CADTH

CADTH COMMON DRUG REVIEW

Patient Input

SIPONIMOD (Mayzent)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Secondary progressive multiple sclerosis

CADTH received patient input from:

Multiple Sclerosis Society of Canada

October 18, 2019

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Mayzent (siponimod)**
Name of the Patient Group	**Multiple Sclerosis Society of Canada**
Author of the Submission	[redacted]
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The Multiple Sclerosis (MS) Society provides programs and services for people with MS and their families, advocates for those living with MS, and funds research to help improve the quality of life for people living with MS and to ultimately find a cure for this disease. The mission of the MS Society is to connect and empower the MS community to create positive change. Since 1948 the MS Society has contributed over $175 million towards MS research. This investment has enabled the advancement of critical knowledge of MS, and the development of a pipeline of exceptional MS researchers.

1. Information Gathering

The MS Society launched an online survey from September 9, 2019 to September 23, 2019 posted to the MS Society website and Facebook sites, in both English and French. The survey was primarily targeted to people diagnosed with SPMS and those affected by SPMS.

A secondary question track was geared to people currently diagnosed with RRMS and those affected by RRMS, to gain qualitative data on the perceived experience of transitioning from RRMS to SPMS. People living with clinically isolated syndrome (CIS), primary-progressive MS, other subtypes of MS, and their loved ones were also provided an opportunity to provide feedback related to the Canadian drug reimbursement approval process specific to MS therapies. In total we received 408 responses to the survey. The highest response rate (93%) was from adults between the ages of 35 to 65 and older. This aligns with a diagnosis of SPMS, as most adults transition after the age of 40. There was also a small representation (6%) from ages ranging from 18-34 years. Almost all respondents were diagnosed with MS (93%), and the remainder self-identified as spouses, family members, caregivers and one colleague.

- ***Supporting parents with cooking, home tasks, respite, and all family gatherings are impacted because my [dad] doesn't get out much and my house is not accessible.***

- ***I feel like a maid serving her master with no quality of life.***

As per the targeted survey, most respondents were living with secondary progressive MS (60%), followed by relapsing-remitting MS (25%) and primary progressive MS (6%). Given some of the challenges in accessing and treating SPMS, 69 of the 95 patients who responded to this question stated they were taking a DMT (73%) while the remainder were not currently treated with a DMT. Based on the survey comments, respondents appear to be Canadian however country of origin was not a survey question.

2. Disease Experience

MS is an unpredictable, often disabling disease of the central nervous system. MS occurs because of damage to myelin, the protective covering wrapped around nerve fibres (axons). Damaged myelin causes an interruption or loss of the usual flow of nerve impulses along the axons resulting in a wide variety of symptoms. Approximately 85 per cent of all people diagnosed with MS have relapsing-remitting MS (RRMS), characterized by unpredictable but clearly defined relapses during which new symptoms appear or existing ones get worse. In between relapses, recovery is complete or nearly complete to pre-relapse function. Most people with RRMS will eventually transition to secondary progressive MS (SPMS), a phase of the disease with progressive worsening and fewer relapses. Typically, SPMS is characterized by irreversible disability progression, independent of a relapse, though people with SPMS may continue to experience relapses MS has an enormous impact on every aspect of daily life including a negative impact on family, their community, and ultimately our society.

- ***Improved, independent function is an economic benefit to our country.***

As the majority of people diagnosed with relapsing-remitting MS will eventually transition to a secondary progressive phase of the disease, the MS Society felt it was important to understand how people felt about this probable transition. Just over half (53%) of all relapsing remitting MS respondents said their prescribing clinician had discussed the possible transition with them . The overall theme that emerged from patient feedback was fear. Fear of the unknown impact that SPMS could bring to their lives including changes to family, employment and health status, especially given the limited number of therapies that are currently indicated for active SPMS (secondary progressive with relapses), with minimal therapeutic benefit only showing a reduction in annual relapse rates and no statistically significant benefit on disability progression. The following quotes were extracted from the English and French surveys:

- ***I am afraid of this transition. I am worried about the fact that there are no treatments for SPMS.***
- ***It would greatly impact my career in the health field. I would no longer be able to follow the career path I want. I could teach as a back up plan, but the possibility of my MS changing is uncomfortable to think about.***
- ***I'm terrified. The cognitive impacts I'm living with could be permanent.***

The highest number of respondents living with SPMS had been diagnosed with SPMS for fifteen years or more (28%), followed by five years or less (25%) and the remainder between five and ten years (18%) and ten to fourteen years (17 %). Response rates were relatively equal within the various transition time frames: fifteen years or more (25%), five to ten years (23%), ten to fourteen years (23%) and less than five years to transition (20%). Approximately three per cent were diagnosed with SPMS at the point of their initial diagnosis.

When asked how a diagnosis of SPMS has impacted their lives, most identified a loss of independence (81%), inability to participate in physical activity (76%), changes with the roles and responsibilities within their family (68%) and inability to maintain employment (56 %). More than eighty per cent of respondents

living with SPMS were not currently taking a DMT, while about thirty per cent were taking some form of therapy, however not all respondents provided the name of the treatment they were taking.

- ***To ward off further disability would have a significant impact on the mental, physical, and emotional wellness of my entire family.***

3. Experiences With Currently Available Treatments

Current disease modifying therapies (DMT) for relapsing forms of MS (relapsing remitting and secondary progressive, with relapses) generally work by targeting the inflammatory process to reduce relapses and slow disease progression however only interferon formulations 1a and 1b carry a Health Canada indication for treatment of secondary-progressive MS with relapses (*active* secondary-progressive MS). A Cochrane Review of interferon treatment of SPMS found a decrease in the annual relapse rate (ARR) however interferons did not demonstrate prevention of the development of permanent physical disability.[1]

Siponimod is the first disease-modifying therapy indicated for SPMS with evidence demonstrating its ability to delay disability progression, including a significant number of patients who were non-relapsing.[2] Siponimod was also shown to slow cognitive function decline and more recent research suggests it may also preserve mobility and brain volume.[3] Siponimod is the only oral treatment indicated specifically for secondary progressive MS.

4. Improved Outcomes

The approval of siponimod to the market is a significant milestone in the therapeutic landscape of progressive MS, as the first DMT targeted to people living with secondary progressive MS. Previously, when a patient converted to SPMS, their DMT had little to no therapeutic benefit, or they were required to stop taking it because they no longer met the reimbursement criteria for relapsing MS. Once a patient converts to SPMS and no longer treated with an effective therapy, progression steadily worsens. Untreated, the burden of disease and increasing disability impacts all areas of a person's life including but not limited to: employment stability or loss, family income, increased need for assistance or caregiving, loss of independence, isolation, cognitive decline and increased mobility challenges.

As the only treatment that has shown a delay in disability progression in people living with SPMS, siponimod fills a significant therapeutic need that has been unmet in MS treatment for over twenty years, when the first DMTs became available for relapsing MS.

- ***Access to the treatment that is best for my wife has been absolutely critical in coping as best as possible with this disease.***

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[1] La Mantia L, Vacchi L, Di Pietrantonj C, Ebers G, Rovaris M, Fredrikson S, Filippini G. Interferon beta for secondary progressive multiple sclerosis. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD005181. DOI: 10.1002/14651858.CD005181.pub3.

[2] Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R, Vermersch P, Arnold DL, Arnould S, Scherz T, Wolf C, Wallström E, Dahlke F; EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet. 2018 Mar 31;391(10127):1263-1273.

[3] https://www.novartis.com/news/media-releases/new-novartis-data-show-mayzent-can-help-preserve-mobility-longer-patients-secondary-progressive-multiple-sclerosis-spms

5. Experience With Drug Under Review

Most of the respondents (80%) had not heard of siponimod through their prescribing neurologist, nor had experience with its treatment (98%). A list of known common and adverse side-effects of siponimod were provided in order to measure the perceived benefit vs risk assessment of the treatment. Based on this question, 36% said they would take siponimod, 35% said they would not take it and 28% did not know.

The reason provided for not taking siponimod was lack of post-market long term data. This is not uncommon for any new treatment as there is little, to no patient education about the medication until after it has been approved by Health Canada.

The following perceived concerns were ranked by siponimod naïve patients from greatest to least: 1) *serious adverse effects, 2) cost, 3) lack of federal/provincial/territorial reimbursement, 4) lack of availability of long-term data, and 5) common side effects.*

- ***Haven't been able to work for 30 years, no extended health coverage, no family support, no money for treatment.***
- ***The choice of MS therapies should be financially available to anyone impacted by MS.***
- ***They need to look at cost and how it affects a household.***
- ***Drugs are too expensive for people with disabilities to purchase as already on low income struggling to live.***
- ***To be able to choose from as many therapies as available is very important.***

Of the 408 respondents, two stated they had experience with siponimod (through clinical trials). Of the two respondents with experience with the medication, one felt it was effective, noting they had fewer relapses, saw an improvement in symptoms, had fewer lesions as seen on MRI, no disability progression (no change in the expanded disability status scale or, EDSS) and felt they had more energy overall. This same respondent had not experienced any side effects while on siponimod. The second respondent who felt siponimod was not effective did not clarify why it was not effective and experienced only common side effects, notably, headache and nausea.

6. Companion Diagnostic Test

Pre-treatment testing for siponimod are standard practices previously established with treatment with other medications from this class [sphingosine-1-phosphate (S1P)]. Data on companion testing was not requested as part of the survey however a list is provided below.

- CYP2C9 Genotype Determination: Test patients for CYP2C9 variants to determine CYP2C9 genotype.
- Complete Blood Count: Review results of a recent complete blood count (CBC).
- Ophthalmic Evaluation: Obtain an evaluation of the fundus, including the macula.
- Cardiac Evaluation: Obtain an electrocardiogram (ECG) to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist and first-dose monitoring is recommended.
- Determine whether patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction

- Vaccinations: Test patients for antibodies to varicella zoster virus (VZV) before treatment with siponimod; VZV vaccination of antibody negative patients is recommended prior to commencing treatment with siponimod.
- Liver Function Tests: Obtain transaminase and bilirubin levels.

7. Summary points

- Secondary progressive MS is the only course of the disease that remains largely untreated.
- Current DMTs for relapsing MS may be effective in reducing relapses in patients with active SPMS (continue to have relapses) however there is no therapeutic benefit to disability progression.
- Siponimod is the first oral DMT indicated specifically for SPMS with statistically significant evidence demonstrating a delay in disability progression, slow cognitive function decline as well as preserve mobility, and brain volume.
- Siponimod fills a significant therapeutic need that has been unmet in MS treatment for more than two decades.
- Treatment with siponimod has the potential to allow people living with SPMS to remain in the workforce, sustain family and social roles and responsibilities longer, improve their quality of life, decrease the need for caregiving (family caregiver or paid caregiver) and reduce the financial burden to health and social systems.

Appendix: Patient Group Conflict of Interest Declaration
No help was received from outside the MS Society to collect, analyze data or complete this submission, or used in this submission.

1. 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.

Novartis, the company marketing siponimod has a direct 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
EMD Serono				X
Hoffmann La Roche				X
Biogen				X
Novartis				X
Sanofi-Genzyme			X	
Pendopharm (Pharmascience)			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.

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Date: October 9, 2019