Summary

WHAT IS SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS?

Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system. Relapsing-remitting MS (RRMS) is the most common disease course and is characterized by periods of worsening neurologic symptoms ("relapses") followed by partial or complete recovery. Incomplete recovery from relapses may contribute to worsening neurologic function ("disability progression"). Over time, RRMS may transition to secondary progressive MS (SPMS). SPMS is characterized by irreversible disability progression that occurs in the absence of, or independent of, relapses.

TREATMENT OPTIONS

There are many disease-modifying therapies (DMTs) approved for patients with RRMS and patients with SPMS who still experience relapses ("active SPMS"). Therapies that delay disability progression in patients with non-active SPMS are lacking.

Siponimod (Mayzent™, Novartis) is a sphingosine-1-phosphate (S1P) receptor modulator approved for relapsing forms of MS, including clinically isolated syndrome, RRMS, and active SPMS. Much of the interest in siponimod, however, has been due to its evaluation in both active and non-active SPMS. Given the lack of therapies for non-active SPMS, ICER reviewed the clinical and cost effectiveness of siponimod in all patients with SPMS, although treatment of non-active SPMS is outside the approved indications for siponimod in the US.

KEY REPORT FINDINGS

Although the degree to which siponimod delays progression independent of its effect on relapse activity remains uncertain, evidence provides high certainty that siponimod provides at least a small net benefit in patients with active SPMS when compared to best supportive care. Economic analyses found that, when compared to best supportive care, siponimod at its current price far exceeds commonly cited thresholds of cost-effectiveness.

POLICY RECOMMENDATIONS

- To provide fair value to patients and the health system, the manufacturer should lower the price of siponimod so it aligns with the added value it brings to patients.
- Evidence and clinical testimony suggested that siponimod does not have a unique role in therapy for any phenotype of MS, including active SPMS. Given its similarities to fingolimod, siponimod should be considered amongst a group of highly effective disease modifying therapies (DMTs) for relapsing forms of MS, including fingolimod, alemtuzumab, natalizumab, and ocrelizumab.
- Payers may wish to specifically consider granting preferential formulary status to fingolimod when its generic formulation comes to the market.
- Patient organizations should view their longer-term mission in support of patients to include active engagement with manufacturers to demand reasonable value-based pricing of the therapies that patients and their families helped bring to the market.

Clinical Analyses

How strong is the evidence that Siponimod improves outcomes in patients with Secondary Progressive MS?

ICER EVIDENCE RATINGS

	Population	Comparator	Evidence Rating
Siponimod	Active SPMS	Best Supportive Care	High certainty of at least a small net health benefit
	Non-Active SPMS	Best Supportive Care	Insufficient evidence
	All SPMS	Other MS Drugs	Insufficient evidence

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

	Siponimod
Worsening disability	Delayed*
Relapses	Significantly fewer occurrences
Worsening ambulatory function	No delay
Cognition	Modest benefit

**Disability progression was reduced in patients with active SPMS. It is uncertain whether siponimod delayed progression in patients with non-active SPMS.*

Clinical Analyses (continued)

HARMS

Siponimod is generally well tolerated; however, rare but serious adverse events can still occur. The FDA label for siponimod includes warnings for infections, macular edema, and liver injury. Siponimod may also cause a temporary decrease in heart rate, a decline in lung function, and may increase blood pressure.

SOURCES OF UNCERTAINTY

Diagnosis: The clinical distinction between RRMS and SPMS is challenging because relapses can occur in SPMS and disability can worsen in RRMS. It is possible that some patients who were enrolled in the clinical trial of siponimod had RRMS rather than SPMS.

Progression independent of relapse activity: It remains uncertain whether siponimod delays disability progression by preventing relapses, and there is insufficient evidence to determine whether patients with non-active SPMS benefit from siponimod.

Patient-reported and patient-centered outcomes: In the clinical trials for siponimod, the manufacturer did not evaluate certain outcomes that are important to patients, including improvement in MS symptoms, caregiver burden, mental health, and quality of life.

Long-term effects: There is insufficient evidence on the long-term safety and effectiveness of siponimod.

Comparisons between siponimod and DMTs: More robust data are needed to determine how siponimod compares to other DMTs.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

For the SPMS patient population, does siponimod meet established thresholds for long-term cost-effectiveness?

The FDA approved siponimod for the treatment of relapsing forms of MS. ICER did not conduct a cost-effectiveness analysis for this indicated population, and instead focused on the use of siponomod for all patients with SPMS, the population studied in the phase III trial.

At its current list price of $88,561 per year, siponimod exceeds commonly accepted thresholds for cost-effectiveness of $50,000-$150,000 per quality-adjusted life years (QALY) gained, when compared to best supportive care in patients with SPMS. Analyses of the cost per life years (LY) gained were less favorable because siponimod contributes substantial costs without providing a meaningful extension of life relative to best supportive care.

	Cost per QALY gained	Cost per LY gained
Overall SPMS Population	$1,150,000	$3,760,000
Active SPMS Population	$433,000	$1,565,024

VALUE-BASED PRICING AND BUDGET IMPACT

ICER is not providing value-based price benchmarks or budget impact estimates for siponimod because our assessment does not reflect the FDA-approved indication. The FDA-approved indication for siponimod is for relapsing forms of MS, and active SPMS is only a portion of the patients with SPMS and does not include RRMS.

Summary of Votes

CLINICAL EVIDENCE

The panel voted that the evidence demonstrated siponimod to be clinically superior to best supportive care for patients with active SPMS. Panel members unanimously found that the evidence was insufficient to demonstrate that siponimod is superior to best supportive care for patients with non-active SPMS.

LONG-TERM VALUE FOR MONEY

Consistent with ICER's value assessment framework, because the incremental cost ratio for siponimod in the SPMS population exceeds $175,000 per QALY, it was deemed "low long-term value for money" without a formal vote by the panel.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

During their deliberation, panel members weighed siponimod's other benefits and contextual considerations. They acknowledged that siponimod is intended to care for patients with a condition of high severity and a high lifetime burden of illness. Nevertheless, a majority of the panel felt that there is uncertainty about the long-term benefits and risks of siponimod, citing the lack of long-term trial evidence.

Policy Recommendations

For Payers

- Evidence and clinical testimony suggested that siponimod does not have a unique role in therapy for any phenotype of MS, including active SPMS. Given its similarities to fingolimod, siponimod should be considered amongst a group of highly effective disease modifying therapies (DMTs) for relapsing forms of MS, including fingolimod, alemtuzumab, natalizumab, and ocrelizumab.

- Payers should offer preferential formulary status to highly effective DMTs with superior safety profiles for patients early in their disease course (i.e., RRMS). For many patients, the evidence is not adequate to determine which DMT would be superior as a first option; therefore, it is reasonable for payers to consider step therapy as a mechanism to achieve lower costs without harming patients. However, any step therapy program must be administered in a way that does not require patients to re-try drugs they have had inadequate response to in the past, nor prevent clinicians and patients from seeking rapid exceptions based on transparent, evidence-based criteria.

- Payers may wish to specifically consider granting preferential formulary status to fingolimod when its generic formulation comes to the market.

For Manufacturers

- To provide fair value to patients and the health system, the manufacturer should lower the price of siponimod so it aligns with the added value it brings to patients.

For Patient Advocacy Organizations

- Patient organizations should view their longer-term mission in support of patients to include active engagement with manufacturers to demand reasonable value-based pricing of the therapies that patients and their families helped bring to the market.

For Regulators

- The FDA should encourage the standardization and implementation of outcome measures that are interpretable, sensitive, and relevant to an SPMS patient population.

For Specialty Societies

- Testimony from patients and clinicians suggested that patients may benefit more from treatment that is provided by clinicians who are experts in the diagnosis and management of different forms of MS.

- Individual clinicians and clinical specialty societies should assume a broad leadership role in advocating for patients by taking four actions: 1) highlight and work to address insurance barriers to appropriate care; 2) be vocal witnesses to the negative effects of excessive prices on patients and families, particularly the underserved; 3) integrate considerations of value into clinical guidelines; and 4) embody a broad model of professionalism that calls upon clinicians to work towards a health system that improves access and provides a sustainable model for future innovation through fair pricing.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer-review.org).