KEY FINDINGS

Intervention	Comparator	Evidence Rating	Annual WAC*	Annual Health-Benefit Price Benchmark	Change from Annual Price to Reach Threshold Price
Ublituximab	Natalizumab, Ofatumumab, and Ocrelizumab	Insufficient evidence to differentiate ublituximab vs. all comparators	$59,000-$102,128**	$16,500-$34,900	45%-84%

* Wholesale Acquisition Cost

**These threshold prices do not include any provider-administered mark-up, which was assumed to be 6% in the cost-effectiveness model used to generate these estimates, where applicable.

"Multiple sclerosis is a burdensome condition, and individuals with MS manage declining function and neurologic symptoms such as weakness, fatigue, vision changes, pain, and balance problems for the rest of their lives. In this report, ICER focused primarily on evaluating the comparative effectiveness of currently available monoclonal antibody treatments, including the recently-approved agent ublituximab, and other first line disease modifying therapies (DMTs). All assessed DMTs demonstrate clinical benefits versus placebo, but there was insufficient evidence to differentiate between the benefit of ublituximab and other monoclonal antibodies. Our analysis also found that monoclonal antibodies would need to be priced considerably lower than they are now to meet traditional standards for cost-effectiveness."

– ICER's Senior Vice President of Health Economics, Jon Campbell, PhD, MS

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility and an important role to play in ensuring that all effective treatment options for patients with relapsing forms of MS, including off-label use of rituximab, are utilized in ways to help improve affordability and access and reduce health inequities.
- Manufacturers should seek to set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the setting of new interventions for MS that are similar in efficacy and safety, manufacturer pricing should reflect these considerations in moderating launch pricing.
- Patient organizations have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system. In particular, patient organizations should follow the model set by the National MS Society in issuing statements and advocating for fair pricing and access to treatments.
- Payers should ensure that savings from lower cost biosimilars and generic formulations are shared with patients through the alignment of copay and coinsurance charges. Specifically, all fairly priced drugs should be placed on the lowest relevant tier and cost sharing for generic drugs with a lower net price must not trigger a higher out-of-pocket cost to the patient compared with branded drugs.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system affecting almost one million Americans, with women affected almost three times more than men. It is characterized by an inflammatory cascade of demyelination and axonal loss, which results in neurologic damage and causes symptoms such as weakness, fatigue, vision changes, pain, and balance problems. The median time for the need of a walking aid is approximately 20 years in untreated people with MS. Since symptoms of MS most commonly appear in the third decade of life and treatment may last for decades, MS has a high economic burden, estimated in 2019 to be $85 billion, which is accounted for by $63.3 billion in direct medical costs and $22.1 billion in indirect and nonmedical costs. Access and cost of medication were mentioned as barriers to treatment by people with MS.

Treatment of MS is focused on preventing relapses, disease progression, worsening of disability, and management of symptoms affecting daily life. Patients, clinicians, and patient groups identified prevention or slowing of disability as the most important outcome. Disease modifying therapies (DMTs) have become standard of care for patients with relapsing-remitting MS (RRMS), which accounts for 85% of cases, and treatment is generally long term if not lifelong. Several classes of oral medications have been developed, including sphingosine 1-phosphate (S1P) receptor modulators (fingolimod [Gilenya®], ozanimod [Zeposia®], siponimod [Mayzent®], ponesimod [Ponvory®]), fumarates (dimethyl fumarate [Tecfidera®], monomethyl fumarate [Bafiertam®], diroximel fumarate [Vumerity®]), and teriflunomide (Aubagio®), all of which modulate the immune system in various ways. Monoclonal antibodies reduce inflammation and prevent the formation of central nervous system lesions either by sequestering lymphocytes in the circulation (natalizumab [Tysabri®]) or by depleting B-cells (rituximab [Rituxan®], ocrelizumab [Ocrevus®], ofatumumab [Kesimpta®]). Ublituximab is a new monoclonal antibody that works via B-cell depletion and was approved by the United States (US) Food and Drug Administration (FDA) on December 28, 2022.

Due to significant disease heterogeneity, current clinical practice guidelines recommend considering the risks and benefits of each treatment strategy on a patient-by-patient basis. As a result, the choice of initial therapy varies based on clinical factors as well as insurance coverage, with some people with MS beginning treatment with a lower efficacy DMT and escalating as needed; other people with MS beginning treatment with more aggressive therapy such as monoclonal antibodies or S1P receptor modulators.

We conducted a review of the clinical and cost effectiveness of oral and monoclonal antibody treatments that are considered first-line DMTs for the treatment of relapsing forms of MS. Because there were very few head-to-head trials between our treatments of interest, we conducted indirect comparisons via a network meta-analysis (NMA). Additionally, because ublituximab is the newest DMT, we assessed its efficacy and value compared with more established DMTs.

We found that all DMTs decreased the annualized relapse rate (ARR) compared with placebo, with the monoclonal antibodies overall having a greater impact on this outcome compared with oral medications. Ublituximab showed comparable reduction in ARR versus other monoclonal antibodies and a relatively greater reduction compared with oral DMTs. For the outcome of confirmed disability progression (CDP), there was more uncertainty in the results. Overall, the monoclonal antibodies had numerically greater effects on CDP than oral DMTs. Changes to CDP at six

Clinical Analyses

months were not statistically different for ublituximab compared with other monoclonal antibodies. We had direct head-to-head randomized controlled trial evidence for ublituximab compared with teriflunomide, which demonstrated a significant reduction in ARR and magnetic resonance imaging lesions in the ublituximab group compared with teriflunomide.

Heterogeneity in clinical trial populations, including changes in diagnostic criteria across time and variability in MS experience, limits our conclusions about the efficacy of first-line oral and monoclonal antibody DMTs. Additionally, uncertainty in the data for CDP outcome limits how informative this outcome is in distinguishing between DMTs, despite its importance to patients, and we were unable to compare agents on other patient-important outcomes due to data limitations. Finally, the data on ublituximab is limited to short-term follow-up from clinical trials; given that MS treatment is expected to span decades, long-term data on the efficacy and safety are needed to fully compare with older DMTs.

Based on the results of the NMA and accounting for the limitations in the evidence base, we found insufficient evidence to differentiate the net health benefit of ublituximab compared with other monoclonal antibodies. Compared with oral DMTs, we had moderate certainty that ublituximab is comparable or better in terms of reductions in ARR and CDP. For teriflunomide, based on head-to-head trial data, we had high certainty that ublituximab has a small net health benefit over teriflunomide. We did not have sufficient evidence to rate ublituximab versus siponimod due to differences in trial populations. Finally, ublituximab showed superior net health benefit compared with no DMT.

Table 1. Evidence Ratings

Intervention	Comparator	Evidence Rating
Adults with RRMS*		
Ublituximab	Natalizumab	I: Insufficient
	Ofatumumab	I: Insufficient
	Ocrelizumab	I: Insufficient
	Rituximab	I: Insufficient
	Fumarate class (dimethyl, diroximel, monomethyl)	C++: Comparable or better
	Fingolimod	C++: Comparable or better
	Ozanimod	C++: Comparable or better
	Ponesimod	C++: Comparable or better
	Siponimod	I: Insufficient
	Teriflunomide	B: Incremental
	Placebo/no disease modifying therapy	A: Superior

*RRMS: relapsing-remitting multiple sclerosis

Economic Analyses

LONG-TERM COST EFFECTIVENESS

To estimate the cost effectiveness of each monoclonal antibody treatment with sufficient comparative clinical effectiveness evidence, we used a decision analytic model with model inputs that included relative treatment effectiveness from our NMA and other sources. The primary cost-effectiveness analyses compared each monoclonal antibody to the market-leading and generically available oral dimethyl fumarate. All treatments had base-case results greater than $150,000 per quality-adjusted life year (QALY) gained and equal-value life year (evLY) gained. Cost effectiveness was driven by each treatments' effect on Expanded Disability Status Scale (EDSS) progression and annualized DMT net price differences between the monoclonal antibodies and generic dimethyl fumarate. Limitations of the EDSS as well as the aforementioned recommendations related to the NMA should be considered when interpreting the cost-effectiveness estimates. The table on page 1 presents the annual health-benefit price benchmarks for monoclonal antibodies for MS. Because the clinical evidence was insufficient to differentiate between the monoclonal antibodies on their ability to slow EDSS progression and the cost effectiveness is primarily driven by slowing EDSS progression, we present one health-benefit price benchmark range across all modeled monoclonal antibodies, rather than a separate range for each intervention.

We are not issuing an access and affordability alert for ublituximab as its budgetary impact over five years is not anticipated to exceed the Institute for Clinical and Economic Review's potential budget impact threshold of $777 million per new therapy per year for the US population, assuming ublituximab will displace similarly priced or more expensive monoclonal antibodies for relapsing forms of MS. If ublituximab will displace biosimilar rituximab or generic oral DMTs, there will be a budget impact.

In summary, we found that oral and monoclonal antibody DMTs used for first-line treatment for relapsing forms of MS were effective in reducing relapses. We are less certain about the impact of these DMTs on CDP, particularly for rituximab, for which we lacked high quality data for CDP. We found insufficient evidence to assess whether there were clinically meaningful differences in efficacy or safety amongst the monoclonal antibodies, though the monoclonal antibodies did appear to be more effective than oral therapies. Ublituximab appeared to be more effective for reducing relapses and possibly slowing disability progression compared with oral therapies and no DMT. The modeled monoclonal antibody treatments, without rituximab, did not meet typical thresholds for cost effectiveness when compared to the market-leading oral, in large part due to differences in net price. These findings should be interpreted in the context of the data-related uncertainties and limitations.

POTENTIAL BUDGET IMPACT

In the analysis that did not include biosimilar rituximab (i.e., ublituximab uptake displaced a market basket consisting of 81% ocrelizumab, 13% natalizumab, and 6% ofatumumab), all patients could be treated at the placeholder base-case net price and each of the threshold prices without crossing the potential budget impact threshold of $777 million.

Public Meeting Deliberations

VOTING RESULTS

For adults with relapsing forms of MS, including clinically isolated syndrome, RRMS, and active secondary-progressive MS:

- All panelists (10-0) found that current evidence is **not adequate** to distinguish a net health benefit of ublituximab when compared to other monoclonal antibodies (natalizumab, ofatumumab, ocrelizumab, and rituximab).
- A majority of panelists (9-1) found that current evidence is **adequate** to demonstrate a net health benefit of ublitixumab when compared to fumarates (dimethyl fumarate, diroximel fumarate, and monomethyl fumarate).
- A majority of panelists (9-1) found that current evidence is **adequate** to demonstrate a net health benefit of ublitixumab when compared to fingolimod.

During their deliberations, panel members also weighed the therapy's other potential benefits, disadvantages, and contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- Magnitude of the lifetime impact on individual patients;
- Patients' ability to achieve major life goals related to education, work, or family life;
- Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life.

After reviewing the clinical evidence and considering the treatments' other potential benefits, disadvantages, and contextual considerations noted above, the New England CEPAC evaluated the long-term value of ublitixumab at its current pricing:

- A majority (9-1) of panelists found that ublitixumab versus dimethyl fumarate represents "low" long-term value for money.

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.org).