

For multiple sclerosis

Do these new drugs meet an important need?

What Is Multiple Sclerosis?

Multiple sclerosis (MS) is a chronic disease of the central nervous system. About 400,000 Americans have MS, although this may be an underestimate. The disease affects about three times as many women as men and some patient groups, such as African Americans, experience a more rapid and severe clinical course.

Our review looks at two types of multiple sclerosis: relapsing-remitting (RRMS) and primary-progressive (PPMS). RRMS affects about 85-90% of patients with MS, while PPMS affects about 10-15%. Patients with RRMS, experience periodic relapses in symptoms which may improve with treatment, while those with PPMS experience steadily worsening symptoms.

Treating MS

For many years, injections of interferons and glatiramer acetate were the most common disease-modifying therapies (DMTs) for MS.

More recently, three oral drugs and several infused therapies have been approved by the Food and Drug Administration (FDA). The most recently-approved drug, daclizumab (Zinbryta®, Biogen and AbbVie), was approved in May 2016, and the FDA will issue a decision on ocrelizumab (Ocrevus®, Genentech) in 2017. Ocrelizumab is being considered for both RRMS and PPMS; if approved for the latter, it will be the first DMT with an indication for PPMS.

Patient Survey

To add context to the clinical evidence, the MS Coalition conducted a survey for this review to assess what patients consider to be the most important factors in choosing a DMT on a scale of 1 (not important) to 5 (very important).

Decision-making factor	Important/Very Important
Delay disability	94%
Prevent relapse / new MRI lesions	94%
Continue working / normal activities	90%
Provider recommends therapy	86%
Other long term risks	71%
Health plan restrictions	69%
Risk of PML*	68%
Out-of-pocket costs	66%
Route of administration	61%
Dosing frequency	58%
Risk of side effects	55%
Monitoring / blood tests	44%

Drugs Under Review

Drug Name (drugs ordered based on route of administration)	Year 1 WAC*
Interferon β-1a (Avonex®, Biogen)	\$81,965
Interferon β-1b (Betaseron®, Bayer)	\$86,659
Interferon β-1b (Extavia®, Novartis)	\$72,359
Glatiramer acetate (Copaxone®, Teva)	\$86,554
Glatiramer acetate (Copaxone®, Teva)	\$76,024
Glatiramer acetate (Glatopa®, Sandoz)	\$63,193
Interferon β-1a (Rebif®, EMD Serono)	\$86,416
Peginterferon β-1a (Plegridy®, Biogen)	\$81,956
Daclizumab (Zinbryta®, Biogen and AbbVie)	\$82,000
Fingolimod (Gilenya®, Novartis)	\$82,043
Teriflunomide (Aubagio®, Sanofi Genzyme)	\$76,612
Dimethyl fumarate (Tecfidera®, Biogen)	\$82,977
Natalizumab (Tysabri®, Biogen)	\$78,214
Alemtuzumab (Lemtrada®, Sanofi Genzyme)	\$103,749
Ocrelizumab (Ocrevus®, Genentech)	Unavailable
Rituximab (Rituxan®, Genentech)	\$33,408

Results based on approximately 2,500 responses.
*Progressive multifocal leukoencephalopathy

*Wholesale acquisition cost. Year 1 annual costs used due to differing administration schedules and duration of treatment between drugs.

How strong is the evidence that DMTs improve patient outcomes?

Performance

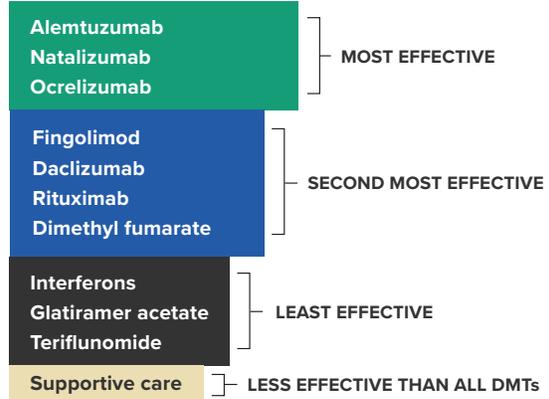
Reduction of Relapse:

For RRMS, all of the DMTs reduce the number of relapses compared to best supportive care. Alemtuzumab, natalizumab, and ocrelizumab were the most effective. Fingolimod, daclizumab, rituximab, and dimethyl fumarate were the next most effective. The interferons, glatiramer acetate, and teriflunomide were the least effective, but still better than best supportive care.

Progression of Disability:

While all the drugs reduce disability progression (excluding rituximab, for which data on this outcome was not available), there is greater uncertainty in the estimates for the effectiveness on this outcome. Alemtuzumab and ocrelizumab were the most effective drugs at reducing disability progression, followed closely by natalizumab and daclizumab. The next most effective drugs were dimethyl fumarate, peginterferon β -1a, interferon β -1b, and fingolimod. Teriflunomide,

Reduction of Relapse:



glatiramer acetate, and the remaining interferons were less effective, but were still superior to best supportive care. For PPMS, ocrelizumab reduced progression compared to best supportive care, but does not yet have FDA approval.

Risks

Patients and physicians must balance the risks and benefits of DMTs for MS.

Interferons and Glatiramer Acetate

- These drugs have more favorable safety profiles compared to more effective agents.
- Flu-like symptoms are common in patients treated with interferons.
- Injection site and infusion reactions are common in drugs with those delivery routes.

Newer Agents

- While more effective, the newer drugs have greater risks for life threatening infections and autoimmune disease.
- Daclizumab, natalizumab, teriflunomide, rituximab, and alemtuzumab have black box warnings due to the risk of very serious adverse events.

How strong is the evidence that DMTs improve patient outcomes? (continued)

Sources of Uncertainty

Trial Duration: The clinical trials testing the drugs were generally one to two years long, which is not enough time to assess the long-term effects of DMTs on disability progression, the most important outcome for patients.

Reported Outcomes: Patient reported outcomes, such as fatigue, mood disorders, and quality of life, were not consistently reported.

Patient Populations: The patient populations included in trials have changed over many years of research, adding uncertainty to comparisons between the earlier and later studies.

Drug Approval: Ocrelizumab is not yet FDA approved, thus has no real-world data to inform estimates of net health benefits.

MRI Outcomes: Because MRI outcomes were measured and reported inconsistently across trials, and study centers used different machines and protocols for assessing lesions, we were unable to compare MRI findings.

Uncommon Serious Adverse Events: The clinical experience with many of the DMTs is limited. The estimates for known rare harms, such as the risk for progressive multifocal leukoencephalopathy (PML), are imprecise and new harms continue to emerge.

ICER Evidence Ratings

Treating RRMS

- The interferons, glatiramer acetate, and teriflunomide provide incremental net health benefits when compared to best supportive care, and are largely similar in their effects on relapse rates and disability progression.
- There is moderate certainty of small to substantial net health benefit for alemtuzumab, natalizumab, and ocrelizumab compared to the interferons and glatiramer acetate.
- There is moderate certainty of comparable or better net health benefit for daclizumab, fingolimod, and dimethyl fumarate compared to the interferons and glatiramer acetate.

Treating PPMS

There is moderate certainty of small to substantial net health benefit for ocrelizumab compared to best supportive care.

What is a fair price for DMTs based on their value to patients and the health care system?

Long-Term Cost-Effectiveness at Net Price

\$38,000 to \$355,000 per QALY

ICER calculated the incremental cost-effectiveness ratio for each of the DMT compared to best supportive care. The incremental cost-effectiveness ratio was measured by calculating the cost per additional quality-adjusted life year (QALY). Ocrelizumab was not included as the list price is not yet available.

The cost per QALY range that is generally accepted as “reasonable” value in the US is \$100,000-\$150,000. Drug costs were obtained from Redbook and average discounts were applied using SSR Health LLC’s data, which combines information on net US dollar sales with unit sales to derive net pricing estimates per unit that include rebates and discounts across all payer types.

Using these net prices, the cost per QALY for alemtuzumab compared to supportive care was \$38,000, which represents good value. When compared to glatiramer acetate, alemtuzumab was more effective and less costly over time, though this drug may only be suitable for a subset of patients due to its safety profile.

Cost per QALY estimates for the remaining DMTs versus supportive care were above the range for reasonable value, representing poor long-term value for money. The newest approved agent, daclizumab, produced an estimate of approximately \$207,000 per QALY gained.

Potential Short-term Budget Impact

\$915 million is the point at which the potential short-term budget impact could be so substantial that policymakers should consider whether special coverage, pricing, or payment mechanisms are needed to assure sustainable access to high-value care for all patients.

Daclizumab

Our budget impact estimates for daclizumab suggest that its use in RRMS would not increase costs to a level that has the potential to strain health-system budgets.

Ocrelizumab

Since ocrelizumab has not yet been FDA approved, budget calculations were based on hypothetical prices at which the drug would meet the \$150,000/QALY threshold. If ocrelizumab is priced in such a way following approval, use of ocrelizumab in all eligible patients would not approach the \$915 million threshold for either the RRMS or the PPMS indication.

What is a fair price for DMTs based on their value to patients and the health care system? (continued)

ICER's Value-Based Price Benchmark

DMT	WAC (per package)	Value-based price benchmark per package	Discount from WAC to reach WTP threshold
Interferon β-1a 30 mcg (Avonex)	\$6,287	\$586-\$1,562	75% to 91%
Interferon β-1b 250 mcg (Betaseron)	\$6,648	\$1,504-\$2,768	58% to 77%
Interferon β-1b 250 mcg (Extavia)	\$5,947	\$1,611-\$2,965	50% to 73%
Glatiramer Acetate 20 mg (Copaxone)	\$7,114	\$1,095-\$2,332	67% to 85%
Glatiramer Acetate 20 mg (Glatopa)	\$5,194	\$1,095-\$2,332	55% to 79%
Interferon β-1a 22 mcg (Rebif)	\$6,629	\$541-\$1,539	77% to 92%
Interferon β-1a 44 mcg (Rebif)	\$6,629	\$624-\$2,090	68% to 91%
Peginterferon β-1a	\$6,287	\$1,623-\$3,017	52% to 74%
Daclizumab	\$6,833	\$1,975-\$4,159	39% to 71%
Fingolimod	\$6,743	\$1,316-\$3,103	54% to 81%
Teriflunomide 14 mg	\$5,877	\$129-\$1,945	67%-98%
Teriflunomide 7 mg	\$5,877	\$802*	86%
Dimethyl Fumarate	\$6,820	\$982-\$3,340	51% to 86%
Natalizumab	\$6,000	\$2,147-\$3,808	37% to 64%
Alemtuzumab	\$20,750	\$65,047-\$101,771	213% to 390% increase
Ocrelizumab (RRMS)**	--	\$34,235-\$58,608	--
Ocrelizumab (PPMS)**	--	\$9,288-\$14,367	--

*Price that would achieve a \$150,000/QALY cost-effectiveness threshold; no price would reach \$100,000/QALY.

**Annual prices are presented for ocrelizumab because package prices are not currently available.

Public Deliberation and Evidence Votes

California Technology Assessment Forum Votes

The California Technology Assessment Forum deliberated on key questions raised by ICER’s report at a public meeting on February 16, 2017. The results of the votes are presented below. More detail on the voting results is provided in the [full report](#).

Voting Summary

- For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of dimethyl fumarate (Tecfidera®, Biogen Inc.) is greater than that of teriflunomide 14 mg (Aubagio®, Sanofi-Genzyme, Inc.)?

Yes: 2 votes	No: 12 votes
---------------------	---------------------

- For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of fingolimod (Gilenya®, Novartis, Inc.) is greater than that of teriflunomide 14 mg?

Yes: 7 votes	No: 7 votes
---------------------	--------------------

- For patients with RRMS, is the evidence adequate to distinguish the net health benefit between dimethyl fumarate and fingolimod?

Yes: 2 votes	No: 12 votes
---------------------	---------------------

- For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of daclizumab (Zinbryta®, Biogen Inc. and AbbVie Inc.) is greater than that of dimethyl fumarate or fingolimod?

Yes: 0 votes	No: 14 votes
---------------------	---------------------

- For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of daclizumab is greater than that of generic glatiramer acetate 20 mg (Glatopa®, Sandoz, Inc.)?

Yes: 7 votes	No: 7 votes
---------------------	--------------------

- For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of ocrelizumab (Ocrevus®, Roche Genentech Inc.) is greater than that of generic glatiramer acetate 20 mg?

Yes: 12 votes	No: 2 votes
----------------------	--------------------

- Given the available evidence for patients with RRMS, what is the long-term value for money of treatment with daclizumab versus treatment with generic glatiramer acetate 20 mg?

Low: 12 votes	Intermediate: 2 votes	High: 0 votes
--------------------------	----------------------------------	--------------------------

- For patients with primary-progressive multiple sclerosis (PPMS), is the evidence adequate to demonstrate that the net health benefit of treatment with ocrelizumab is greater than that of best supportive care?

Yes: 11 votes	No: 3 votes
----------------------	--------------------

Key Policy Implications and Recommendations

CTAF engaged in a moderated discussion about how best to apply evidence on DMTs for MS in policy and practice. The roundtable included two clinical experts, two patient representatives, two payer representatives, and a drug manufacturer representative. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. Below are the top-line policy implications; for more information please see the [full report](#).

Manufacturers

- Link launch prices of new DMTs to the added value they bring to patients compared to existing clinical options. Cease annual price increases that exceed medical inflation without new evidence of improved outcomes.
 - If the current net costs of MS drug therapies were rolled back to their 2011 net costs, several of their prices would align with ICER's value-based price benchmarks. Better alignment of prices with clinical value would relax pressure on payers to impose restrictive step therapy and prior authorization requirements.
- Leverage clinical trial data to identify characteristics that determine which patients are likely to respond best to specific drugs.

Payers

- In line with recommendations from key patient groups, implement policies to allow patients to remain on a treatment that works regardless of coverage or formulary changes, and without onerous prior authorization documentation required of providers each year.
- If DMT prices come into alignment with the value they bring to patients, reduce step therapy barriers to these therapies.

Regulators

- Require that pivotal trials of MS agents be conducted against an active comparator.

Patient Advocacy Groups

- Engage with manufacturers in the design and conduct of pre- and post-approval studies of MS therapies.
 - Patient advocacy groups can advocate for inclusion of consistent patient-centered outcomes like fatigue, cognitive function, and overall quality of life to be included in pre-approval studies and participate in MS patient registries to help answer questions about long-term outcomes like disability progression.
- Advocate for value-based pricing of MS therapies.

Specialty Societies

- Develop guidelines that include treatment sequencing and a definition of patients at high risk for more aggressive disease. Consider including assessments of value as part of the guideline development process.

Clinicians

- Discuss potential cost burdens with patients as part of the shared decision-making process.

Researchers

- Work with patients to standardize the patient-centered outcomes that are included in trials of MS drugs.
- Conduct studies of new drugs for MS that include long-term data on disability progression.

Conclusion

Comparative Clinical Effectiveness

Alemtuzumab, natalizumab, and ocrelizumab are the most effective DMTs for reducing relapses in patients with RRMS, but are associated with rare, life-threatening infections and autoimmune disease. The same DMTs are also effective for reducing disability progression, but there is greater uncertainty with the other therapies. For PPMS, ocrelizumab, if approved by the FDA, would be the first effective therapy for reducing disability progression.

Comparative Value

Alemtuzumab consistently demonstrated improved health outcomes and good value compared to both supportive care and generic glatiramer acetate 20 mg. Caution in considering the cost-effectiveness findings for alemtuzumab is required, however, given its safety concerns. In most cases, cost-effectiveness ratios for the remaining DMTs were well above commonly accepted willingness-to-pay thresholds in the U.S. health care system.

About ICER

The Institute for Clinical and Economic Review ([ICER](http://www.icer-review.org)) 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](http://www.ctaf.org)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](http://www.midwestcepac.org)) and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](http://www.newenglandcepac.org)). 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).