Cigna Drug and Biologic Coverage Policy

Subject: Multiple Sclerosis Therapy

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain standard Cigna benefit plans. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2016 Cigna

Coverage Policy

Multiple Sclerosis Therapy contains the following products:
- Alemtuzumab (Lemtrada™)
- Dimethyl fumarate (Tecfidera®)
- Fingolimod (Gilena®)
- Glatiramer acetate (Copaxone®, Glatopa™)
- Interferon beta-1a (Avonex®, Rebif®)
- Interferon beta-1b (Betaseron®, Extavia®)
- Natalizumab (Tysabri®)*
- Peginterferon beta-1a (Plegridy™)
- Teriflunomide (Aubagio®)

* Natalizumab (Tysabri®) is also indicated for Crohn’s disease. Use for this indication is addressed in a separate coverage policy. Please refer to the related coverage policy link above.

NOTE: Receipt of sample product does not satisfy any criteria requirements for coverage.

Cigna covers the following multiple sclerosis therapy products as medically necessary when the following criteria are met:

<table>
<thead>
<tr>
<th>Product</th>
<th>Criteria for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aubagio®</strong>&lt;br&gt;(teriflunomide)</td>
<td>Monotherapy treatment of relapsing forms of multiple sclerosis AND for Individual &amp; Family Plans ONLY: Failure or not a candidate (e.g., stabilized condition where therapeutic interchange is inappropriate) for one preferred product [dimethyl fumarate (Tecfidera), glatiramer acetate (Copaxone*), interferon beta-1a (Avonex,</td>
</tr>
<tr>
<td>Product</td>
<td>Criteria for Use</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------</td>
</tr>
</tbody>
</table>
| **Avonex® (interferon beta-1a)** | ANY of the following indications:  
- Monotherapy treatment of relapsing forms of multiple sclerosis OR  
- Clinically isolated syndrome (CIS) OR  
- Secondary progressive multiple sclerosis (SPMS) with relapses  
**AND for Individual & Family Plans ONLY:** Failure, documented intolerance, or not a candidate (e.g., stabilized condition where therapeutic interchange is inappropriate) for Avonex or Rebif AND unable to use Extavia |
| **Betaseron® (interferon beta-1b)** | ANY of the following indications:  
- Monotherapy treatment of relapsing forms of multiple sclerosis OR  
- Clinically isolated syndrome (CIS) OR  
- Secondary progressive multiple sclerosis (SPMS) with relapses  
**AND for Individual & Family Plans ONLY:** Failure, documented intolerance, or not a candidate (e.g., stabilized condition where therapeutic interchange is inappropriate) for Avonex or Rebif |
| **Copaxone®, Glatopa™ (glatiramer acetate)** | Monotherapy treatment of relapsing forms of multiple sclerosis OR clinically isolated syndrome (CIS)  
**AND for Individual & Family Plans ONLY:** Failure, documented intolerance, or not a candidate (e.g., stabilized condition where therapeutic interchange is inappropriate) for Avonex or Rebif |
| **Extavia® (interferon beta-1b)** | ANY of the following indications:  
- Monotherapy treatment of relapsing forms of multiple sclerosis OR  
- Clinically isolated syndrome (CIS) OR  
- Secondary progressive multiple sclerosis (SPMS) with relapses  
**AND for Individual & Family Plans ONLY:** Failure, documented intolerance, or not a candidate (e.g., stabilized condition where therapeutic interchange is inappropriate) for Avonex or Rebif |
| **Gilenya® (fingolimod)** | Monotherapy treatment of relapsing forms of multiple sclerosis AND for Individual and Family Plans: Failure or not a candidate (e.g., stabilized condition where therapeutic interchange is inappropriate) for one preferred product [dimethyl fumarate (Tecfidera), glatiramer acetate (Copaxone*), interferon beta-1a (Avonex, Rebif)] |
| **Lemtrada™ (alemtuzumab)** | Monotherapy treatment of relapsing forms of multiple sclerosis (MS) AND inadequate response to TWO prior therapies or not a candidate (e.g., stabilized condition where therapeutic interchange is inappropriate). Prior therapies include the following:  
- Dimethyl fumarate (Tecfidera)  
- Fingolimod (Gilenya)  
- Glatiramer acetate (Copaxone*)  
- Interferon beta-1a (Avonex or Rebif), peginterferon beta-1a (Plegridy) or interferon beta-1b (Betaseron, Extavia)  
- Natalizumab (Tysabri)  
- Teriflunomide (Aubagio) |
| **Plegridy™ (peginterferon beta-1a)** | Monotherapy treatment of relapsing forms of multiple sclerosis AND for Individual & Family Plans ONLY: Contraindication per FDA label, documented intolerance, or not a candidate (e.g., stabilized condition where therapeutic interchange is inappropriate) for interferon beta-1a (Avonex, Rebif) |
| **Rebif® (interferon beta-1a)** | ANY of the following indications:  
- Monotherapy treatment of relapsing forms of multiple sclerosis OR  
- Clinically isolated syndrome (CIS) OR  
- Secondary progressive multiple sclerosis (SPMS) with relapses |
<table>
<thead>
<tr>
<th>Product</th>
<th>Criteria for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecfidera® (dimethyl fumarate)</td>
<td>Monotherapy treatment of relapsing forms of multiple sclerosis</td>
</tr>
</tbody>
</table>
| Tysabri® (natalizumab) | Monotherapy treatment of relapsing forms of multiple sclerosis and **ONE** of the following:  
- Failure, contraindication per FDA label, or documented intolerance to one disease modifying therapy. For Individual & Family Plans, preferred products include dimethyl fumarate (Tecfidera), glatiramer acetate (Copaxone*), interferon beta-1a (Avonex, Rebif)  
- Not a candidate (e.g., therapy for aggressive initial disease course) for alternate disease modifying therapy  
- History of a beneficial clinical response with natalizumab |

* Also available as Glatopa™

Cigna does not cover the use of Multiple Sclerosis Therapy for any other indication(s) because it is considered experimental, investigational or unproven.

When coverage is available and medically necessary, the dosage, frequency, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Multiple Sclerosis Therapy.

### FDA Approved Indications

<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aubagio</strong> (teriflunomide)</td>
<td>Treatment of patients with relapsing forms of multiple sclerosis.</td>
</tr>
<tr>
<td><strong>Avonex</strong> (interferon beta-1a)</td>
<td>Treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.</td>
</tr>
<tr>
<td><strong>Betaseron</strong> (interferon beta-1b)</td>
<td>Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.</td>
</tr>
<tr>
<td><strong>Copaxone, Glatopa</strong> (glatiramer acetate)</td>
<td>Treatment of patients with relapsing forms of multiple sclerosis.</td>
</tr>
<tr>
<td><strong>Extavia</strong> (interferon beta-1b)</td>
<td>Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.</td>
</tr>
<tr>
<td><strong>Gilenya</strong> (fingolimod)</td>
<td>Treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.</td>
</tr>
<tr>
<td><strong>Lemtrada</strong> (alemtuzumab)</td>
<td>Treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.</td>
</tr>
<tr>
<td><strong>Plegridy</strong> (peginterferon beta-1a)</td>
<td>Treatment of patients with relapsing forms of multiple sclerosis.</td>
</tr>
<tr>
<td><strong>Rebif</strong> (interferon beta-1a)</td>
<td>Treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.</td>
</tr>
<tr>
<td><strong>Tecfidera</strong></td>
<td>Treatment of patients with relapsing forms of multiple sclerosis.</td>
</tr>
<tr>
<td>Product</td>
<td>FDA Approved Indications</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tbody>
</table>
| Tysabri (natalizumab)   | **Multiple Sclerosis (MS)**  
Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing treatment with Tysabri, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. See important information regarding the risk of PML with Tysabri [see Warnings and Precautions (5.1)]. |
|                         | **Crohn's Disease (CD)**   
Tysabri is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. Tysabri should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α [see Warnings and Precautions (5.1)]. |
<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gilenya</strong></td>
<td><strong>Recommended Dose</strong>&lt;br&gt;The recommended dose of Gilenya is 0.5 mg orally once daily. Fingolimod doses higher than 0.5 mg are associated with a greater incidence of adverse reactions without additional benefit. Gilenya can be taken with or without food. Patients who initiate Gilenya and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring [see Reinitiation of Therapy Following Discontinuation].</td>
</tr>
</tbody>
</table>
| **(fingolimod)** | **First Dose Monitoring**<br>Initiation of Gilenya treatment results in a decrease in heart rate [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]. After the first dose of Gilenya, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients. The first dose of Gilenya should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. In order to assess patient response to the first dose of fingolimod, observe all patients for 6 hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Obtain in all patients an electrocardiogram (ECG) prior to dosing, and at the end of the observation period. Additional observation should be instituted until the finding has resolved in the following situations:<br>- The heart rate 6 hours post-dose is <45 bpm<br>- The heart rate 6 hours post-dose is at the lowest value postdose (suggesting that the maximum pharmacodynamic effect on the heart may not have occurred)<br>- The ECG 6 hours postdose shows new onset second degree or higher atrioventricular (AV) block<br>Should postdose symptomatic bradycardia occur, initiate appropriate management, begin continuous ECG monitoring, and continue observation until the symptoms have resolved. Should a patient require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated after the second dose of Gilenya. Patients with some preexisting conditions (e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, sinoatrial heart block) may poorly tolerate the Gilenya-induced bradycardia, or experience serious rhythm disturbances after the first dose of Gilenya. Prior to treatment with Gilenya, these patients should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation, and, if treated with Gilenya, should be monitored overnight with continuous ECG in a medical facility after the first dose. Gilenya is contraindicated in patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure) [see Contraindications (4)]. Since initiation of Gilenya treatment results in decreased heart rate and may prolong the QT interval, patients with a prolonged QTc interval (>450 msec males,
<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilenya (oral)</td>
<td>&gt;470 msec females) before dosing or during 6 hour observation, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility [see Drug Interactions (7)]. Experience with Gilenya is limited in patients receiving concurrent therapy with drugs that slow heart rate or atrioventricular conduction (e.g., beta blockers, heart-rate lowering calcium channel blockers such as diltiazem or verapamil, or digoxin). Because the initiation of Gilenya treatment is also associated with slowing of the heart rate, concomitant use of these drugs during Gilenya initiation may be associated with severe bradycardia or heart block. The possibility to switch to drugs that do not slow the heart rate or atrioventricular conduction should be evaluated by the physician prescribing these drugs before initiating Gilenya. Patients who cannot switch should have overnight continuous ECG monitoring after the first dose [see Drug Interactions (7)]. Clinical data indicate effects of Gilenya on heart rate are maximal after the first dose although milder effects on heart rate may persist for, on average, 2 to 4 weeks after initiation of therapy at which time heart rate generally returns to baseline. Physicians should continue to be alert to patient reports of cardiac symptoms. Re-initiation of Therapy Following Discontinuation If Gilenya therapy is discontinued for more than 14 days, after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of Gilenya treatment and the same precautions (first dose monitoring) as for initial dosing should apply. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of 1 day or more, during week 3 and 4 of treatment first dose procedures are recommended after treatment interruption of more than 7 days.</td>
</tr>
</tbody>
</table>
| Lemtrada (alemtuzumab) | The recommended dosage of Lemtrada is 12 mg/day administered by intravenous infusion for 2 treatment courses:  
  - First Treatment Course: 12 mg/day on 5 consecutive days (60 mg total dose)  
  - Second Treatment Course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course.  
  Laboratory Testing and Monitoring to Assess Safety Conduct the following laboratory tests at baseline and at periodic intervals for 48 months following the last treatment course of Lemtrada in order to monitor for early signs of potentially serious adverse effects:  
  - Complete blood count (CBC) with differential (prior to treatment initiation and at monthly intervals thereafter)  
  - Serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter)  
  - Urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter)  
  - A test of thyroid function, such as thyroid stimulating hormone (TSH) level (prior to treatment initiation and every 3 months thereafter)  
  - Conduct baseline and yearly skin exams to monitor for melanoma |
| Plegridy (peginterferon beta-1a) | Plegridy is administered subcutaneously. The recommended dosage of Plegridy is 125 micrograms injected subcutaneously every 14 days. Treatment initiation Patients should start treatment with 63 micrograms on day 1. On day 15 (14 days |
Rebif (interferon beta-1a)

The recommended dose of Rebif is either 22 mcg or 44 mcg injected subcutaneously three times per week. Rebif should be administered, if possible, at the same time (preferably in the late afternoon or evening) on the same three days (e.g., Monday, Wednesday, and Friday) at least 48 hours apart each week.

Generally, patients should be started at 20% of the prescribed dose three times per week and increased over a 4-week period to the targeted dose, either 22 mcg three times per week (see Table 1) or 44 mcg three times per week (see Table 2). Patients prescribed a targeted dose of 22 mcg three times per week should use the prefilled syringes for titration.

**Table 1: Titration Schedule for a 22 mcg Prescribed Dose**

<table>
<thead>
<tr>
<th>Week of Use</th>
<th>Dose</th>
<th>Syringe to Use</th>
<th>Amount of syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1 Titration</td>
<td>4.4 mcg</td>
<td>8.8 mcg syringe</td>
<td>Use half of syringe</td>
</tr>
<tr>
<td>Week 2 Titration</td>
<td>4.4 mcg</td>
<td>8.8 mcg syringe</td>
<td>Use half of syringe</td>
</tr>
<tr>
<td>Week 3 Titration</td>
<td>11 mcg</td>
<td>22 mcg syringe</td>
<td>Use half of syringe</td>
</tr>
<tr>
<td>Week 4 Titration</td>
<td>11 mcg</td>
<td>22 mcg syringe</td>
<td>Use half of syringe</td>
</tr>
<tr>
<td>Week 5 and after</td>
<td>22 mcg</td>
<td>22 mcg syringe or autoinjector</td>
<td>Use full syringe or autoinjector</td>
</tr>
</tbody>
</table>

*Use only prefilled syringes, not autoinjectors, to titrate to the 22 mcg Prescribed Dose.

**Table 2: Titration Schedule for a 44 mcg Prescribed Dose**

<table>
<thead>
<tr>
<th>Week of Use</th>
<th>Dose</th>
<th>Syringe to Use</th>
<th>Amount of syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1 Titration</td>
<td>8.8 mcg</td>
<td>8.8 mcg syringe or autoinjector</td>
<td>Use full syringe or autoinjector</td>
</tr>
<tr>
<td>Week 2 Titration</td>
<td>8.8 mcg</td>
<td>8.8 mcg syringe or autoinjector</td>
<td>Use full syringe or autoinjector</td>
</tr>
<tr>
<td>Week 3 Titration</td>
<td>22 mcg</td>
<td>22 mcg syringe or autoinjector</td>
<td>Use full syringe or autoinjector</td>
</tr>
<tr>
<td>Week 4 Titration</td>
<td>22 mcg</td>
<td>22 mcg syringe or autoinjector</td>
<td>Use full syringe or autoinjector</td>
</tr>
<tr>
<td>Week 5 and after</td>
<td>44 mcg</td>
<td>44 mcg syringe or autoinjector</td>
<td>Use full syringe or autoinjector</td>
</tr>
</tbody>
</table>

**Prefilled syringes or autoinjectors can be used to titrate to the 44 mcg Prescribed Dose.

Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved.

Tecfidera (dimethyl fumarate)
The starting dose for Tecfidera is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally.
Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 4 weeks, the recommended dose of 240 mg twice a day should be resumed. Discontinuation of Tecfidera should be considered for patients unable to tolerate return to the maintenance dose. The incidence of flushing may be reduced by administration of Tecfidera with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to Tecfidera dosing may reduce the incidence or severity of flushing.

Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy.

**Tysabri (natalizumab)**

Only prescribers registered in the MS TOUCH® Prescribing Program may prescribe Tysabri for multiple sclerosis [see Warnings and Precautions (5.2)]. The recommended dose of Tysabri for multiple sclerosis is 300 mg intravenous infusion over one hour every four weeks.

### Drug Availability

<table>
<thead>
<tr>
<th>Product</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aubagio (teriflunomide)</td>
<td>Available as 7 mg and 14 mg tablets each in cartons of 5 tablets or 28 tablets.</td>
</tr>
</tbody>
</table>
| Avonex (interferon beta-1a) | • For injection: 30 micrograms lyophilized powder in a single-use vial  
  • Injection: 30 micrograms per 0.5 mL solution in a single-use prefilled syringe  
  • Injection: 30 micrograms per 0.5 mL solution in a single-use prefilled autoinjector |
| Betaseron (interferon beta-1b) | For injection: 0.3 mg lyophilized powder in a single-use vial for reconstitution.  
  The optional BETACONNECT autoinjector is not supplied with Betaseron, but is available for patients with a prescription for Betaseron by calling the BETAPLUS patient support program. |
| Copaxone, Glatopa (glatiramer acetate) | **Copaxone**: Available as 20 mg per mL in a single-dose, prefilled syringe supplied in 30-count cartons and 40 mg per mL in a single-dose, prefilled syringe supplied in 12-count cartons.  
  **Glatopa**: Available as 20 mg per mL in a single-dose, prefilled syringe supplied in 30-count cartons. |
| Extavia (interferon beta-1b) | For injection: 0.3 mg lyophilized powder in a single-use vial for reconstitution. |
| Gilenya (fingolimod) | Supplied as 0.5 mg capsules. Available in bottles of 30 capsules and a carton of 7 capsules containing 1 blister card of 7 capsules per blister card.  
  A Risk Evaluation and Mitigation Strategy (REMS) was required by the FDA and involves a communication plan to healthcare providers. |
| Lemtrada (alemtuzumab) | Injection: 12 mg/1.2 mL (10 mg/mL) in a single-use vial. Lemtrada is a solution that requires dilution prior to intravenous infusion.  
  Lemtrada is available only through a restricted program under a REMS called the Lemtrada REMS Program, because of the risks of autoimmunity, infusion reactions, and malignancies. Notable requirements of the Lemtrada REMS Program include the following:  
  • Prescribers must be certified with the program by enrolling and completing training.  
  • Patients must enroll in the program and comply with ongoing monitoring requirements.  
  • Pharmacies must be certified with the program and must only dispense to certified healthcare facilities that are authorized to receive Lemtrada. |
### General Background

#### Disease Overview

Multiple sclerosis is classified based on the clinical course of the disease. About 85% of patients are initially diagnosed with relapsing-remitting multiple sclerosis (RRMS). Relapsing-remitting disease is associated with a recurring pattern of symptom exacerbation or relapse, followed by marked recovery. Symptoms often completely resolve between relapses early in the disease course, but symptom resolution may be incomplete later on, leading to progressive disease (i.e., secondary progressive multiple sclerosis, SPMS). The majority of patients with RRMS will eventually develop SPMS. Primary progressive multiple sclerosis (PPMS) occurs in about 15% of patients and is characterized by a continual decline without relapses or resolution of symptoms. Less than 5% of patients have progressive/relapsing multiple sclerosis (PRMS) with a steady functional decline from disease onset along with superimposed relapses. (Goodin, 2012) No medications are currently FDA-approved to slow progression of PPMS. (National MS Society, 2012)

#### Pharmacology

- **Aubagio (teriflunomide)**

### Availability

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Plegridy</strong> (peginterferon beta-1a)</td>
<td>• Healthcare facilities must enroll in the program and verify that patients are authorized before infusing Lemtrada. Healthcare facilities must have on-site access to equipment and personnel trained to manage infusion reactions. Further information, including a list of qualified healthcare facilities, is available at 1-855-676-6326.</td>
</tr>
</tbody>
</table>
| **Pen**                          | • Injection: 125 micrograms of Plegridy per 0.5 mL of solution in a single-dose prefilled pen  
  • Injection: Starter Pack containing 63 micrograms per 0.5 mL of solution in a single-dose prefilled pen and 94 micrograms per 0.5 mL solution in a single-dose prefilled pen |
| **Prefilled Syringe**            | • Injection: 125 micrograms of Plegridy per 0.5 mL of solution in a single-dose prefilled syringe  
  • Injection: Starter Pack containing 63 micrograms per 0.5 mL of solution in a single-dose prefilled syringe and 94 micrograms per 0.5 mL of solution in a single-dose prefilled syringe |
| **Rebif** (interferon beta-1a)   | • Injection: 8.8 mcg per 0.2 mL in a graduated, single-dose Rebif prefilled syringe  
  • Injection: 22 mcg per 0.5 mL in a graduated, single-dose Rebif prefilled syringe  
  • Injection: 44 mcg per 0.5 mL in a graduated, single-dose Rebif prefilled syringe  
  • Injection: 8.8 mcg per 0.2 mL in a single-dose prefilled Rebif Rebidose autoinjector  
  • Injection: 22 mcg per 0.5 mL in a single-dose prefilled Rebif Rebidose autoinjector  
  • Injection: 44 mcg per 0.5 mL in a single-dose prefilled Rebif Rebidose autoinjector |
| **Tecfidera** (dimethyl fumarate) | Available as delayed-release capsules containing 120 mg or 240 mg of dimethyl fumarate. Tecfidera is available as a 30-day starter pack (containing a 7-day bottle of 14 – 120 mg capsules and a 23-day bottle of 46 – 240 mg capsules). The 120 mg capsules are available as a 7-day bottle containing 14 capsules and the 240 mg capsules are available as a 30-day bottle containing 60 capsules. |
| **Tysabri** (natalizumab)        | Tysabri injection is supplied as 300 mg natalizumab in 15 mL in a sterile, single-use vial free of preservatives. Each package contains a single-use vial.  
  A Risk Evaluation and Mitigation Strategy (REMS) was required by the FDA and involves a medication guide, elements to assure safe use, and an implementation plan. Tysabri is available only through registered infusion centers participating in the TOUCH® Prescribing Program. |
Teriflunomide is an immunomodulator and anti-inflammatory. The exact mechanism of action for teriflunomide in MS is unknown, but it likely relates to a reduction in activated lymphocytes in the CNS. Teriflunomide inhibits dihydroorotate, a key enzyme in de novo pyrimidine synthesis, interfering with the production of de novo pyrimidines necessary for lymphocyte proliferation and function. This results in a reduced number of activated lymphocytes entering the CNS.

- **Copaxone/Glatopa (glatiramer acetate)**
  Glatiramer acetate is a synthetic mixture of the amino acids L-alanine, L-lysine, L-tyrosine, and L-glutamic acid. Glatiramer acetate appears to interfere with immune mediated responses responsible for the pathogenesis of multiple sclerosis. Glatiramer acetate modifies immune response by activating and inducing glatiramer-specific suppressor T-cells in the periphery.

- **Gilenya (fingolimod)**
  Gilenya is a sphingosine 1-phosphate receptor modulator. It is unknown what mechanism Gilenya uses to exert therapeutic effects in MS. Gilenya may reduce central nervous system inflammation by decreasing lymphocyte movement into the CNS. The lymphocyte count decreases to about 60% of baseline 6 hours after the first Gilenya dose.

- **Interferon beta-1a and beta-1b (Avonex, Betaseron, Extavia, Rebif)**
  Interferon beta products have the same mechanism of action. The amino acid sequence, specific activity, source, molecular weight, and pharmacokinetic parameters differ slightly, although these differences have not correlated into known differences in clinical efficacy or safety.

- **Lemtrada (alemtuzumab)**
  Alemtuzumab is a humanized monoclonal antibody produced in Chinese hamster ovary cells using recombinant DNA technology. It is directed against CD52, a glycoprotein present on the surface of lymphocytes. Binding of alemtuzumab to the CD52 cell surface antigen leads to lysis and depletion of T-lymphocytes and B-lymphocytes. The exact mechanism of action of alemtuzumab in MS is not completely understood, but may be related to changes in the immune system associated with lymphopenia and subsequent reconstitution of lymphocytes. (Coles, 2013)

- **Plegridy (peginterferon beta-1a)**
  Peginterferon beta-1a is a pegylated, recombinant version of the endogenous interferon beta-1a molecule. The interferon beta-1a molecule is created using Chinese hamster ovary cells. The parent interferon molecule is then covalently linked to a pegylation chain to improve its metabolic stability. The exact mechanism of action of peginterferon beta-1a is not known. Proposed mechanisms of action include the promotion of anti-inflammatory cytokine production, the blockade of inflammatory cytokine production, and inhibition of activated T-cell movement across the blood brain barrier through altered expression of interferon-dependent gene products and markers. (Rice, 2014; Tavazzi, 2014)

- **Tecfidera (dimethyl fumarate)**
  The exact mechanism of action of dimethyl fumarate is not known. It is believed to inhibit pro-inflammatory pathways and exhibit neuroprotective effects.

- **Tysabri (natalizumab)**
  Natalizumab is an integrin-4 receptor antagonist labeled for the treatment of MS and CD. Natalizumab is a human recombinant immunoglobulin-4 monoclonal antibody directed against the integrin alpha-4 adhesion molecule. It is the first medication of this type in a new class of selective adhesion molecule inhibitors. Natalizumab binds to the alpha-4 subunit of integrins alpha-4-beta-1 and alpha-4-beta-7 expressed on the surface of leukocytes (except neutrophils). Integrin alpha-4-beta-7 binds to the mucosal vascular addressin cell adhesion molecule-1 (MadCam-1) in the gastrointestinal endothelium. When natalizumab binds to alpha-4 integrins, it disrupts integrin interaction with MadCam-1, preventing the passage of leukocytes into the gut.

**Guidelines**
The most recent MS treatment recommendations are available as a consensus statement from MS Coalition (2015) and guidelines from the Association of British Neurologists (2015). Additional MS treatment guidelines are available from the National MS Society (2008) and the American Academy of Neurology (2002).

The MS Coalition and Association of British Neurologists (ABN) emphasize the importance of early treatment initiation, but do not recommend any agent over another. Per the MS Coalition, the disease-modifying therapy (DMT) of choice is patient-specific and depends on preferred route of administration, patient comorbidities, side effects, MS severity, and previous MS therapies. The MS Coalition highlights the importance of access to all DMTs due to the many patient-specific factors involved with determining the treatment of choice and recommends against switching from one agent to another unless the reason is medical. (Multiple Sclerosis Coalition, 2015) The ABN separates available disease modifying therapy into 2 categories based on relative efficacy. Category 1 or moderate efficacy products include interferons, peginterferon, glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 or high efficacy should be reserved for those with active MS and include alemtuzumab and natalizumab. (ABN, 2015)

The American Academy of Neurology (AAN) and the National MS Society (NMSS) note that the traditional first-line treatments for relapsing MS are the injectable DMTs: interferon beta (Avonex, Betaseron, Extavia, Rebif) or glatiramer acetate (Copaxone). (NMSS, 2008; Goodin, 2002) In addition, interferon beta currently is recommended by experts from the AAN for the management of patients with relapsing forms of secondary progressive multiple sclerosis (SPMS). (Goodin, 2002) The AAN issued a position statement in 2015 advocating access to all disease modifying therapies for individuals with MS and that step therapy should be based on clinical and safety information and not just cost. (Corboy, 2015)

Natalizumab (Tysabri) and mitoxantrone (Novantrone) are reserved for patients with more aggressive disease. (NMSS, 2008; Goodin, 2002) Because natalizumab may be responsible for an increased risk of PML, the retired 2008 AAN assessment for its use in MS recommends that natalizumab be reserved for selected patients with RRMS who have failed other therapies either through continued disease activity or medication intolerance, or who have a particularly aggressive initial disease course. (Goodin, 2008) In addition, combination therapy with an interferon beta and natalizumab should not be used since this combination may increase the risk of PML. There is no data to support the use of natalizumab combined with other disease-modifying agents as compared to natalizumab monotherapy and for that reason the AAN recommends the use of natalizumab in combination with agents not inducing immune suppression be reserved for properly controlled and monitored clinical trials. (Goodin, 2008)

All 3 oral DMTs are FDA-approved for use in relapsing forms of MS with no limitations of use based on previous treatment with injectable DMTs. The DMT of choice for treating relapsing MS is typically patient-specific and depends on many factors including disease course, comorbidities, patient preference for administration route, and side effects and monitoring requirements of the medication. (NMSS, 2012) Acute episodes are generally treated with intravenous or oral glucocorticoids such as methylprednisolone. (Goodin, 2002)

**Clinical Efficacy**

- **Comparative Evidence**

Multiple clinical trials have been conducted comparing interferon beta and glatiramer acetate. More recently the BEYOND trial evaluated interferon beta-1b 250 mcg or 500 mcg subcutaneously every other day compared with glatiramer acetate 20 mg once daily. Patients enrolled were followed for 2-3.5 years. No differences were found in relapse risk, expanded disability status scale (EDSS) progression, or MRI changes. Injection site reactions were more common with glatiramer acetate and flu-like symptoms were more common with interferon beta-1b. (O’Connor, 2009) REGARD, an open-label trial, compared interferon beta-1a (Rebif) 44 mcg three times per week and glatiramer acetate 20 mg once per day and patients were followed for nearly 2 years (96 weeks). The authors note that there was no difference in the time to first relapse between the glatiramer acetate and interferon beta arms, although the overall relapse rate was lower than anticipated. Influenza-like illness, headache, myalgia, and increased alanine aminotransferase occurred more frequently in the interferon beta group and injection site reactions and dyspnea were more common in the glatiramer acetate group. (Mikol, 2008) The BECOME study evaluated interferon beta-1b (Betaseron) 250 mcg every other day and glatiramer acetate 20 mg once daily. There was no difference between the two groups in terms of the primary endpoint (number of combined active lesions (CAL) per patient per scan during the first year) or in the numbers of new lesions or clinical relapses for 2 years. (Cadavid, 2009)
Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (CONFIRM) was a placebo-controlled, phase 3 trial that evaluated oral dimethyl fumarate (BG-12), glatiramer acetate, and placebo. The adjusted mean annualized relapse rates were significantly lower with dimethyl fumarate 240 mg twice daily (0.22), dimethyl fumarate 240 mg 3 times daily (0.2), and glatiramer acetate (0.29) compared with placebo (0.4, p<0.01 for all) after 2 years of treatment. The reduction in annualized relapse rate remained statistically significant in additional sensitivity analyses that included patients who had switched to an alternate DMT or used different criteria for defining a relapse. Neither dimethyl fumarate nor glatiramer acetate statistically significantly reduced the percentage of patients with sustained disability progression compared with placebo. Outcomes related to MRI lesions were statistically significantly improved with each dose of dimethyl fumarate and glatiramer acetate compared with placebo. (Fox, 2012) Dimethyl fumarate was not directly compared to glatiramer acetate and the design of CONFIRM was not to test the superiority or non-inferiority of dimethyl fumarate and glatiramer acetate. Results from the post-hoc analyses that were conducted require further study prospectively.

TRANSFORMS was a one year phase III study comparing two doses of fingolimod (0.5 mg and 1.25 mg) against interferon beta-1a in 1,292 people with RRMS. Relapse rates at one year were 0.33 for interferon beta-1a, 0.16 for fingolimod 0.5 mg and 0.2 for fingolimod 1.25 mg. In addition 80-83% of the fingolimod groups remained relapse-free over the year compared with 69% of those on interferon beta-1a. (Cohen, 2010)

Three randomized, controlled, rater-blinded trials (CAMMS223, CARE-MS I, and CARE-MS II) compared alemtuzumab with interferon beta-1a (Rebif) over 2 to 3 years. One trial included MS patients who had active disease despite treatment with a DMT (CARE-MS I), and the other 2 trials included treatment-naïve patients. The CARE-MS II trial excluded individuals who had used azathioprine, cyclosporine, methotrexate, or natalizumab within 6 months. (Coles, 2012) The annualized relapse rate was significantly lower with alemtuzumab (0.08 to 0.26) relative to interferon beta-1a (0.36 to 0.52, p<0.001) in all 3 trials. (Cohen, 2012; Coles, 2008; Coles, 2012) The proportion of patients with sustained accumulation of disability was lower with alemtuzumab (8.5% to 13%) relative to interferon beta-1a (21% to 26%, p<0.0084) in the trial of previously-treated patients and in 1 of the trials of treatment naive patients. (Coles, 2008; Coles, 2012) The proportion of patients with sustained accumulation of disability was similar with alemtuzumab (8%) and interferon beta-1a (11%, p=0.22) in the third trial. (Cohen, 2012)

The TENERE trial compared the efficacy, safety, and tolerability of teriflunomide and interferon beta-1a subcutaneous (Rebif) in individuals who met McDonald criteria for MS with a relapsing clinical course. Participants (n = 324) were randomized to receive teriflunomide 7 mg daily, teriflunomide 14 mg daily, or interferon beta-1a titrated to 22 mcg to 44 mcg three times per week. The primary endpoint was a composite evaluating time to treatment failure, which included confirmed relapse or permanent treatment discontinuation (for any reason). There was no significant difference between the teriflunomide groups and interferon beta-1a for the primary composite endpoint (37.8%, 48.6%, and 42.3% for the teriflunomide 14 mg/day, teriflunomide 7 mg/day, and interferon beta-1a groups, respectively). More individuals had confirmed relapse in the teriflunomide 7 mg/day group (42.2%) and more discontinued treatment in the interferon beta-1a group (24%). The secondary endpoint of adjusted annualized relapse rate was 0.26, 0.41, and 0.22 for the teriflunomide 14 mg/day, teriflunomide 7 mg/day, and interferon beta-1a groups, respectively with a significant difference found between the teriflunomide 7 mg/day and interferon beta-1a groups (p = 0.03). (Vermersch, 2014)

A Cochrane review of immunomodulators and immunosuppressants for MS was published in 2013 and included 44 trials and 17,401 participants. The majority of the trials utilized interferon beta, glatiramer acetate or natalizumab (66%) and 23 (52%) of the trials were in RRMS. The median duration of the trials was 2 years. Of note, this review did not include any data for the oral DMTs (i.e., dimethyl fumarate, fingolimod, teriflunomide). The authors concluded, based on high quality evidence, that natalizumab and Rebif (interferon beta-1a) reduce relapses compared to placebo and that they are more efficacious than Avonex (interferon beta-1a) in RRMS. The network meta-analysis concluded that the most effective drug was natalizumab, followed by interferon beta-1a (Rebif), then mitoxantrone, glatiramer acetate, and interferon beta-1b (Betaseron). In addition the conclusion was reached that, for disease progression, natalizumab and interferon beta-1a were more protective than placebo based on moderate quality evidence. With regards to progressive MS, none of the reviewed agents were effective in preventing disability progression over 2-3 years. (Filippini, 2013) Another Cochrane review included 5 trials (n = 2,858) comparing interferons-beta and glatiramer acetate in RRMS and concluded that the effects are similar or only demonstrated small differences in terms of clinical and MRI activity measures. (LaMantia, 2014)
A network meta-analysis was conducted including 39 trials and 25,113 patients with RRMS. Fifteen treatments, comprised of FDA approved disease-modifying therapies, as well as azathioprine, immunoglobulins, and investigational agents (daclizumab and laquinimod) were included. The median trial duration was 24 months and 60% were placebo-controlled. The results were that alemtuzumab, mitoxantrone, natalizumab, and fingolimod were most effective in reducing the recurrence of relapses in RRMS during the first 24 months of treatment. (Tramacere, 2015)

**Combination Therapy**

There is insufficient evidence from large, randomized controlled trials to support the use of any combination of disease-modifying therapy with alemtuzumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta, natalizumab, peginterferon beta, or teriflunomide. Natalizumab is specifically indicated as monotherapy.

The CombiRx trial evaluated use of glatiramer acetate in combination with interferon beta-1a (30mcg intramuscularly once weekly) compared to each individually over 3 years. The combination of glatiramer acetate and interferon beta-1a was not superior to glatiramer acetate alone with regards to the primary endpoint of annualized relapse rate. Combination therapy and glatiramer acetate alone did demonstrate a benefit in terms of risk of relapse compared to interferon beta-1a alone. An extension phase is ongoing and may determine if observed differences in MRI results with the combination group will produce a clinical difference. (Lublin, 2013)

Teriflunomide in combination with interferon beta was compared with interferon beta alone in a phase II trial. Disease activity assessed by MRI demonstrated that combination therapy reduced the number of gadolinium-enhancing T1 lesions compared with interferon beta therapy alone. There were no significant differences in the annualized relapse rate between combination teriflunomide and interferon beta versus interferon beta alone; however, this study was designed with safety and tolerability as the primary endpoint. (Freedman, 2012)

SENTINEL evaluated the addition of natalizumab to interferon beta-1a in a two-year, randomized, multi-center, placebo-controlled, double-blind study of 1,171 interferon beta-1a (Avonex)-treated patients who continued to experience disease activity. Subjects were randomized to add natalizumab 300 mg or placebo to their regimen of interferon beta-1a every four weeks for up to 116 weeks. Combination therapy of interferon beta-1a and natalizumab reduced the clinical relapse rate at 1 year by 54% compared with interferon beta-1a alone. This reduction was maintained after 2 years of combination therapy. Natalizumab combined with interferon beta-1a also reduced the risk of sustained disability progression and reduced new or enlarging MRI lesions. There were 2 cases of PML, one of which was fatal, in subjects receiving natalizumab therapy. (Rudick, 2006)

**Clinically Isolated Syndrome (CIS) – Glatiramer acetate**

The PreCISE trial randomized patients presenting with clinically isolated syndrome with unifocal manifestation and brain lesions detected by MRI to treatment with either glatiramer acetate or placebo. The primary endpoint was time to a second exacerbation or clinical definite multiple sclerosis (CDMS) and the risk of developing CDMS was reduced by 45% with glatiramer acetate compared with placebo. Following the interim data analysis, the placebo arm of the trial was stopped and patients could begin to receive treatment with glatiramer acetate. (Comi, 2009) Based on the results of the PreCISE trial, the FDA expanded the indication of Copaxone to include individuals who have experienced a first clinical episode and have MRI features consistent with MS. A further analysis of patients in PreCISE who received placebo at randomization and later received glatiramer acetate (i.e., delayed treatment) concluded that early treatment reduced the risk of CDMS by 41%. (Comi, 2013)

**Natalizumab (Tysabri)**

The AFFIRM trial enrolled 942 individuals with relapsing MS, who received either natalizumab 300 mg or placebo by intravenous infusions every four weeks for more than two years. Individuals were excluded if they had received treatment with interferon beta, glatiramer acetate, or both for greater than 6 months. The primary end points were the rate of clinical relapse at one year and the rate of sustained progression of disability as measured by the Expanded Disability Status Scale (EDSS) at two years. Results showed that natalizumab significantly reduced the risk of progression of disability by 42% and significantly reduced the rate of clinical relapses by 68% over two years. The adverse events fatigue (27% vs. 21%, p = 0.048) and allergic reaction (9% vs. 4%, p=0.012) were the most common adverse events reported in the natalizumab group compared to the placebo group. (Polman, 2006) Natalizumab was also evaluated in the SENTINHEL trial, which evaluated the addition of natalizumab to interferon beta-1a. (Rudick, 2006)
• Secondary Progressive Multiple Sclerosis (SPMS) – Interferon beta

A Cochrane review of the evidence for SPMS evaluated five randomized controlled trials which included a total of 3,122 patients (1,829 received interferon beta and 1,293 received placebo). Interferon beta did not decrease the risk of progression sustained at 6 months after three years of treatment. Interferon beta does not prevent the development of permanent physical disability in SPMS, although it significantly reduces the risk of relapse and of short-term relapse-related disability. The authors of the review concluded that no new randomized controlled trials for interferon beta versus placebo in SPMS will probably be undertaken because research is now focusing on innovative drugs. (Lamantia, 2012)

Experimental, Investigational, and Unproven Uses

Fingolimod has been studied for use in progressive primary MS (PPMS). A phase III randomized study of 907 patients (INFORMS) has been completed to assess the efficacy and safety of fingolimod compared to placebo in patients with PPMS. The primary endpoint was 3-month confirmed disease progression. Fingolimod did demonstrate a significant benefit over placebo in slowing disease progression in PPMS. (Lublin, 2016) At this time, there is insufficient published data in terms of safety and efficacy to support the use of fingolimod for this indication.

Although not indicated for the condition, fingolimod has also been granted orphan status by the FDA for chronic inflammatory demyelinating polyneuropathy (CIDP). A placebo-controlled trial evaluating the safety and efficacy of fingolimod 0.5mg once daily for CIDP is anticipated to be completed March 2017.

Coding/Billing Information

Note: Dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, peginterferon beta-1a and teriflunomide are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

Note:
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

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<th>HCPCS Codes</th>
<th>Description</th>
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<td>J0202</td>
<td>Injection, alemtuzumab, 1 mg</td>
</tr>
<tr>
<td>J9010</td>
<td>Injection, alemtuzumab, 1 mg (Code deleted 12/31/2015)</td>
</tr>
<tr>
<td>J2323</td>
<td>Injection, natalizumab, 1 mg</td>
</tr>
</tbody>
</table>

References


32. Novartis Pharmaceuticals Corporation. Extavia (interferon beta-1b) for injection, for subcutaneous use [product information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2015.


42. TEVA Pharmaceuticals USA, Inc. Copaxone (glatiramer acetate injection) for subcutaneous use [product information]. North Wales, PA: TEVA Pharmaceuticals USA, Inc.; October 2014.
