Drugs for Multiple Sclerosis

Most patients with multiple sclerosis (MS) present with the relapsing-remitting form of the disease. Treatment usually includes disease-modifying drugs, various other drugs for managing symptoms such as fatigue, depression, and pain, and corticosteroids for acute exacerbations.

**INJECTABLE AGENTS — Interferons** — Interferon beta was the first disease-modifying drug approved for treatment of MS. Interferons have several immune-modulating and anti-inflammatory effects. They can reduce clinical relapse rates by 30-35% and decrease the number of new T2 or gadolinium-enhancing brain lesions seen on MRI. Whether these effects delay or prevent long-term disability is unclear. Interferons frequently cause injection-site reactions and a flu-like syndrome. Pegylated interferon beta-1a (Plegridy) injected SC every 2 weeks appears to be similar in efficacy and adverse effects to older interferon formulations that must be injected every-other-day SC or weekly IM.

**Pregnancy** — Interferons are classified as category C (no adverse effects in animals; no adequate studies in pregnant women) for use during pregnancy. Extensive data available on exposure of pregnant women to interferon beta suggest that it is safe to use.

**Glatiramer Acetate (Copaxone, Glatopa)** — Glatiramer acetate is a mixture of synthetic polypeptides containing four naturally occurring amino acids (glutamic acid, alanine, tyrosine, and lysine). Its exact mechanism of action is unknown, but the drug has several immune-modulating effects including suppression of T-cell activation, and induction and activation of suppressor T-cells. Glatiramer acetate can reduce clinical relapse rates by about 30% and decrease the number of new T2 or gadolinium-enhancing brain lesions seen on MRI. Glatiramer may be the safest of all the drugs used to treat MS, but it must be injected daily or three times a week SC.

**Recommendations for Treatment of Multiple Sclerosis**

- Interferon beta (Avonex, Plegridy, and others) and glatiramer acetate (Copaxone, Glatopa), both given by injection, have been used for first-line treatment.
- Glatiramer acetate is better tolerated than interferon and equally effective, but it requires more frequent injections.
- Use of oral agents or IV natalizumab (Tysabri) for first-line treatment is increasing.
- Natalizumab is highly effective and needs to be infused only every 4 weeks, but its adverse effects, especially progressive multifocal leukoencephalopathy (PML), are a concern.
- Among the oral drugs, fingolimod (Gilenya) and dimethyl fumarate (Tecfidera) appear to be more effective than teriflunomide (Aubagio), but head-to-head trials are lacking.

**Pregnancy** — Glatiramer acetate is classified as category B (no adverse effects in animals; no adequate studies in pregnant women) for use during pregnancy. Extensive data available on exposure of pregnant women to glatiramer acetate suggest that it is safe to use.

**Natalizumab (Tysabri)** — A recombinant humanized monoclonal antibody, natalizumab prevents leukocyte migration across the blood-brain barrier, which may interrupt the inflammatory cascade in MS. Natalizumab has decreased relapse rates by 68%, new or enlarging T2 brain lesion development by 83%, and disease progression rates by 42%, but progressive multifocal leukoencephalopathy (PML), a potentially fatal infection caused by the JC virus, has occurred in about 0.2% of patients; those who have anti-JC virus antibodies or are immunosuppressed have the highest risk. The risk increases with the duration of treatment; it is very low during the first 2 years of treatment in patients without anti-JC virus antibodies. Natalizumab was voluntarily withdrawn from the market in 2005 and re-introduced in 2006 with a Risk Evaluation and Mitigation Strategy (REMS) program which restricts its use to certified healthcare providers and settings. Based on cross-trial comparisons, it appears to be the most effective drug currently available for treatment of MS, but its safety remains a concern.
Table 1. FDA-Approved Drugs for Relapsing-Remitting Multiple Sclerosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reduction in Clinical Relapse Rate</th>
<th>Usual Maintenance Dosage</th>
<th>Frequent or Serious Adverse Effects</th>
<th>Cost 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable</td>
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<tr>
<td>Interferon beta-1a – Avonex (Biogen-Idec)</td>
<td>30%-35% 2</td>
<td>30 mcg IM once/wk</td>
<td>Injection-site reactions, flu-like symptoms, depression, transaminase</td>
<td>$72,072.00</td>
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<tr>
<td>Interferon beta-1a – Rebif (EMD Serono)</td>
<td></td>
<td>44 mcg SC 3x/wk</td>
<td>elevations, possible cardiac toxicity, autoimmune disorders, allergic reactions, hepatotoxicity, seizures, suicidal ideation, lymphopenia with interferon beta-1b</td>
<td>$77,797.20</td>
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<tr>
<td>Pegylated interferon beta-1a – Plegridy (Biogen-Idec)</td>
<td></td>
<td>125 mcg SC q2 wks</td>
<td></td>
<td>$72,072.00</td>
</tr>
<tr>
<td>Interferon beta-1b – Betaseron (Bayer) Extavia (Novartis)</td>
<td></td>
<td>250 mcg SC every other day</td>
<td>Injection-site reactions, transient post-injection systemic reactions (flushing, chest pain, palpitations, and dyspnea)</td>
<td>$78,920.60</td>
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<tr>
<td>Glatiramer acetate – Copaxone (Teva) Glatopa (Sandoz)</td>
<td>~30% 2</td>
<td>20 mg SC once/d or 40 mg 3x/wk</td>
<td></td>
<td>$80,216.10</td>
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<tr>
<td>Preparations</td>
<td></td>
<td>20 mg SC once/d</td>
<td></td>
<td>$63,192.50</td>
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<tr>
<td>Natalizumab – Tysabri (Biogen-Idec)</td>
<td>68% 3</td>
<td>300 mg IV q4 wks</td>
<td>Headache, fatigue, arthralgia, depression, infections, hypersensitivity reactions, hepatotoxicity, PML</td>
<td>$71,773.00</td>
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<tr>
<td>Alemnatumab – Lemtrada (Genzyme)</td>
<td>50-55% 4</td>
<td>12 mg IV once/d x 5d followed 1 year later by 12 mg IV once/d x 3d</td>
<td>Infusion reactions (rash, headache, pyrexia, nausea, urticaria), nasopharyngitis, auto-immune disorders (immune cytopenias [especially thrombocytopenia], glomerular nephropathies, thyroid disorders), infections, pneumonitis, malignancies</td>
<td>$59,250.00</td>
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<tr>
<td>Mitoxantrone – generic</td>
<td>~60% 6</td>
<td>12 mg/m² IV q3 mos</td>
<td>Nausea, alopecia, amenorrhea, cardiotoxicity at cumulative doses &gt;100 mg/m², myelosuppression, acute and chronic myeloid leukemia</td>
<td>$1330.40</td>
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<tr>
<td>Oral</td>
<td></td>
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<tr>
<td>Fingolimod – Gilenya (Novartis)</td>
<td>~55% 8</td>
<td>0.5 mg PO once/d</td>
<td>Transaminase elevations, bradycardia, AV block, macular edema, mild hypertension, lymphopenia, decreased pulmonary function, hypersensitivity reactions, malignancies, serious viral and fungal infections, PML</td>
<td>$78,135.60</td>
</tr>
<tr>
<td>Teriflunomide – Aubagio (Genzyme)</td>
<td>~30% 9</td>
<td>7 or 14 mg PO once/d</td>
<td>Diarrhea, nausea, alopecia, transaminase elevations, neutropenia, leucopenia, peripheral neuropathy, hyperkalemia, hypophosphatemia, hypertension, hepatic failure, acute renal failure, Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td>$74,379.70</td>
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<tr>
<td>Dimethyl fumarate – Tecfidera (Biogen-Idec)</td>
<td>~50% 10</td>
<td>240 mg PO bid</td>
<td>Flushing, abdominal pain, nausea, vomiting, diarrhea, lymphopenia, anaphylaxis, angioedema, PML</td>
<td>$73,168.00</td>
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</table>

PML = progressive multifocal leukoencephalopathy

1. Approximate WAC for 1 year’s treatment at the usual maintenance dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. April 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy.
5. Cost for second year of treatment; cost for first year’s treatment is $98,750.
7. Cost for treatment of a patient with a body surface area of 1.7 m² using 12.5-mL multi-dose vials containing 25 mg (2 mg/mL).

Pregnancy – Natalizumab is classified as category C (fetotoxicity in animals; no adequate studies in pregnant women) for use during pregnancy. An observational study in pregnant women found that exposure to natalizumab during the first trimester of pregnancy did not increase the risk of adverse pregnancy outcomes.12

Alemtuzumab (Lemtrada) – A humanized monoclonal antibody directed against the lymphocyte cell surface molecule CD52, alemtuzumab causes rapid depletion of CD52-positive B- and T-cells. It has been shown to be more effective than subcutaneous interferon beta-1a in preventing relapses.13 The drug has an attractive dosing schedule; it is given as a daily IV infusion for
5 consecutive days, followed 12 months later by an additional 3 days of treatment. However, because of the occurrence of serious autoimmune effects, infusion reactions, and malignancies, the FDA has approved labeling recommending that alemtuzumab generally be used only for patients who have had a suboptimal response to at least two other disease-modifying drugs for MS and has restricted its availability with a REMS program.

Pregnancy – Alemtuzumab is classified as category C (embryolethality in animals; no adequate studies in pregnant women) for use during pregnancy. It can induce thyroid disorders; placental transfer of anti-thyroid antibodies resulting in neonatal Graves’ disease has been reported. The manufacturer recommends that women of childbearing age use effective contraception while taking the drug and for four months after stopping it.

Mitoxantrone – An anthracenedione also used to treat cancer, mitoxantrone inhibits DNA replication. It has decreased relapse frequency and slowed progression of disability in patients with severe MS, but it is potentially cardiotoxic, it can cause persistent amenorrhea in women, and it has been associated with a risk of developing acute or chronic myeloid leukemia, particularly with higher cumulative doses. It has decreased relapse frequency and slowed progression of disability in patients with severe MS, but it is potentially cardiotoxic, it can cause persistent amenorrhea in women, and it has been associated with a risk of developing acute or chronic myeloid leukemia, particularly with higher cumulative doses. Use of mitoxantrone for treatment of MS has declined because of concerns about its long-term risks.

Pregnancy – Mitoxantrone is classified as category D (may cause fetal harm) for use during pregnancy.

ORAL AGENTS – Fingolimod (Gilenya) – The first oral drug approved for treatment of MS, fingolimod blocks lymphocyte egress from lymph nodes, reducing the number of lymphocytes in peripheral blood and the central nervous system. A one-year study found that fingolimod was more effective than IM interferon beta-1a in reducing relapse rates and decreasing the number of new or enlarging brain lesions seen on MRI. PML has occurred in patients treated with fingolimod for 2 years or more.

Pregnancy – Fingolimod is classified as category C (developmental toxicity in animals; no adequate studies in pregnant women) for use during pregnancy. The manufacturer recommends that women of childbearing age use effective contraception while taking the drug and for two months after stopping it.

Teriflunomide (Aubagio) – A pyrimidine synthesis inhibitor, teriflunomide reduces T- and B-cell activation, proliferation, and function. Teriflunomide has significantly reduced some MRI measures of disease activity (lesion volume, number of gadolinium-enhancing and unique active lesions), but cross-trial comparisons suggest that it is less effective than fingolimod or dimethyl fumarate in decreasing relapse rates.

Pregnancy – Teriflunomide is teratogenic in animals and is contraindicated for use during pregnancy. It is eliminated very slowly; women who wish to become pregnant and men wishing to father a child should discontinue the drug and undergo an accelerated elimination procedure (cholestyramine or activated charcoal for 11 days).

Dimethyl Fumarate (Tecfidera) – An antioxidant that induces expression of anti-inflammatory proteins, dimethyl fumarate has significantly reduced relapse rates and development of new or enlarging T2 brain lesions. In cross-trial comparisons, it appears to be more effective than teriflunomide. An increasing number of cases of PML have been reported following use of dimethyl fumarate, particularly in patients with lymphopenia for more than 6 months.

Pregnancy – Dimethyl fumarate is classified as category C (embryofetal toxicity in animals at doses twice the approved human dose; no adequate studies in pregnant women) for use during pregnancy.
14. VM Rivera et al. Results from the 5-year, phase IV RENEW (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) study. BMC Neurol 2013; 13:80.