Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

zilucoplan (Zilbrysq)

(UCB Canada Inc.)

Indication: Indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Patients continued to receive standard therapy throughout the pivotal trial.

March 11, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC 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. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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CADTH Reimbursement Review Patient Input

Name of the Drug and Indication	**Zilucoplan** **Generalized Myasthenia Gravis (gMG)** **SR0838-000**
Name of Patient Group	**Muscular Dystrophy Canada**
Author of Submission	**Homira Osman, PhD**

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

Muscular Dystrophy Canada is registered with CADTH.

Muscular Dystrophy Canada (MDC) supports people affected by muscular dystrophies and related muscle diseases. Together, these rare conditions are referred to as “neuromuscular disorders.” Neuromuscular disorders are a group of diseases that weaken the body’s muscles. The causes, symptoms, age of onset, severity and progression vary depending on the exact diagnosis and the individual.

Since 1954, Muscular Dystrophy Canada has been the leading health charity and voice of the neuromuscular community in Canada. MDC is a sophisticated network of informed professionals, service specialists, and volunteers who deeply understand neuromuscular disorders. MDC represents 30,896 Canadians impacted by neuromuscular disorders including 12,047 persons with neuromuscular disorders, and 19,155 family members/caregivers.

MDC’s mission is to enhance the lives of those impacted by neuromuscular disorders by continually working to provide ongoing support and resources while relentlessly searching for a cure through well-funded research.

MDC has a full spectrum of programs, services, and supports for the thousands of Canadians of all ages living with a neuromuscular disorder that include: systems navigation, education and knowledge translation, access to financial supports for critical life-changing equipment and services to improve quality of life, peer-to-peer networking, emotional support, evidence- based information for new treatments, medical advances, and clinical trials and advocacy. Plus, MDC invests in transformative research to work towards more answers, therapies, and hopefully, potential cures.

Funded by Canadians from coast to coast, our investment in the research community is advancing the development of important new treatments. Our programs and services play a critical role in informing and supporting members of the neuromuscular community by funding equipment to improve daily life; hosting family and caregiver retreats; providing emotional and educational support; and with providing access to vital resources and support systems. Our advocacy efforts focus on enhancing public policy at all levels of government to bring about positive change. We are currently working to bring new treatments and trials to Canada. Advances in medicine have resulted in individuals with neuromuscular disorders living longer but not necessarily living better. As their disorder progresses and changes, so do their needs and financial strains.

Our desire is to provide support through all stages of disease progression by providing the tools, resources and support individuals need to live a full and rich life.

At the MDC, we follow the principle *Nothing About Us Without Us* closely. Individuals with Myasthenia Gravis and their circle of support are actively involved in every aspect of our organization - from leadership and decision-making roles to serving on committees and participating in collaborative research efforts. By integrating the perspectives and experiences of those affected by Myasthenia Gravis, we strive to ensure that our efforts are aligned with the needs and priorities of the patient community

Myasthenia gravis (MG) is one of the neuromuscular disorders that falls under MDC's umbrella. There is expected to be approximately 10, 000 patients affected by MG in Canada.

MG is a rare and chronic autoimmune disease in which autoantibodies attack specific proteins in the neuromuscular junction, resulting in muscle weakness. Many patients develop generalized MG resulting in severe fatigable muscle weakness with difficulties in facial expression, speech, swallowing, and mobility.

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include ***when*** *the data were gathered; if data were gathered* ***in Canada*** *or elsewhere; demographics of the respondents; and* ***how many*** *patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.*

Muscular Dystrophy Canada has Neuromuscular Service Support Staff in all provinces across Canada. As part of the System Navigation Program, the Neuromuscular Service Support Staff provide front-line support to thousands of Canadians affected by neuromuscular disorders. The program operates on collaboration and patient engagement principles. Neuromuscular Service Support Staff work directly with patients and family members to identify non-medical needs (e.g., housing, transportation, access to equipment, information on clinical trials) and provide them access to the right resources in a personalized customized manner. Neuromuscular Service Support Staff work in partnership with patients and their families to address barriers, network and make connections with others in the community, share education materials and resources, enhance life skills and self-coping strategies, embrace inclusion and ultimately provide supports to help positively improve the overall well-being and quality of life of the patient and their family members.

The Neuromuscular Service Support Staff identified and contacted adults living with Myasthenia gravis to participate in a healthcare experience survey (available in English and French) and semi-structured virtual (phone, Zoom) interviews. We shared the survey with members by e-blasts, personalized invites and Canadian patient online groups (i.e., Canadian Snowflakes -Myasthenia Gravis Support Group).

MDC also conducted a Myasthenia Gravis Canadian Journey Mapping project, where 1-hour interviews, roundtable sessions, surveys, health-related quality of life measures (i.e., EQ-VAS, EEQ-5D, MG-ADL, MG QOL) were completed.

The following submission reflects data from a total of 127 individuals impacted by MG, the majority of which have a confirmed diagnosis of generalized Myasthenia Gravis through clinical reports. The respondents included 43 males and 84 females between ages 22 to 78 from all provinces in Canada.

In addition to previously collected information on Myasthenia Gravis, we recently sought the opinion on the value of having zilucoplan approved for use in Canada for those affected by generalized Myasthenia Gravis. 47 Canadians (33 females, 14 males) with MG specifically provided input on their knowledge of zilucoplan and their everyday experiences with MG. A qualitative descriptive approach, employing the technique of constant comparison, was used to produce a thematic analysis. We have included patients' quotes to ensure their voices are captured in this report and to provide context for quantitative elements. A report capturing all patient comments is also available for review.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

We asked participants to describe how Myasthenia gravis affects their daily life and quality of life, as well as which aspects of the condition are more important to manage. Based on the responses, the survey identified 7 key themes that were frequently reported, listed in order of frequency: 1) significant impact on productivity, 2) significant impact on fatigue, energy levels and quality of sleep, 3) significant impact on respiratory health, 4) significant impact on mobility and strength, 5) significant impact on independence, 6) significant impact on relationships and social participation, 7) significant impact on eyes/vision and speech and swallowing.

Individuals affected by Myasthenia gravis conveyed through their quotes that the impact of MG extends beyond physical symptoms, and that it affects their mental health, quality of life, and the wellbeing of their families.

Significant Impact on Productivity (at Work and Home)

*"Because of myasthenia gravis, I have not been able to work and this has become a huge driver of my **financial problems**."*

*"I am **not able to work** in the same way since I have been diagnosed. I try to do some work, but everyday is unpredictable and I need to have a job that is flexible."*

*"I have had at least 61 sick days in the past year alone. This is **unpaid work leave** because of MG."*

*"I am **unable to work**, need to rest frequently, need help with activities like washing my hair, etc."*

*"I had to **retire** from my job because of MG."*

"I retired because the stress of my job plus MG did not mix well."

"I have worked while experiencing a MG crisis – it was horrible. I am fearful for the next crisis."

"I am on disability leave because of my MG."

"I am no longer able to work and rely fully on my husband for my meals, clean home and being moved from one place to another."

"I wasn't able to work today because I was very tired. It gets in the way of my ability to work. And this impacts my finances in a huge way."

"I am not able to do the work I was once able to because I can't strain my eyes and read for more than 20 minutes."

"I feel useless at home. Everything now falls on my husband. Taking care of the children, cleaning, cooking and taking care of everything that revolves around IVIG treatment. MG is unreliable and my ability to support is unreliable."

"I had to move to part time and modified work."

"I can walk into the office but might need to be carried out by my partner. I no longer feel productive or competent at work."

"MG forced me into retiring earlier than I would have otherwise."

"I can no longer work. This impacts my finances and how I spend money."

Significant Impact on Fatigue/Energy Levels & Quality of Sleep

*"I am unable to do anything without **feeling tired**."*

*"I can do one task and then **need a break**."*

*"Think of the spoon theory: In the theory, each spoon represents a **finite unit of energy**. Healthy people may have an unlimited supply of spoons, but people with MG have to think carefully and plan ahead on where to spend their energy to just to get through the day."*

*"I experience **fatigue** daily at some point, usually in the evening"*

*"I get **very tired** from even a conversation or reading an article."*

*"If I overdo things I will need to rest. It could hit me the same day or the next day. I may **be fatigued a good part of the day**."*

"If I do too much, I know I will pay for it the next day. I will need a full day to recover. Imagine how you feel after travelling on different time zones, this is me every time I do something as simple as going to get groceries or cleaning my home."

*"I **tire very easily**. Do 10 minutes of housework then have to rest. Some days I can do this and some days I can't do anything."*

*"I typically **require a 15 or 20 minute rest** after having a shower!"*

*"Most days I have to sleep for a couple of hours in the afternoon **due to fatigue**."*

From our MG Canadian Journey Mapping project, we used photo voice methodology. One of the participants shared:

"I use this metaphor of "I feel like Cinderella" or I have to do X, Y, Z before I turn into a pumpkin. Daily, I guess this is what I feel. All of us share this experience that you only have so many things you can do in a particular day and particularly any task that exacerbates MG symptoms. Pretty much everyday, if I wake up feeling quite good, I realize, like Cinderella at midnight the coach turns into the pumpkin and that was it. She has to go home and resume a sort of oppressed life. I'm not suggesting mine is oppression, but at a certain point in the day when I run out of energy and the MG starts to flare up, I have to shut down whatever plans I have or whatever I'm doing and just be able to rest and not make things worse so that's new."

Significant Impact on Respiratory Health

*"The most bothersome aspect of MG is definitely the impact on **breathing."***

*"I can feel **my lungs are weaker** because of MG."*

"I am immunosuppressed because of the MG drugs and I feel weak respiratory wise. The combination of the two is awful."

*"It is scary **how difficult it is to breathe** sometimes and that's why I have a ventilator near by."*

*"I had to go **on a ventilator in ICU three times** now because of MG crises."*

*"**Choking on food or saliva interferes with breathing** as diaphragm muscles become weak."*

"Breathing is most affected, limiting my ability to walk, climb stairs, or bend over to tie my shoes."

*"I have terrible **shortness of breath**."*

Significant Impact on Mobility & Strength

*"My **legs are weak.** By the time I get to the top of the stairs, I have to drag my legs up to the top of the stairs."*

*"I have **lost the ability to walk** without support."*

"Sometimes I can walk into the grocery store, but will need to carried out by a family member or use a wheelchair on the way out."

*"I used to walk around the neighbourhood after dinner, now **I can't even walk inside my house**."*

"I can walk short distances but always keep a walker or cane near by because you never know when the MG will flare up or when I will turn into a rag doll."

*"I **can't walk** without a walker, I **can't stand** for any length of time, **can't sleep at night** because it aches."*

"I can't do stairs anymore. We had to remodel our entryway because it was becoming increasingly difficult to get inside the house on my own."

*"Some days it is **difficult to just walk**. Muscles seem be tense and not allowing me to do things."*

*"I **cannot walk down the street without falling**. I cannot hold up a blow dryer to dry my hair."*

Significant Impact on Independence & Social Participation

"My independence has taken the biggest hit."

"I can still bake, but it takes me hours more. I can clean, but then the rest of the day I need to rest. While I am able to do things, it takes me away from other things. I only have energy for some tasks."

"Brushing my hair, blow-drying my hair has become taxing and some days it feels impossible to do that."

"I am unable to drive because of the weakness in my eyes and generalized weakness."

"MG has taken a huge toll on my relationships and on my ability to carry activities out on my own. I rely on my partner for many reasons and there is guilt."

*"Standing to cook or do dishes takes 3x longer. On bad/weak **days I feel like a prisoner in my own house.**"*

"We are not able to travel because heat bothers me, stress is a trigger for MG."

*"I have symptoms everyday. **Difficulty completing activities of daily living**. No longer able to work. Can only drive short distances. I miss out on socializing due to mobility and fatigued."*

"I need to take Mestinon daily and have to try hard to avoid a Myasthenia flare up. Prior to diagnosis, I have spent long weeks and even months ***quite disabled and dependent on others for care****. It affects social life, professional life, and all areas of my life."*

"I feel like I can't be left alone – I feel I am on the verge of the next myasthenic crisis."

*"****Not able to do dishes and laundry and everyday normal tasks****. some days it's not bad and then it will go for a couple of days and then it will flare up."*

*"****Not being able to do anything with others****. I can't get in a vehicle and can't lift my legs. I can't go out to see other people. I did have a scooter but it got burned up and I don't have a scooter anymore."*

"Visiting with friends and family tire me out. Can't get to church. Can't go to play darts. It is very depressing knowing that there is no cure and that this is my way of life now."

"I am ***very restricted in my abilities and require assistance****.* ***Loss of independence, social interaction and employment****."*

*"****Loss of independence is awful.*** *I can't do activities on spur of moment, have to be carefully planned and at times have to decline, have had to drop out of some activities."*

"It has tremendously affected my independence. I cannot drive. They took my license away. I don't have a scooter. Not being able to be with my friends or anything. The only way to see people is for them to come to me."

"I am a very independent person and now I am ***scared to be alone*** *for long periods of time."*

"I can't drive at night or for long periods, I can't clean my own house, I can't cook for long periods of time, etc."

"I have to ***have someone drive me*** *to any appointments out of time. I also have to* ***have help with some activities for daily living.****"*

"I have to ask my husband to puree my foods and brush my hair. I have lost complete independence and that is the most bothersome aspect of MG."

Significant Impact on Eyes, Speech & Swallowing

"I have to ***puree my foods*** *and chug it down."*

"I tend to ***choke on my own saliva*** *and food."*

"I had ***slurred speech as though I was intoxicated****."*

"My ***voice gives out on me*** *and sounds very strained after a short conversation sometimes."*

*"****Not being able to speak*** *is very hard."*

"The ability to swallow and have my facial muscles work properly is very important as it affects my daily life at work. When they don't, it's very frustrating because you cannot take too much Mestinon to correct it. It's time released and dosage is every 4 hours."

"Choking on food or saliva interferes with breathing as diaphragm muscles become weak."

"I think people not understanding or even knowing about it as it's one of those invisible illnesses. I'm not in a wheelchair and outwardly appear to be "fine", but it's what's going on inside is something only I know unless I start ***slurring my speech****. When that happens, people who don't know me or anything about me having MG, might think I'm intoxicated.*

"Breathing is often affected, ***limiting my ability to walk, climb stairs, or bend over to tie my shoes****."*

"One of the first symptoms of MG is ***a defect in eye sight*** *and then a weakness in muscle, if one is lucky and MG is diagnosed at an early age (I was 24 and I think that I was fortunate that I had knowledgeable physicians) that the shock of the diagnosis is easier to accept."*

"It ***affects my eyes*** *the most."*

"I was diagnosed 34 years ago with MG and have been on Mestinon for the whole time. I do get fatigued when I am in a situation that requires a lot of speaking (work, meetings) in my mouth, face, throat and eyes. ***I have to get lots of rest and prepare ahead of time*** *with my Mestinon so it will be controlled."*

"I frequently go ***cross eyed****."*

*"****Ptosis****, difficulty chewing and swallowing. Multiple acute hospitalizations."*

"Double vision interferes with reading."

"I have ***double vision*** *and just could not do ordinary everyday things that others take for granted, like drive myself for coffee!"*

"Double vision is the most bothersome as it affects my ability to drive, read ,etc."

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

When MDC asked how MG is being managed with available treatments or therapies, three main themes emerged in response: negative experiences with steroids/prednisone, the slow onset of medication effects, and a feeling of trial and error with medications. People affected by MG reported that while supportive treatments have had positive health outcomes, there are concerns about the long-term and sustained benefits of these treatments, as highlighted by quotes from individuals.

Negative experience with prednisone

"The first thing the neurologist put me on was prednisone. But it was also the first thing I keep asking to be tapered off of. The side effects are awful."
"I was placed on prednisone straight away but the moodiness and weight gain killed me."
"If I don't take my medication, I'd be dead. No side effects except I was on prednisone and getting depressed and putting on weight. It's a bad pill to be on so the doctor cut it back."
"Prednisone helped MG a bit at first but I don't know how helpful it is now."
"I am on prednisone but I don't like it. I can't afford it and have to choose between food and medication and it causes diabetes which is my main concern."
"I have been on prednisone for four years. It took several rounds of IVIGs waiting for Mycophenolate to work."

"I was put on prednisone increased to 50 mg . Not helping mg. Put my blood sugars out of wak. So had to go on insulin. That gave me neuropathy with nerve pain and numbness. Put on cellcept 500 mg 2 times a day while slowly decreasing prednisone. And increased cellcept to 750. So now I am taking mestinon 30 mg 3 times a day, cellcept 750 2times a day, and prednisone 2.5 mg every other day. My swallowing is somewhat better as it doesn't happen as often. I still get cross eyed and still get tired easily.

Conventional treatments take a long time to take effect

"My doctor told me it could take 6 maybe even 9 months for the treatment to take effect."
"Imagine living half the year waiting for a drug to show benefit and then to find out you need to be switched to something else.
"I was told it would take a while for the benefits to kick in."
"My whole life revolves around MG. I feel the effects of lack of IVIG close to the end of the month. Then I am knocked for a day or two after IVIG. It takes effect but loses its effect by the third week."

Experience with Trial and Error

"Treatments have been many and honestly too overwhelming. It's a guessing game i.e. trial and error. Seronegative patients not eligible for any of the advanced treatments. Not fair. ***I get IVIG which means I am stuck at the hospital for up to 7 hours 2 days every 3 weeks.*** *Immune suppressants caused frequent infections and pneumonia, prednisone caused a vascular necrosis in both hips resulting in fractures."*
"It feels like I am put on a drug only to see if I will fail it or it will work enough to stop me from complaining."
"I have been tried on so many drugs and so many different dosages. It feels like a big game of trial and error – which is not how you want to feel about your treatment plan."
"I want to be given Rituxan but my doctor says I am not worse enough for that… I want to be given a chance to try a different treatment."
"It feels like the treatments I have tried only half address or control MG. And so then I am tried on something else. Another line of treatment."

Experience with IVIG

"IVIG is really the one thing that worked for me."
"Prednisone- huge negative psychological symptoms with psychosis Azathioprine- not effective ***IVIG- my savior****. Every two weeks."*
"Standard treatments such as ***IVIG has helped****. Equally important are the dietary, relaxation, exercise and physio routines I practice daily."*
"Mestinon - does not seem to have an affect on my symptoms. Azothiaprine- started taking in January of 2022. I don't think it's made any improvement for me. IVIG - used last Christmas at the time of my diagnosis because my symptoms were mostly bulbar and neurologist was concerned that I could be headed towards crisis. ***IVIG worked for me and I felt so much better****… for a couple of weeks Also used before my thymectomy to make sure that I was as strong as possible before surgery."*

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Patients identified three aspects of MG that they want better controlled, these included: decreased intensity of exacerbations and side effects, maintenance of independence, and less serious hospital admissions. Patients stated that they would be willing to deal with side effects of medications if these aspects of MG were better controlled. Patients stated that current medications seem to be decreasing the number of exacerbations but not the impact on overall quality of life.

Desires for treatment include:

"A treatment that helps me to work, to care for my children, to help around the house."

"Target treatment for MG would be something that would stop the myasthenic crises."

"A treatment that address the respiratory and general weakness would be important."

"Sometimes I have trouble swallowing the pills and they get stuck in my throat. I would love them to be more of a capsule that floats when you swallow rather than a chalky pill. If it gets stuck it's awful because it starts to dissolve and the taste is just awful!"

"Something that could take away the aches and the pain all over especially in my legs. I can't sleep in a bed. I sleep in a remote controlled chair.

"I would like a treatment that does not lead to diabetes."

"Target treatment for MG instead of general immunosuppression."

"I would like to see more options available. I would also like to see costs of infusions to be lowered."

"I would like a drug that is convenient to take, takes effect quickly and so benefits are observed – like Mestinon and IVIG but doesn't have that low period that requires recovery."

"I would love to have a drug that I could take once a day in the morning and that could be time released over 24 hours. Right now, I have to make sure I take my Mestinon 30 minutes prior to eating and that can be tricky sometimes to schedule when I'm not in control of that or at work."

"A treatment that lasts long and doesn't take so long to work."

"I would like a treatment that addresses all symptoms without creating side effects that are sometimes worse than the symptoms would certainly be nice, though. Remission for all."

"More muscle strength and stamina. Would love to be able to go for a walk."

"I would like for there to be treatments that don't cause other serious problems like compromised immunity, cancer, etc."

"Less side effects, something that would improve quality of life and regain our independence."

When patients, families, and caregivers evaluate different therapies, they take into account factors such as how the treatment is delivered, potential side effects, duration and frequency of treatments, convenience (e.g., travel time and parking for clinic visits), and financial impact (costs). It was consistently found that therapies with low invasiveness, minimal hospital visits, low risk of side effects, and low cost were highly valued. Patients appreciated treatments that could be administered outside of the hospital (i.e., at home or with community health resources), allowing them to have more control and flexibility. Patients not only valued but which symptoms a drug addressed/managed and how few side effects there were. Health related quality of life was noted as a key priority vs. convenience of a drug. Participants mentioned they travelled 13 hours at times for specialist care or IVIG or plasma exchange and so they will move mountains as long as the treatment is right and will help with minimizing the negative experiences that come with MG. If families were considering

switching to a different therapy, they would weigh the potential side effects of the new therapy against those of the current therapy. They would also consider the ease of access to the treatment and whether it was covered by private or provincial insurance.

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

N/A

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

100% reported that they did have diagnostic testing completed with at least a blood test; but many also had single fiber electromyography to confirm diagnosis.**85%** of respondents reported significant difficulty getting diagnosed. Early findings of the Canadian MG Journey Mapping project indicates **7 years from time of first bothersome symptom to diagnosis**, with the range up to 23 years. The vast majority found it to be a cost-effective but lengthy process with many missed opportunities. They noted significant diagnostic odyssey - delays, misdiagnoses and costs incurred. For those who received a diagnosis as part of a crisis or medical event/hospitalization, the diagnosis was reported as smooth (**25**%). Below are quotes that further highlight the experiences of patients and caregivers with the testing:

Dismissive

"I was worked up for a stroke and Bell's palsy.. and when it wasn't either of those, I was told to go home. That was the end of testing."
"I went to the ER five times before I was seen by neurology."

"I was told my results didn't show anything. Then they called me and said maybe there is something, it might be artifact. Turns out I have a rare form of MG."
"I have sero negative MG and was dismissed many times because the results did not match up with what the doctor expected for typical MG."

Easy/Smooth Experience with Testing

"There were many tests.
"Easy access to testing. I had headaches from the testing, and it started with a twitch with my left eye. My doctor sent me to the hospital and the doctors confirmed I had MG. It was covered by the province (Ontario). I had to pay for gas to go to the hospital."
"OHIP covered the cost of the testing. But getting to the right test was a mission."
"It took a bit of time and a few visits to my GP, walk-in clinics and ER departments before we came up with the possibility of MG. Eventually, my GP ordered one simple blood test that showed that I am ACHR+. He then sent out a referral request for a neurologist."
"I was rushed to hospital because I couldn't breathe. I had just had a triple bypass and valve replaced two weeks prior was only five minutes away from hospital and diagnosed within the hour of arrival I believe they did blood tests. OHIP payed then but now living in BC. treatment started right away."

Delayed Diagnosis

"I visited 3 doctors in two different countries before getting properly diagnosed. It took 4 years."
"I had to pay for the blood test which gets sent to the University of British Columbia. I was tested for the generalized form of MG which I do not have. It was ruled out and I was told I do not have MG. Because I was not tested for MuSK MG I was hospitalized for 3 months. The blood test that was $50.00 was missed and so the hospital stay was very costly to the system."
"I went to the doctor and then was sent on a huge runaround of doctors. I was sent to a dentist as they thought it was TMJ! After a few months I finally was sent to a neurologist but he wouldn't even consider me because I was only 24. My family doctor was amazing and even sat with me in his office and had me describe my symptoms while he flipped through his medical book. He was the one who thought I had MG. Finally, after a few months of my above symptoms happening to me daily, I woke up one morning and I could not swallow my own saliva! I sounded drunk, couldn't speak, move my tongue, etc. that I headed to Emergency and they dealt with it asap. There they tested me with the tension test and came to a diagnosis."
"I have had a very hard time getting diagnosed. There has not been agreement among the physicians who have assessed me. Some say I have MuSK MG based on clinical assessment and also positive MuSK antibodies. The physician who I was sent to did not believe I have MG because I did not have a positive SFEMG. She did not believe my symptoms were caused by MG and she did not consider my antibodies for MuSK relevant at all. It has been in reliably frustrating dealing with physicians like her. I am very relieved to have a neurologist now who understands there can be quite a diversity in MG presentations."
"It took almost 2 years after that to finally get positive blood results. All genetic testing and muscle biopsy done in that time."

Costs Related to Diagnosis

"Testing done through academic centre so no cost to me."
"Pretty much right after that, I was scheduled for a thymectomy within a month and put on Mestinon. In Canada, there was no payment for the surgery but the drugs were expensive. Fortunately I had good benefits coverage at work. I haven't had coverage for the past 8 years so that's out of pocket for me and costly. Mestinon monthly is about $125 which is not a lot I realize but it is on top of everything else. It's another expense for sure but a vital one."

"Was tested at one neurologist who sent me for bloodwork at a cost of $145.00. He then sent me to a neuromuscular specialist who was 60 miles away. He tested me and had more blood work done. The bloodwork was sent from Toronto to Vancouver. It took 4 months for the results. Then Covid came along

and had difficulty getting a follow up appointment. So after 18 months I was diagnosed with generalized mg. Yes I had to pay for travelling and parking. It was an extra cost out of my budget."

"I saw one neurologist who sent me for a blood test because he thought I may have myasthenia gravis, but he said it came back negative. He thought I may have had a stroke. That was negative. I had double vision, weak muscles, I couldn't without falling down, so I was covered in bruises. The doctor more or less told me it was all in my head. I was falling at work, I was falling down stairs and I had to lift my leg from the gas pedal in my car to the break with my hand because it would not move by itself. I went back to see this doctor and showed him how I was covered in bruises and he sent me to see someone at the University Hospital. There the Neurologist give me a test, and the doctor said you have MG. All in all it took two years. Most frustrating."

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

"CDEC should know that sustaining benefit is key for patients with MG. It is not just about accessing treatments, it is about enhancing effectiveness and tolerance over the long term is needed. There is a need for improved treatment options for MG."

"CDEC should know that just because there are drugs approved for generalized MG, we are not good. We are not cured. We need better treatment options and paths for improvement. This drug has potential to cut back on time for infusion and to show positive effects, especially on mobility and energy. We desperately need you to vote positively in favour of this drug. We sit on online forums and groups with those in the US and are envious that they have access and are doing very well with FDA approved drugs – but it is out of reach for us. It is time to do the right thing."

Appendix: 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 two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
UCB			X $25, 000 – restricted educational initiatives that did not involve the company at all.	

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: Homira Osman, PhD
Position: VP, Research & Public Policy
Patient Group: Muscular Dystrophy Canada
Date: March 11, 2024

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0838-000
Generic Drug Name (Brand Name): Zilucoplan
Indication: Myasthenia Gravis
Name of Clinician Group: Neuromuscular Disease Network for Canada (NMD4C)
Author of Submission: Dr. Hans Katzberg and
and

Vera Bril, MD, FRCPC
Hanns Lochmuller, MD, MSc, FRCPC
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Angela Genge, MD, FRCPC
Michelle Mezei, MD, FRCPC
Dubravka Dodig, MD, FRCPC

1. About Your Clinician Group

The Neuromuscular Disease Network for Canada (NMD4C) is the new pan-Canadian network that brings together the country's leading clinical, scientific, technical, and patient expertise to improve care, research, and collaboration in neuromuscular disease.

Launched in January 2020 with funding from the Canadian Institutes of Health Research (CIHR) and Muscular Dystrophy Canada (MDC), NMD4C builds on existing national initiatives such as the Canadian Neuromuscular Disease Registry (CNDR), the Canadian Pediatric Neuromuscular Group (CPNG), and the former neuromuscular network CAN-NMD. The mission of NMD4C is to improve the care, research and treatment of NMDs for all Canadians. Its vision is to be a comprehensive, inclusive, open and enduring network through which Canadian stakeholders can share expertise and data and collaborate on joint activities and research for the benefit of Canadian patients.

The network's goals are to:

- Formalize and sustain a network of NMD stakeholders united around a cohesive three-year work plan
- Train and educate the next generation of NMD stakeholders (clinicians, scientists, and patient advocates)
- Raise the standard of care for NMD and access to therapies across Canada
- Strengthen biomedical and clinical infrastructure to build research capacity in Canada

2. Information Gathering

Clinicians with experience treating generalized Myasthenia Gravis (gMG), including clinicians with experience with MG treatments including new biologics were asked to contribute to this submission. These expert clinicians contribute to the knowledge of gMG and its treatments and are involved in clinical and observational research, clinical guidelines development and health technology assessment. The clinicians contributing herein are familiar with the data from clinical trials on treatments for gMG, and, specifically, for zilucoplan.

3. Current Treatments and Treatment Goals

The treatment landscape for Myasthenia Gravis (MG) encompasses a range of strategies, from supportive care and symptom alleviation to disease-modifying approaches.

- In acute MG crises, where critical bulbar and respiratory functions may be compromised, critical care including ventilatory support becomes essential. Allied health professionals play a crucial role in ensuring patient safety, such as implementing safe swallowing techniques and possibly using feeding tubes, alongside engaging physical and occupational therapists to enhance mobility and daily activities in the face of MG-induced muscle weakness.

- For symptomatic relief, pyridostigmine is commonly prescribed in either immediate or controlled-release forms. The immediate-release form, typically taken 3-4 times daily at 60 mg, offers temporary improvement in muscle strength, including limb, neck, bulbar, and ocular muscles, helping with symptoms like double vision and eyelid droop. Despite its transient effect, many patients continue pyridostigmine alongside immunotherapies for the functional benefits it provides. The 180 mg controlled-release version is also used, often at night, to alleviate morning symptoms.

- Disease-modifying treatments include thymectomy, particularly for acetylcholine receptor antibody-positive MG patients under 60, due to the thymus gland's role in disease pathogenesis. This is vital for patients with thymic tumors, though they may still require ongoing immunotherapy. In acute exacerbations or crises, treatments like intravenous immunoglobulin (IVIG) and plasmapheresis are preferred for their quick, significant effects, helping to prevent or manage crises. IVIG is administered at 2 grams per kilogram over 2-5 days, but its benefits are short-lived, necessitating further immunotherapy.

- Long-term immunotherapy options include steroids, such as prednisone up to 1 mg/kg, and steroid-sparing agents like azathioprine (2-3 mg/kg/day), mycophenolate mofetil (up to 3g/day), or alternatives such as myfortic (up to 720 mg twice daily), methotrexate (up to 25 mg/week), and tacrolimus. These treatments often have a slow onset and are frequently used in combination with steroids due to their gradual effectiveness. For patients with limited response or tolerance to these options, maintenance IVIG or plasmapheresis may be employed to maintain stability and prevent hospitalizations. Eculizumab, a complement inhibitor, and rituximab, a B-cell inhibitor, have shown promise for refractory MG, including in patients with MuSK antibody-positive MG or those who are refractory to acetylcholine receptor antibody treatments. In select refractory cases, additional therapies like cyclophosphamide or cyclosporine may be considered. Efgartigimod, a neonatal Fc receptor blocker designed to reduce pathogenic IgG antibodies, is now available in Canada and offers a novel approach for patients with refractory MG, particularly those who have not responded adequately to traditional therapies. Ravalizumab, an investigational monoclonal antibody targeting the C5 complement protein, is also approved in Canada and offers long-term treatment option for MG by preventing the formation of the membrane attack complex, thereby reducing muscle weakness and fatigue. Both agents represent emerging therapies that could significantly impact the management of MG, especially in patients who have exhausted other treatment avenues.

- The overarching goals of MG therapy are to reduce morbidity and mortality, minimize hospital visits, and enhance the quality of life. Given that many MG patients are young, actively working, and caring for families, maintaining vocational activities is also a critical treatment outcome. While most individuals can recover from severe MG crises, preventing recurrent attacks and managing prolonged or inadequately treated MG is vital to avoid persistent and challenging weakness.

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.

In Canada, patients with highly active Myasthenia Gravis (MG) who do not respond adequately to existing treatments face significant challenges. The effectiveness of traditional immunotherapies, such as steroids and steroid-sparing agents, as well as surgical options like thymectomy, can be limited for these individuals. Moreover, these treatments often require a considerable amount of time to become effective—months in the case of oral medications and potentially years for thymectomy. During this period, patients may experience substantial impairments that negatively impact their functionality, quality of life, and, in severe cases, pose life-threatening risks. It's not uncommon for patients, who have been stable on a regimen of immunotherapies, to experience a disease flare-up, necessitating a change in treatment or an increase in steroid dosage, both of which can lead to significant side effects.

Treatments such as IVIG and plasmapheresis present their own set of challenges, including difficulties with venous access, the need for frequent sessions, and the accumulation of side effects and risks associated with each treatment. Additionally, some patients may not respond to these therapies or may find their effectiveness wanes over time. Rituximab offers limited benefits for many MG cases and raises concerns due to prolonged immunosuppression, with over six months of impact, and lacks robust evidence of efficacy in non-MuSK MG. While eculizumab has been introduced for treating refractory acetylcholine receptor MG, it is considered only after multiple other therapies have been attempted, leaving patients with significant disability and suboptimal management in the interim. In Canada, the approval of Vyvgart (efgartigimod alfa) and ravalizumab mark significant progress in meeting the unmet needs of Myasthenia Gravis (MG) patients. Vyvgart introduces a novel approach by reducing pathogenic IgG antibodies, offering hope to those unresponsive to or intolerant of existing treatments. This could lead to quicker symptom relief and a more favorable safety profile compared to traditional options. Ravalizumab, targeting the C5 complement protein, is poised to offer a new management strategy for MG by preventing the formation of the membrane attack complex. Its recent approval provides an additional targeted therapy option for patients inadequately served by current treatments, including those who cannot tolerate other complement inhibitors. These advancements promise improved tolerability, enhanced patient compliance, and convenience, addressing critical gaps in the treatment landscape for MG in Canada. Vyvgart and ravalizumab represent hopeful additions for patients who are not responding to first line therapies and those with refractory MG, aiming to diversify treatment options and cater to individual patient needs more effectively. The impact of these therapies will become clearer as further data emerge and clinical experiences accumulate, however, are currently only available in a limited capacity as authorization and reimbursement for these treatments are approved and implemented. In addition, most of these new treatments need to be administered in a supervised setting in a medical facility. Patients and clinicians have expressed the need for new additional treatments for refractory gMG that offer sustained efficacy, limited side effects and are able to be administered outside of the hospital setting in order to enhance patient autonomy.

As such, there is a pressing need for additional new, safe, and effective treatments for both refractory and active but non-refractory MG. This includes therapies that offer improved side effect profiles. The long-term use of steroids, necessary for controlling the disease at various stages, can lead to severe acute and chronic complications, especially in patients with comorbidities such as diabetes, a history of hematological issues, or liver dysfunction, which may limit the use of certain medications. Additionally, there is a gap in treatments for seronegative patients or those with thymoma, who are often excluded from clinical trials and treatment guidelines, as well as for pediatric patients who face similar exclusions. Addressing these unmet needs is crucial for enhancing the care and quality of life of individuals living with MG.

5. Place in Therapy

5.1. How would Zilucoplan fit into the current treatment paradigm?

Mechanism of Action and Complementarity

Zilucoplan is a subcutaneously administered peptide that specifically inhibits the complement C5 protein, preventing the formation of the membrane attack complex (MAC) that can damage the neuromuscular junction in MG patients. This targeted approach directly addresses the pathophysiology of MG, particularly in patients with acetylcholine receptor antibody-positive (AChR-Ab+) MG, where the complement system plays a crucial role. Given this mechanism, zilucoplan could complement existing treatments by targeting a pathway that is not addressed by most current therapies, such as acetylcholinesterase inhibitors, corticosteroids, and other immunosuppressants.

Addressing the Underlying Disease Process

While there are treatments available that modulate the immune system's activity or increase the availability of acetylcholine at the neuromuscular junction, zilucoplan's focus on the complement system offers a direct intervention in the disease's underlying process. It is not the first therapy to address the disease process in MG, as treatments like eculizumab and ravalizumab (other complement inhibitors) have been approved for use in AChR-Ab+ MG. However, its approval would reinforce the shift towards targeting specific components of the immune system involved in MG.

Placement in the Treatment Paradigm

Zilucoplan is unlikely to be recommended as a first-line treatment. Initial management of MG typically involves acetylcholinesterase inhibitors and may escalate to corticosteroids or other immunosuppressive agents depending on disease severity and response., experience significant side effects, or have specific clinical features making them suitable candidates for complement inhibition. It

could be used in combination with other treatments, as a later-line option or for patients who have an inadequate response to these therapies. More specifically, Zilucoplan is likely to be considered in the treatment of adult patients with AChR antibody positive refractory gMG, defined as not achieving symptom control after an adequate trial of two or more immunosuppressive therapies (ISTs), either in combination or as a monotherapy in the previous 12 months, OR at least one IST and chronic plasma exchange (PLEX), intravenous immunoglobulin (IVIg), or subcutaneous immunoglobulin (SCIg) at least every 3 months in the previous 12 months.

Suitability for Specific Patient Populations

Given its targeted mechanism and the nature of clinical trials that often focus on patients with refractory or difficult-to-treat MG, zilucoplan might initially be reserved for those who are intolerant to other treatments or in whom other treatments are contraindicated. Over time, its use could potentially expand based on real-world effectiveness and safety data.

Expected Shift in Treatment Paradigm

Zilucoplan is expected to add a valuable tool to the MG treatment arsenal, particularly for patients with AChR-Ab+ MG. While it may not replace the current treatment paradigm particularly in the early phases of management, its availability would signify an important step towards more personalized and targeted therapies in MG management. Given that Zilucoplan is a once daily subcutaneous injection which can be self-administered at home, this offers a convenient option for patients which provides autonomy and control by patients over their own management and care.

Recommendation on Treatment Initiation

It would be prudent to recommend that patients try established first-line treatments before initiating zilucoplan, except in cases where these treatments are contraindicated or have proven ineffective. This approach is consistent with the stepwise management strategy commonly adopted in autoimmune diseases including immune neuromuscular conditions, where more general immunosuppressive therapies are tried before moving to targeted treatments. The rationale behind this perspective is based on the need to balance efficacy, safety, cost, and the long-term management strategy of MG, considering that zilucoplan's long-term safety profile and place in therapy are still being established.

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

Zilucoplan, a complement inhibitor, has been shown to be an effecting strategy in managing symptoms related to Myasthenia Gravis (MG), especially for those with acetylcholine receptor (AChR) antibody-positive MG. The process of selecting candidates for zilucoplan treatment in clinical practice mirrors criteria from the clinical trials showing efficacy, emphasizing the importance of a thorough clinical evaluation, electrophysiology and the use of specific laboratory tests to confirm AChR antibody positivity. Zilucoplan has been shown to be particularly effective in patients who have confirmed AChR antibody positivity, a group that represents a significant subset of the MG population. This specificity is due to zilucoplan's mechanism of action, which targets the complement system involved in the autoimmune attack on the neuromuscular junction characteristic of this condition. Patients eligible for this treatment should have a certain degree of disease severity, usually measured by standardized scales such as the Myasthenia Gravis Activities of Daily Living (MG-ADL) score or the Quantitative Myasthenia Gravis (QMG) score, to ensure that the study population is likely to show a measurable response to treatment.

Although not likely indicated as a first line agent in patients with MG, patients earlier in the disease course prior to development of advance or fixed weakness may experience a more significant benefit from zilucoplan. In addition, patients with very active disease course manifested through multiple acute exacerbations in spite of existing immunotherapies may be ideal candidates for zilucoplan, as the drug can significantly impact disease progression and symptom severity in these groups. Given that the pivotal trial, RAISE, included 50.5% of patients classified as having refractory gMG as a pre-specified subgroup, this refractory group would also likely be well suited for Zilucoplan.

Currently, zilucoplan efficacy is not confirmed in patients with seronegative MG (those lacking AChR antibodies), as the drug's mechanism is less likely to be effective in these individuals. Other exclusion factors might include a history of certain infections or conditions that could be exacerbated by complement inhibition, ongoing treatment with other immunosuppressants that could interfere with the drug's efficacy or safety profile, or previous adverse reactions to complement inhibitors.

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?

Given the serious impact of Myasthenia Gravis (MG) on patients, the effectiveness of therapies is often evaluated by outcomes such as improved survival rates, reduced need for emergency room visits, hospitalizations, and intensive care unit admissions. The frequency and necessity of rescue and maintenance treatments, such as IVIG and plasmapheresis, also indicate the success of a new therapy, especially if these interventions are required regularly or continuously. Additionally, the requirement for other medications, including the dosage and length of steroid treatment, is a critical outcome measure due to the considerable side effects associated with these drugs.

Moreover, assessing the degree of muscle weakness in various areas—such as bulbar, limb, axial, respiratory, and ocular—is crucial for evaluating patient outcomes. This can be achieved through both patient and physician-reported outcomes. The Quantitative Myasthenia Gravis Scale (QMGS), a physician-administered test that primarily uses timed tests to measure skeletal muscle fatigability, is a tool that has been employed in both clinical and research settings. Patient-reported outcomes include the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale, increasingly used as a primary endpoint in MG trials to measure the impact of MG on daily activities. Outcomes that combine physician and patient-reported elements, such as the Myasthenia Gravis Impairment Index (MGII) and the MG Composite (MGC), are validated and utilized in trials. The MG-QOL-15, a health-related quality of life scale specific to MG, is another outcome measure used to assess the effectiveness of MG treatments.

These outcome measures are not only pivotal in clinical trials but are also commonly employed in clinical practice to monitor MG patients. Established benchmarks exist for clinically significant responses across these measures. While there may be some variability in physician-reported outcomes, many of the fatigability tests are timed, reducing susceptibility to physician bias. The timing of these assessments varies with the clinical context; for acute MG exacerbations, evaluations may be conducted daily until stability is achieved. In chronic MG management and trials, the frequency of assessments can range, occurring every few weeks. In clinical settings, follow-up intervals vary based on patient condition, typically ranging from every 3 to 6 months for stable patients, during which these outcome measures are reviewed.

5.4 What factors should be considered when deciding to discontinue treatment with Zilucoplan?

When considering the discontinuation of zilucoplan treatment for patients with Myasthenia Gravis (MG), several critical factors must be taken into account to ensure patient safety and optimal management of the disease. These factors include:

1. Disease Progression: Specific indicators of disease progression, such as the loss of strength, function or mobility, increased difficulty in swallowing or breathing, or a significant and sustained increase in the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification, MG-ADL or other MG clinical scales, warrant a thorough review of the treatment strategy. Such progression may suggest that zilucoplan is not sufficiently controlling the disease, and alternative therapies may need to be considered.

2. Adverse Events: The occurrence of certain adverse events may necessitate the discontinuation of zilucoplan. These include severe allergic reactions, infections (given the role of the complement system in immune defense), or any other severe side effects that outweigh the benefits of treatment. The type, frequency, and severity of these adverse events should be closely monitored, with particular attention to those that are life-threatening or significantly impair quality of life.

3. Requirement for Additional Treatment: The need for additional treatments to manage MG symptoms effectively, or to treat conditions that zilucoplan cannot address, may also influence the decision to discontinue. This includes situations where immunosuppressive therapy needs to be intensified or where symptomatic treatments for MG are not adequately controlling symptoms. The introduction of therapies that may interact negatively with zilucoplan or that duplicate the immunological impact, thereby increasing the risk of adverse effects, should prompt a reevaluation of the use of zilucoplan.

Throughout this process, it is crucial to engage in a detailed discussion with the patient about the risks and benefits of continuing versus stopping treatment. This decision-making process should be individualized, taking into account the patient's clinical status, response to treatment, and personal preferences. Regular monitoring through clinical assessment is essential to guide these decisions. Additionally, the potential impact of discontinuing zilucoplan on the patient's quality of life and overall disease management strategy must be carefully considered, ensuring that any transition to alternative therapies is managed safely and effectively.

5.5 What settings are appropriate for treatment with Zilucoplan? Is a specialist required to diagnose, treat, and monitor patients who might receive Zilucoplan?

Zilucoplan is a convenient once-daily subcutaneous treatment option that can be self-administered at home by patients and/or caregivers. The treatments can be coordinated ideally through the following medical settings:

1. Specialty Clinic: Given the complexity of MG and the specific action mechanism of zilucoplan, treatment is most appropriately managed in a specialty clinic setting. Such clinics are typically staffed by healthcare professionals who have specialized knowledge and experience in managing autoimmune neuromuscular disorders. This environment ensures that patients receive comprehensive care, including access to the full range of diagnostic tools and treatment options.

2. Hospital Outpatient Clinic: Treatment can also be effectively managed in a hospital outpatient clinic, especially for initial diagnosis, treatment initiation, and during periods where closer monitoring is necessary. This setting provides the advantage of easy access to various healthcare services, including laboratory tests and imaging, which are essential for the initial assessment and ongoing monitoring of treatment efficacy and safety.

3. Community Setting: For stable patients who are already on a zilucoplan regimen, ongoing treatment and monitoring might be managed in a community setting, provided there is adequate coordination with a specialist. This approach allows for greater convenience and accessibility for the patient. However, it requires that the community healthcare providers have sufficient knowledge of MG and the use of zilucoplan, or that they can consult with specialists as needed.

Requirement for a Specialist

The diagnosis, initiation of treatment, and ongoing management of patients on zilucoplan ideally require the involvement of specialists due to the complexity of MG and the specialized nature of this treatment. Relevant specialties include:

- Neurology: Specifically, neurologists who specialize in neuromuscular diseases are best equipped to diagnose MG, initiate treatment with zilucoplan, and monitor patients for efficacy and adverse effects. Their expertise is crucial for interpreting diagnostic tests, such as antibody titers and electrophysiology test, and for adjusting treatment regimens based on patient response.

- Neuromuscular Specialists: Within and external to neurology, subspecialists who focus on neuromuscular disorders have the detailed knowledge required for managing complex cases of MG, including those that may be resistant to standard treatments.

6. Additional Information

<Enter Response Here>

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.

   <Enter Response Here>

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.

<Enter Response Here>

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: Hans Katzberg
Position: Neurologist, Associate Professor of Neurology
Date: 10-03-2024

☒ 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

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

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

Declaration for Clinician 2

Name: Vera Bril
Position: Neurologist, Professor of Neurology
Date: 11-03-2024

☒ 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

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
CSL	X			
Grifols	X			
Alnylam	X			
ArgenX		X		

AstraZenica (Alexion)	X			
Ionis	X			
Janssen	X			
Akcea	X			
Octapharma	X			
Sanofi	X			
Takeda	X			
Johnson&Johnson (Momenta)	X			
Hoffman)-La Roche	X			
Immunovant	X			
Japan Tobacco	X			
Pfizer	X			

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

Declaration for Clinician 3

Name: Hanns Lochmuller
Position: Neurologist, Senior Scientist
Professor of Neurology, University of Ottawa Faculty of Medicine and The Ottawa Hospital Department of Medicine
Date: 3-8-2024

☒ 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. *None to disclose.*

Table 3: Conflict of Interest Declaration for Clinician 3

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

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

Declaration for Clinician 4

Name: Elizabeth Pringle
Position: Neurologist, Associate Professor (Neurology) University of Ottawa
Date: 3-8-2024

☒ 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 4: Conflict of Interest Declaration for Clinician 4

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

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

Declaration for Clinician 5

Name: Kristine Chapman
Position: Neurologist, Clinical Professor; Director, Neuromuscular Disease
Date: 3-8-2024

☒ 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. *None to disclose.*

Table 5: Conflict of Interest Declaration for Clinician 5

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

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

Declaration for Clinician 6

Name: Angela Genge
Position: Neurologist; Professor, Department of Neurology and Neurosurgery at McGill University
Date: 3-9-2024

☒ 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. *None to disclose.*

Table 6: Conflict of Interest Declaration for Clinician 6

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

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

Declaration for Clinician 7

Name: Michelle Mezei
Position: Neurologist; Clinical Professor, Division of Neurology, UBC
Date: 3-9-2024

☒ 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. *None to disclose.*

Table 7: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Argenx Canada Inc	X			
Alexion		X		

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

Declaration for Clinician 8

Name: Dubravka Dodig
Position: Neurologist at UHN/Toronto Western Hospital
Date: 3-12-2024

☒ **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 8: Conflict of Interest Declaration for Clinician 8
* Place an X in the appropriate dollar range cells for each company.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Alexion AstraZeneca	☐	☐	☒	☐
Argenx	☐	☒	☐	☐