EP, there is an overlap in symptomology and will often require oral corticosteroids for adequate asthma control[28], which may in turn delay both the presentation of the vasculitic phase and the diagnosis of EGPA by masking other EGPA features.[21] The typical latency between asthma presentation and the vasculitic phase of the disease is estimated to last for an average of 3 to 9 years but has been reported as long as 30 years.[28]

Quality of Life and Disease Burden of EGPA

Asthma symptoms that remain persistent in patients with EGPA are one of the most important factors that negatively affect patient quality of life when other symptoms of the disease are controlled.[28,29]

Overall, patients with EGPA and other forms of AAV, have lower health-related quality of life (HRQoL) than the general population ($p<0.00001$)[30] especially those with relapsing remitting disease ($p<0.00625$).[31] Fatigue is consistently reported as the most impactful symptom on the EGPA patient's health related quality of life.[32,33]

In addition to impairments in HRQoL, EGPA has a negative impact on patients' ability to work and in some cases leads to a job change or retirement.[32] In instances where EGPA has led to unemployment, patients experience a considerable reduction of HRQoL, independent of severity and extent of disease, as evidenced by lower scores in the majority of HRQoL dimensions.[32] A large study of 410 patients with AAV including 44 patients with EGPA reported that 26.0% of patients of working age were unable to work due to ill health.[34]

Treatment and Management of EGPA

The goals of treatment of EGPA are to induce remission, prevent relapses, limit disease-related damage, minimize treatment-related morbidity and improve survival. Treatment is tailored based on the severity of symptoms (e.g. with or without organ- or life-threatening manifestations) and the patient's prognosis as determined by their Five Factor Score (FFS).[35] Patients with more severe disease usually receive more intense immunosuppressive agents. Treatment recommendations for EGPA are complex, given the challenges to study treatments in rare disease, and the heterogeneity of its presentation.[22,26] These recommendations and guidelines also vary slightly across regions.[15,35,36]

Oral corticosteroids (OCS) and systemic GCs are the foundation in the standard of care for EGPA.[22,37] For patients with severe disease (major organ involvement, life-threatening manifestations, and/or a FFS $\geq$1, high-dose GC are used to achieve remission with the addition of cyclophosphamide (CYC) or rituximab (RTX).[35,36] These patients are then switched to either azathioprine (AZA) or methotrexate (MTX) maintenance (less often leflunomide (LEF) or mycophenolate mofetil (MMF)).[35]

For the non-severe EGPA patient (without organ- or life-threatening manifestations and/or the absence of poor prognostic factors (FFS=0)), GCs alone are usually sufficient to induce remission. Non-severe patients with relapsing or refractory EPGA can similarly be switched to AZA or MTX for maintenance remission.[35,36] In the last several years, there has been emergence of a new class of therapies targeting interleukin-5 (IL-5). Mepolizumab (humanized monoclonal antibody targeting circulating IL-5) was investigated as add-on therapy in patients with relapsing or refractory EGPA (the MIRRA trial) without organ or life-threatening manifestations. Since the publication of this trial, there have been large retrospective cohorts supporting the use of mepolizumab in reducing disease activity and prednisone dose.[38,39]

Despite adequate control of the vasculitic manifestations with GCs, a large proportion of patients become GC-dependent due to ongoing symptoms mostly related to asthma exacerbations or ENT symptoms.[29,40] Treatments to limit the use of GC is an ongoing struggle. As a consequence, drug-related adverse effects are a challenge, requiring the clinician to balance disease control with long term toxicities. The advent of anti-IL5 therapies has allowed us to move one step forward in optimizing care of patients with EGPA.

Mepolizumab (NUCALA)

In the phase III MIRRA trial, mepolizumab + standard care (SC) was studied against placebo + SC in adults with relapsing or refractory EGPA without organ or life-threatening manifestations. The two primary end points were met. Participants receiving 300 mg of mepolizumab + SC spent a significantly greater time in remission over the 52-week treatment period than participants receiving placebo + SC ($p<0.001$); 28% of participants receiving mepolizuamb + SC spent 24 weeks or more in remission vs. 3% of participants receiving placebo + SC.[41] The mepolizumab + SC group was nearly 10 times more likely to achieve sustained remission at weeks 36 and 48 of the study than the group receiving placebo + SC (32% vs. 3%, respectively; $p<0.001$).[41]

The MIRRA trial also found the annualized relapse rate was 50% lower in the mepolizumab + SC group compared with the placebo + SC group (annual rate of relapse: 1.14 vs. 2.27, respectively; $p<0.001$); the time to first relapse was also significantly longer for those treated with mepolizumab + SC vs. placebo +

SC (relapse within the 52-week period: 56% vs. 82%, p<0.001).[41] No significant difference was found between the mepolizumab group and the placebo group in the proportion of participants who had an adverse event, serious adverse event, cardiovascular adverse event, and systemic or local-site reaction.[41]

The clinical trial program demonstrates mepolizuamb is an effective and well-tolerated option for non-severe patients with relapsing or refractory EGPA. The evidence has led Health Canada to grant NUCALA the indication as an add-on to corticosteroids for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

Summary

EGPA is a complex rare disease with heterogeneous manifestations. Due to the variations in symptomology between patients, EGPA is associated with a high risk of morbidity due to complexities in navigating the healthcare environment leading to delayed diagnosis. Further, the significant comorbidities associated with the disease, such as persistent severe asthma, and end-organ damage significantly impact patients HRQoL and reduces their ability to achieve their full productive potential in society.

Current treatments for EGPA require physicians to balance disease control with long-term drug toxicities. It is important to note that other options exist, and effective collaboration between industry, CADTH, and the provincial health authorities is essential for patients to be able to access these medications. This includes mepolizumab, an effective and well-tolerated option for non-severe patients with relapsing or refractory EPGA.

We look forward to exploring solutions with CADTH and the provincial health authorities to improve access to NUCALA in this rare disease with significant unmet need.

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GlaxoSmithKline Inc.

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