# Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

## Title: Multiple Sclerosis Agents

*See also:* *Tysabri (natalizumab) and Lemtrada™ (alemtuzumab) (IV Multiple Sclerosis Agents) medical policy*

- **Prime Therapeutics will review Prior Authorization requests.**
  **Prior Authorization Form:**
  http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6070KS-MUSC.pdf

  **Link to Drug List (Formulary):**
  http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

**Professional**
Original Effective Date: January 1, 2012
Revision Date(s): November 1, 2012; July 8, 2013; January 1, 2014; April 1, 2014; October 28, 2014; January 1, 2015; June 1, 2015; June 26, 2015; April 15, 2016; October 1, 2016; January 1, 2017; April 1, 2017
Current Effective Date: April 1, 2017

**Institutional**
Original Effective Date: January 1, 2012
Revision Date(s): November 1, 2012; July 8, 2013; January 1, 2014; April 1, 2014; October 28, 2014; January 1, 2015; June 1, 2015; June 26, 2015; April 15, 2016; October 1, 2016; January 1, 2017; April 1, 2017
Current Effective Date: April 1, 2017

**State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.**

**The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.**

**The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.**

**If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.**

## DESCRIPTION

The intent of the Multiple Sclerosis Agents Prior Authorization (PA) Program is to encourage appropriate selection of patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies, and also to encourage use of a preferred multiple sclerosis (MS) agents. The program allows continuation of therapy with a nonpreferred MS agent when there is documentation that the patient is receiving the requested agent and has no contraindication(s) to therapy. The program requires the patient will not receive another MS disease modifying agent concomitantly with the requested agent. The intent of the quantity limit within the program is to encourage appropriate prescribing quantities as recommended by Food and Drug Administration (FDA) approved product labeling and/or clinical studies and/or guidelines. Requests for larger quantities will be reviewed when patient-specific documentation has been provided.

### Target Drugs

| Disease Modifying Agents (DMA) | |
|---|---|
| **Preferred Agents** | **Non-Preferred Agents** |
| **Aubagio**® (teriflunomide) | **Extavia**® (interferon β-1b) |
| **Avonex**® (interferon β-1a) | **Zinbryta**™ (daclizumab) |
| **Betaseron**® (interferon -1b) | |
| **Copaxone**® (glatiramer) | |
| **Gilenya**™ (fingolimod) | |
| **Glatopa** ™ (glatiramer)* | |
| **Plegridy™** (peginterferon β-1a) | |
| **Rebif**® (interferon β-1a) | |
| **Tecfidera**™ (dimethyl fumarate) | |

* generic for Copaxone 20 mg/mL injection

### FDA Approved Indications and Dosage[1-6,23,25,26,28,31]

<table>
<tr><th>Available Products</th><th>Indication</th><th>Dosage and Administration</th></tr>
<tr><td>Aubagio<br>(teriflunomide) tablet</td><td>Relapsing forms of MS</td><td>7 mg or 14 mg orally once daily</td></tr>
<tr><td>Avonex<br>(interferon β-1a)<br>intramuscular injection</td><td>Relapsing forms of MS [a]</td><td>30 mcg intramuscularly once weekly</td></tr>
<tr><td>Betaseron, Extavia<br>(interferon β-1b)<br>subcutaneous injection</td><td>Relapsing forms of MS [a]</td><td>Patients should be started at 0.0625 mg subcutaneously every other day, and increased over a six-week period to 0.25 mg every other day. See recommended titration table:
<table>
<tr><th></th><th>Recommended Titration</th><th>Dose</th><th>Volume</th></tr>
<tr><td>Weeks 1-2</td><td>25%</td><td>0.0625 mg</td><td>0.25 ml</td></tr>
<tr><td>Weeks 3-4</td><td>50%</td><td>0.125 mg</td><td>0.50 ml</td></tr>
<tr><td>Weeks 5-6</td><td>75%</td><td>0.1875 mg</td><td>0.75 ml</td></tr>
<tr><td>Week 7+</td><td>100%</td><td>0.25 mg</td><td>1.0 ml</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Available Products</th><th>Indication</th><th>Dosage and Administration</th></tr>
<tr><td>Copaxone<br>(glatiramer acetate)<br>subcutaneous injection</td><td>Relapsing forms of MS</td><td>20 mg subcutaneously daily or 40 mg subcutaneously three times per week at least 48 hours apart (doses are not interchangeable)</td></tr>
<tr><td>Gilenya<br>(fingolimod)<br>tablet</td><td>Relapsing forms of MS</td><td>0.5 mg orally once daily</td></tr>
<tr><td>Glatopa<br>(glatiramer acetate)<br>subcutaneous injection</td><td>Relapsing forms of MS</td><td>20 mg injected subcutaneously once daily (Glatopa 20mg/mL dose is not interchangeable with glatiramer acetate 40mg/mL dose)</td></tr>
<tr><td>Plegridy<br>(peginterferon β-1a)<br>subcutaneous injection</td><td>Relapsing forms of MS</td><td>The dose should be titrated, starting with 63 mcg on day 1, 94 mcg on day 15 and 125 mcg on day 29 followed by maintenance dose thereafter. The maintenance dose is 125 mcg subcutaneously every 14 days.</td></tr>
<tr><td>Rebif<br>(interferon β-1a)<br>subcutaneous injection</td><td>Relapsing forms of MS</td><td>22 mcg or 44 mcg injected subcutaneously three times per week. Patients should be started at 20% of the prescribed dose three times a week and increased over a 4-week period to the targeted dose, either 22 mcg or 44 mcg three times a week.<br>See recommended titration table:
<table>
<tr><th></th><th>Recommended Titration</th><th>Titration Dose for 22 mcg</th><th>Titration Dose for 44 mcg</th></tr>
<tr><td>Weeks 1-2</td><td>20%</td><td>4.4 mcg</td><td>8.8 mcg</td></tr>
<tr><td>Weeks 3-4</td><td>50%</td><td>11 mcg</td><td>22 mcg</td></tr>
<tr><td>Weeks 5+</td><td>100%</td><td>22 mcg</td><td>44 mcg</td></tr>
</table></td></tr>
<tr><td>Tecfidera<br>(dimethyl fumarate)<br>capsule</td><td>Relapsing forms of MS</td><td>Starting dose: 120 mg orally twice daily for 7 days<br>Maintenance dose: 240 mg twice daily</td></tr>
<tr><td>Zinbryta<br>(daclizumab)<br>subcutaneous injection</td><td>Relapsing forms of MS[b]</td><td>150 mg subcutaneously once monthly</td></tr>
</table>

RRMS- Relapsing-remitting multiple sclerosis; CD- Crohn's disease

a - Approved for patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis

b- Due to its safety profile, it is recommended to reserve Zinbryta for patients who have had an inadequate response to two or more drugs indicated for treatment of MS

## POLICY

### Prior Authorization and Quantity Limit Criteria for Approval – Through Preferred Agent

#### Initial Evaluation

The requested agent will be approved when ALL of the following are met:

1. ONE of the following:
   a. The patient is not currently being treated with a disease modifying agent (DMA) other than the requested agent
      **OR**
   b. The patient is currently being treated with another DMA other than the requested agent AND this DMA will be discontinued before starting the requested agent

   **AND**
2. ONE of the following:
   a. There is documentation that the patient is currently being treated with the requested agent
      (paid claim within the past 90 days, or patient claim within the past 120 days and physician states the patient is currently taking the requested medication in the past 90 days)
      **OR**
   b. The prescriber states the patient is using the requested agent AND is at risk if therapy is changed
      **OR**
   c. ALL of the following:
      1) The patient has an FDA labeled indication for the requested agent
         **AND**
      2) If the agent is a nonpreferred agent ONE of the following:
         a) The patient's medication history indicates use of TWO preferred disease modifying agents for MS (i.e. Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)
            **OR**
         b) The patient has a documented intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to ALL preferred disease modifying agents (i.e. Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)

         **AND**
      3) If **Gilenya**, the prescriber has performed an electrocardiogram 6 months and prior to initiating treatment.

   **AND**

3. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   **AND**
4. ONE of the following:
   a. The requested quantity (dose) is NOT greater than the program quantity limit
      **OR**
   b. ALL of the following:
      1) The requested quantity (dose) is greater than the program quantity limit
         **AND**
      2) The requested quantity (dose) is less than or equal to the FDA labeled dose
         **AND**
      3) The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit
      **OR**
   c. ALL of the following:
      1) The requested quantity (dose) is greater than the program quantity limit
         **AND**
      2) The requested quantity (dose) is greater than the FDA labeled dose
         **AND**
      3) The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis

**Length of Approval**: 12 months
**NOTE**: For agents requiring a starter dose for initial use, the starter dose will approved per the dose table and the maintenance dose will be approved for the remainder of 12 months.

## Renewal Evaluation

The requested agent will be renewed when ALL of the following are met:

1. The patient has been previously approved for the requested therapy through the PA process
   **AND**
2. The patient is NOT currently being treated with an additional disease modifying agent (DMA)
   **AND**
3. The patient has had clinical benefit from treatment with the requested agent
   **AND**
4. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   **AND**

5. ONE of the following:
   a. The requested quantity (dose) is NOT greater than the program quantity limit
      **OR**
   b. ALL of the following
      1) The requested quantity (dose) is greater than the program quantity limit
         **AND**
      2) The requested quantity (dose) is less than or equal to the FDA labeled dose
         **AND**
      3) The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

      **OR**
   c. ALL of the following:
      1) The requested quantity (dose) is greater than the program quantity limit
         **AND**
      2) The requested quantity (dose) is greater than the FDA labeled dose
         **AND**
      3) The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis

**Length of approval:** 12 months

### Dosing table for agents requiring a starter dose

| Agent | Starting Dose | Maintenance dose |
|---|---|---|
| **Plegridy** | 63 mcg on day 1, 94 mcg on day 15, and 125 mcg on day 29. (Requires 1 starter pen or syringe) | 125 mcg every 14 days following the starting dose |
| **Rebif** | 20% of the prescribed maintenance dose three times per week. Increase the dose up to the target maintenance dose over a 4 week period | 22 mcg to 44 mcg three times per week |
| **Tecfidera** | 120 mg twice a day for 7 days (requires 1 starter kit) | 240 mg twice daily following the starting dose |

| Class Ia antiarrhythmics | Class III antiarrhythmics |
|---|---|
| ▪ Norpace (disopyramide)<br>▪ Pronestyl (procainamide)<br>▪ quinidine | ▪ Cordarone, Pacerone (amiodarone)<br>▪ Betapace (sotalol)<br>▪ Tikosyn (dofetilide)<br>▪ Multaq (dronedarone)<br>▪ Corvert (ibutilide) |

| Agent | Contraindications |
|---|---|
| **Aubagio** (teriflunomide) | Severe hepatic impairment, pregnancy, hypersensitivity to teriflunomide, leflunomide, or any of the inactive ingredients in Aubagio, current leflunomide treatment |

| Agent | Contraindications |
|---|---|
| **Avonex** (interferon β-1a) | Patients with a history of hypersensitivity to natural or recombinant interferon beta, or any other component of the formulation, patients with a history of hypersensitivity to albumin (human) |
| **Betaseron** (interferon β-1b) | History of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol |
| **Copaxone** (glatiramer) | Known hypersensitivity to glatiramer acetate or mannitol |
| **Extavia** (interferon β-1b) | History of hypersensitivity to natural or recombinant interferon beta, Albumin (Human), USP, or any other component of the formulation. |
| **Gilenya** (fingolimod) | Recent (within the last 6 months) myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure, history of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker, Baseline QTc interval ≥500 msec, Treatment with Class Ia or Class III anti-arrhythmic drugs, Hypersensitivity to fingolimod or its excipients |
| **Glatopa** (glatiramer) | Known hypersensitivity to glatiramer acetate or mannitol |
| **Plegridy** (peginterferon β-1a) | History of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation |
| **Rebif** (interferon β-1a) | History of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation |
| **Tecfidera** (dimethyl fumarate) | None |
| **Zinbryta** (daclizumab) | Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN, History of autoimmune hepatitis or other autoimmune condition involving the liver, History of hypersensitivity to daclizumab or any other component of the formulation |

| Brand (generic) | Quantity Limit |
|---|---|
| **Aubagio® (teriflunomide)** | |
| 7 mg tablet | 1 tablet daily |
| 14 mg tablet | 1 tablet daily |
| **Avonex® (interferon β-1a)** | |
| 30 mcg vial | (1 kit of 4 vials/28 days) |
| 30 mcg/0.5 mL prefilled syringe | (1 kit of 4 syringes/28 days) |
| 30 mcg/0.5 mL Autoinjector pen | (1 kit of 4 syringes/28 days) |
| **Betaseron® (interferon β-1b)** | |
| 0.3 mg vial + syringe with diluent | 14 vial/syringe units (1 box)/28 days |
| **Copaxone® (glatiramer)** | |
| 20 mg/mL syringe | 1 syringe/day (30 syringes/30 days) |
| 40 mg/mL syringe | 12 mLs per 28 days (40 mg/mL 3 times a week) |
| **Extavia® (interferon β-1b)** | |
| 0.3 mg vial + syringe with diluent | 15 vial/syringe units (1 box)/30 days |
| **Gilenya™ (fingolimod)** | |
| 0.5 mg tablet | 1 tablet/day |
| **Glatopa™ (glatiramer)** | |
| 20 mg/mL prefilled syringe | 1 syringe/day (30 syringes/30 days) |

| Brand (generic) | Quantity Limit |
|---|---|
| **Plegridy™ (peginterferon β-1a)** | |
| Starter kit- syringe | 1 kit/180 days |
| Starter kit- pen-injector | 1 kit/180 days |
| 125 mcg/0.5 mL syringe | 2 syringes/28 days (1 carton of 2 syringes/28 days) |
| 125 mcg/0.5mL pen-injector | 2 pens/28 days (1 carton of 2 pens/28 days) |
| **Rebif® (interferon β-1a)** | |
| 22 mcg/0.5 mL | 3 syringes/week (1 carton 12 syringes/28 days) |
| Rebif Rebidose 22 mcg/0.5mL | 3 syringes/week (1 carton 12 syringes/28 days) |
| 44 mcg/0.5 mL | 3 syringes/week (1 carton 12 syringes/28 days) |
| Rebif Rebidose 44 mcg/0.5 mL | 3 syringes/week (1 carton 12 syringes/28 days) |
| Titration pack:<br>(6 x 8.8 mcg/0.2 mL + 6 x 22 mcg/0.5 mL) | 1 kit/180 days |
| Rebif Rebidose Titration Pac | 1 kit/180 days |
| **Tecfidera™ (dimethyl fumerate)** | |
| Starter kit | 1 kit / 180 days |
| 120 mg capsules | 14 capsules / 180 days |
| 240 mg capsules | 2 capsules daily |
| **Zinbryta™** (daclizumab) | |
| 150 mg/mL syringe | 1 syringe/30 days |

## RATIONALE

### Multiple Sclerosis

Multiple sclerosis (MS) is an immune mediated disease that affects the central nervous system (CNS). It is characterized by demyelization and inflammation of the CNS. Diagnosis of MS is primarily based on clinical presentation. The core requirement for the diagnosis is demonstration of CNS lesion dissemination and presence of symptoms such as visual loss, motor function loss, difficulty with balancing, and vertigo. There are currently four major types of MS: Relapsing MS (RRMS), Primary Progressive MS (PPMS), Secondary Progressive MS, and Progressive-Relapsing MS (PRMS). MS is primarily treated with corticosteroids and disease modifying agents (DMAs). Most of the currently FDA approved DMAs are indicated for treatment of RRMS.

The goal of treatment with DMAs is to reduce the number and severity of relapses, reduce the number of new lesions appearing on magnetic resonance imaging, and reduce long-term progression of MS.[8,9] There are several agents currently FDA approved for treatment of relapsing remitting MS (RRMS). These include Avonex and Rebif (both interferon beta-1a), Plegridy (peginterferon beta-1a), Betaseron and Extavia (both interferon beta-1b), Copaxone (glatiramer acetate), Lemtrada (alemtuzumab), Tysabri (natalizumab), mitoxantrone, Gilenya (fingolimod), Aubagio (teriflunomide), Tecfidera (dimethyl fumarate), and Zinbryta (daclizumab). Guidelines from the United States and Europe consider glatiramer and interferon beta (INFβ) as appropriate first line therapies for treatment of RRMS.[8,9,29] The INFβ agents are considered appropriate for patients at high risk of developing clinically definite MS, or those who already have RRMS or secondary progressive MS and are experiencing relapses. Currently there are three interferon beta-1a agents (Rebif, Avonex, and Plegridy). The three products differ in dose and frequency of dosing (three times a week, once weekly, and once every other week respectively). There is a probable dose or frequency of dosing response curve associated with use of INFβ agents. Interferon beta-1a has been associated with less neutralizing antibody formation than interferon

beta-1b (Betaseron, Extavia). The clinical effects of these neutralizing antibodies are uncertain. Their presence has been associated with a possible decrease in interferon efficacy. The route of administration of the INFβ agents does not have apparent effects on efficacy but side effect profiles differ between routes of administration. Because glatiramer works by a different mechanism than interferons, the side effect profile is different from interferons and may make this agent an option for some patients unable to tolerate interferons.[9] Glatiramer is considered an appropriate option for patients with RRMS or those experiencing a first clinical episode with MRI imaging consistent with MS. Natalizumab is recommended for patients with relapsing forms of MS who have had an inadequate response to, or are unable to tolerate other MS therapies.[8,9]

Concurrent use of more than one injectable DMA has been studied in clinical trials. The combinations of INFβ with natalizumab and glatiramer with natalizumab have been studied. Although a beneficial effect was seen (such as improved magnetic resonance imaging (MRI) parameters), there may be more adverse reactions associated with combination therapies. The study with a combination of INFβ and natalizumab was halted due to reported cases of progressive multifocal leukoencephalopathy (PML).[21] The adverse effects seen with combination therapies are similar to those reported with the individual agents, but it is unclear if the risk for developing these adverse effects is higher in combination therapy. Some of the clinical effects of glatiramer may occur by entry of regulatory glatiramer-reactive cells into the central nervous system (CNS) across a disrupted blood-brain-barrier (BBB) and effects on CNS resident cells. It is possible that combining glatiramer with therapies that close the BBB like INFβ and natalizumab may limit the effectiveness of glatiramer.[21] The benefits of combination therapies and the safety concerns associated with concurrent therapy still need further investigation.

A National MS Society consensus statement recommends changing from one disease modifying therapy to another only for medically appropriate reasons (e.g., lack of efficacy, adverse effects, or if better treatments options become available).[8] This consensus statement was written prior to the approval of the oral MS therapies.

Teriflunomide is a pyrimidine synthesis inhibitor. The exact mechanism for its therapeutic effect in MS is unknown but thought to reduce the number of activated lymphocytes in the CNS. Clinical trial results showed a significant reduction in annualized relapse rates at both doses of teriflunomide compared to placebo. There was not an active comparator in the study but reductions in annual relapse rates were similar (30% to 50%) to the injectable disease modifying agents. Teriflunomide is contraindicated in severe hepatic impairment and pregnancy. There is a boxed warning for hepatoxicity and teratogenicity. The most common adverse events include increased ALT, alopecia, diarrhea, influenza, nausea and paresthesia.[23]

The therapeutic effects of dimethyl fumarate in MS is unknown but its metabolite has been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway which is involved in the cellular response to oxidative stress. Clinical trial results for Study 1 which was a placebo controlled study, showed a significant reduction in the proportion of relapsing remitting patients with relapses at 2 years. The proportion of patients relapsing were 27% (n=410) versus 46% (n=408) [p=<0.0001] for the dimethyl fumarate and placebo groups respectively, with a relative risk reduction of 49%. The annualized relapse rate was 0.172 for the treated group and 0.364 for placebo [p<0.0001] with a relative risk reduction of 53%. Study 2 was also a placebo controlled study that included an open label active comparator with a primary endpoint of annualized relapse rate at 2 years. The results of this trial showed a statistically significant

reduction in annualized relapse rates compared to placebo. The annualized relapse rate for dimethyl fumarate was 0.224 (n=359) and 0.401 (n=363) for placebo [p=<0.0001], with a relative risk reduction of 44%. The proportion of patients relapsing was similar to those in Study 1.[25]

The most common adverse events (≥10% and ≥2% placebo) include flushing, abdominal pain, diarrhea, and nausea.

| **REVISIONS** | |
|---|---|
| 03-13-2012 | Policy added to the bcbsks.com web site. Policy was effective January 1, 2012. |
| 11-01-2012 | Revised Title From: "Multiple Sclerosis Interferon Agents Step Therapy Program Summary" To: "Multiple Sclerosis Agents Prior Authorization (Through Preferred) Program Summary" |
| | Description section updated |
| | In Policy section:<br>▪ Expanded to the current policy language from:<br>"Non-preferred Multiple Sclerosis Agents will be approved when BOTH of the following are met:<br>1. ONE of the following:<br>a. The patient is not currently being treated with a disease modifying agent (DMA) (see description) for multiple sclerosis (MS) OR<br>b. The patient is currently being treated with a DMA for MS AND the DMA will be discontinued before starting the requested agent AND<br>2. ONE of the following:<br>a. The patient's medication history indicates use of a preferred multiple sclerosis agent OR<br>b. There is documentation that the patient is currently using the requested nonpreferred multiple sclerosis agent OR<br>c. The prescribing physician states the patient is using the requested nonpreferred multiple sclerosis agent AND is at risk if therapy is changed OR<br>d. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a preferred multiple sclerosis agent<br>Length of approval: 12 months" |
| | Rationale section added |
| | References updated |
| 07-08-2013 | Revised title from "Multiple Sclerosis Agents Prior Authorization (Through referred) Program Summary" to "Multiple Sclerosis Agents (also addresses Tysabri's use in Crohn's disease)" |
| | In Description section:<br>▪ Description updated<br>▪ Updated the Disease Modifying Agents (DMA) chart to remove the reference to "Target Drugs" in the title and added the drugs Aubagio® (teriflunomide) and Tecfidera (dimethyl fumarate).<br>▪ Updated the FDA Approved Indication and Dosage chart including adding the drugs Aubagio® (teriflunomide) and Tecfidera (dimethyl fumarate) to the chart. |
| | In Policy section:<br>▪ Added "Through Preferred Agents" to the header.<br>▪ Under the Initial Evaluation portion, added "ALL of" to read "The requested agent will be approved when ALL of the following are met:"<br>▪ Revised 1 a and 1 b to the current language from,<br>"The requested agent will be approved when the following are met: |

| **REVISIONS** | |
|---|---|
| | 1. ONE of the following:<br>a. The patient is not currently being treated with a n additional disease modifying agent (DMA) for (MS) OR<br>b. The patient is currently being treated with a n additional DMA for MS AND the DMA will be discontinued before starting the requested agent."<br>▪ Added 2 c 2) "The patient does not have any contraindications to therapy with the requested agent AND"<br>▪ Revised 2 c 3) and 2 c 3) a) to the current language from,<br>3) The requested agent is a nonpreferred agent AND ONE of the following:<br>a) The patient's medication history indicates use of a preferred agent for MS OR<br>▪ In 2 c 4) relocated the following contraindications for Gilenyto a chart titled FDA Labeled Contraindications,<br>d) Prolonged QT interval ≥ 500 ms<br>i) Use of antineoplastic, immunosuppressive,<br>Class Ia (e.g. disopyramide, procainamide, quinidine) or Class III (e.g. amiodarone, dronedarone, sotalol, dofetilide, ibutilide) antiarrhythmics or immune modulating therapies<br>j) Mobitz Type II second or third-degree AV block without a functioning pacemaker<br>k) ANY of the following in the last 6 months:<br>i. Myocardial infarction<br>ii. Unstable angina<br>iii. Stroke<br>iv. TIA<br>v. Decompensated heart failure requiring hospitalization<br>▪ Added indications 5 a and 5 b,<br>"AND 5) If Tysabri, the request will be approved for moderate to severe Crohn's Disease (CD) when ONE of the following additional criteria is met:<br>a The patient's medication history includes use of a conventional CD therapy (aminosalicylates, metronidazole, ciprofloxacin, corticosteroids, methotrexate, or immunomodulators such as azathioprine or 6-mercaptopurine) OR<br>b the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity, to conventional CD therapy"<br>▪ Under the Renewal Evaluation added "ALL of" to read, "The requested agent will be renewed when ALL of the following are met:"<br>▪ In item 2 added "for the intended FDA labeled indication" to read, "The patient is NOT currently being treated with an additional disease modifying agent (DMA) for the intended FDA labeled indication."<br>▪ Added the following four charts: "FDA Labeled Contraindications", "Class Ia and Class II antiarrhythmics", Contraindicated as Concomitant Therapy", and "Quantity Limits" |
| | Rationale section updated |
| | Added Coding section<br>▪ Added HCPCS codes: J1595, J1826, J1830, J2323<br>▪ Added the statement: "There are no specific J codes for the remaining drugs listed in this policy." |
| | References updated |
| 01-01-2014 | In Title section:<br>▪ Revised Title from: "Multiple Sclerosis Agents (also addresses Tysabri's use in Crohn's disease)", to: "Multiple Sclerosis Agents".<br>▪ Added the See also policy of "Tysabri (natalizumab)" |
| | In Description section:<br>▪ Description section updated<br>▪ Updated Disease Modifying Agents (DMA) chart changing Tecfidera (dimethyl |

| **REVISIONS** | |
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| | fumarate) from a non-preferred to a preferred agent.<br>▪ Removed Tysabri (natalizumab) from the chart as it is now addressed in a stand-alone policy. |
| | In Policy section:<br>▪ In Item 2 a added look-back information<br>In Initial Evaluation<br>▪ In 1 a removed "for the requested indication (MS or CD)" to read, "The patient is not currently being treated with a disease modifying agent (DMA)"<br>▪ In 1 b removed "for the requested indication" to read, "The patient is currently being treated with a DMA AND the DMA will be discontinued before starting the requested agent.<br>▪ In 2 c 2) added "FDA labeled" to read, "The patient does not have any FDA labeled contraindications to therapy with the requested agent"<br>▪ In 2 c 3) a) added "2" and removed "the requested FDA labeled indication (CD) to read, "The patient's medication history indicates use of 2 preferred agents for MS"<br>▪ In 2 c 3) b) added "at least 2" to read, "The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least 2 preferred agents (i.e. Betaseron, Copaxone, Rebif, or Tecfidera)"<br>▪ Removed item 2 c 3) c) "If Gilenya, the patient's medication history indicates the use of Tysabri"<br>▪ In 2 c 4) added "performed an electrocardiogram within the past 6 months and has" to read, "The prescribing physician has performed an electrocardiogram within the past 6 months and has confirmed that the patient does not have ANY of the following prior to initiating treatment:"<br>▪ Removed indications for Tysabri in 2 c:<br>"5) If Tysabri, the request will be approved for moderate to severe Crohn's Disease (CD) when ONE of the following additional criteria is met:<br>a) The patient's medication history includes use of a conventional CD therapy (aminosalicylates, metronidazole, ciprofloxacin, corticosteroids, methotrexate, or immunomodulators such as azathioprine or 6-mercaptopurine) OR<br>b) the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity, to conventional CD therapy"<br>In Renewal Evaluation<br>▪ In 2 removed "for the intended FDA labeled indication" to read, "The patient is NOT currently being treated with an additional disease modifying agent (DMA)"<br>▪ Added item 3 "The patient does not have any FDA labeled contraindications to therapy with the requested agent. AND"<br>▪ Updated the FDA Labeled Contraindications chart by removing Tysabri<br>▪ Removed the Contraindicated as Concomitant Therapy chart for Tysabri<br>▪ Updated the Quantity Limits chart |
| | Rationale section updated |
| | In Coding section:<br>▪ Removed HCPCS code: J2323 |
| | References updated |
| 04-01-2014 | Policy posted July 15, 2014. |
| | Administrative Update |
| | In Description section:<br>▪ Updated the FDA Approved Indications and Dosage to include an updated dosage for Copaxone (glatiramer acetate) of 40 mg three times weekly. |
| | In the Policy section:<br>▪ Removed the Contraindicated as Concomitant Therapy chart.<br>▪ In the Quantity Limits chart replaced "Target Drugs" with "Disease Modifying Agents |

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| | (DMA)"<br>▪ Updated the Quantity Limits chart for Copaxone from 1 carton of 30-20 mg/mL syringes/30 days to 12-40 mg/mL syringes/28 days |
| | References updated |
| 10-28-2014 | In Policy section - Initial Evaluation<br>▪ In Item 2 b and 2 c 4) replaced "prescribing physician" with "prescriber"<br>▪ In Item s c 3) b) added "(defined as an intolerance to the drug or its excipients, not to the route of administration)" to read, "The patient has a documented intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to at least 2 preferred agents (i.e. Betaseron, Copaxone, Rebif, or Tecfidera)"<br>▪ In Quantity Limits chart clarified Copaxone quantity limits from "12 syringes/28 days" to "12 mLs per 28 days (40 mg/mL 3 times a week)" |
| | Description, Rationale and Reference sections reviewed with no updates. |
| 01-01-2015 | Description section updated adding Plegridy (peginterferon-1a) to the Preferred Agents and updating the FDA Approved Indications and Dosage chart. |
| | In Policy section:<br>▪ In Initial Evaluation Item 1 revised from "The requested agent will be approved when ALL of the following are met:<br>1. ONE of the following:<br>a. The patient is not currently being treated with a disease modifying agent (DMA) OR<br>b. The patient is currently being treated with a DMA AND the DMA will be discontinued before starting the requested agent. AND" to<br>"The requested agent will be approved when ALL of the following are met:<br>1. The patient will not be taking an additional disease modifying agent (DMA) at the same time as the requested agent"<br>▪ In Item 2 c 3) a) removed "2" and added "1" to read, "The patient's medication history indicates use of 1 preferred agent for MS"<br>▪ In Item 2 c 3) b) removed "at least 2" and added "ALL" and "Plegridy" to read, "The patient has a documented intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to ALL preferred agents (i.e. Betaseron, Copaxone, Plegridy, Rebif, or Tecfidera)"<br>▪ In Item 2 c 4) added the following conditions:<br>"d) Prolonged QT interval of ≥ 500 msec<br>i) Use of antineoplastic, immunosuppressive or immune modulation therapies in the past 120 days<br>j) A history of second degree or greater heart block without a functioning pacemaker<br>k) Currently using a Class Ia or Class III antiarrhythmic<br>l) In the last 6 months has had: Myocardial infarction, Unstable angina, Stroke, Transient ischemic attack, Decompensated heart failure requiring hospitalization"<br>▪ In Item 3 revised from "a. The prescribed dosage is within the program limit (FDA approved labeled dosage) OR<br>b. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis" to<br>"a. The requested quantity (dose) is NOT greater than the program quantity limit OR<br>b. ALL of the following<br>1) The requested quantity (dose) is greater than the program quantity limit AND<br>2) The requested quantity (dose) is less than or equal to the FDA labeled dose AND<br>3) The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit OR |

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| | c. ALL of the following:<br>1) The requested quantity (dose) is greater than the program quantity limit AND<br>2) The requested quantity (dose) is greater than the FDA labeled dose AND<br>3) The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis."<br>▪ In Renewal Evaluation Item 4 revised from "a. The prescribed dosage is within the program limit (FDA approved labeled dosage) OR<br>b. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis" to<br>"a. The requested quantity (dose) is NOT greater than the program quantity limit OR<br>b. ALL of the following<br>1) The requested quantity (dose) is greater than the program quantity limit AND<br>2) The requested quantity (dose) is less than or equal to the FDA labeled dose AND<br>3) The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit OR<br>c. ALL of the following:<br>1) The requested quantity (dose) is greater than the program quantity limit AND<br>2) The requested quantity (dose) is greater than the FDA labeled dose AND<br>3) The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis."<br>▪ Updated FDA Labeled Contraindications chart and added Plegridy to Quantity Limits chart |
| | Rationale section updated |
| | Removed Coding section and applicable codes. |
| | References updated |
| 06-01-2015 | Policy published 04-28-2015. |
| | Description section updated to include update of the FDA Approved Indications and Dosage chart to include adding Lemtrada (alemtuzumab). |
| | In Policy section:<br>▪ In Header added "and Quantity Limit" to read "Prior Authorization and Quantity Limit Criteria for Approval"<br>▪ In Initial Evaluation Item 1 removed, "The patient will not be taking an additional disease modifying agent (DMA) at the same time as the requested agent AND" and replaced with, "1. ONE of the following:<br>a. The patient is not currently being treated with a disease modifying agent (DMA) other than the requested agent OR<br>b. The patient is currently being treated with another DMA other than the requested agent AND this DMA will be discontinued before starting the requested agent AND"<br>▪ In Initial Evaluation Item 2 b revised "preferred" to "target" to read, "...using the target agent..."<br>▪ In Initial Evaluation Item 2 c removed "The patient does not have any FDA labeled contraindications to therapy with the requested agent AND"<br>▪ In Item 2 c 3) removed "request will be approved when the following additional criteria are met:", "has confirmed that the patient does NOT have ANY of the following", and the following conditions "a) Bradycardia (sitting heart rate <55 bpm), b) Congestive heart failure, c) Sick sinus syndrome, d) Prolonged QT interval of ≥ 500 msec, e) Ischemic cardiac disease, f) Irregular heart beat, g) Current neutropenia, h) Current chronic or acute infection(s), i) Use of antineoplastic, immunosuppressive or immune modulation therapies in the past 120 days, j) A history of second degree or greater heart block without a functioning pacemaker, k) Currently using a Class Ia or Class III antiarrhythmic, l) In the last 6 months has had: Myocardial infarction, Unstable angina, Stroke, Transient |

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| | ischemic attack, Decompensated heart failure requiring hospitalization" and "has confirmed that the patient does NOT have ANY of the following:" to read, If Gilenya, the prescriber has performed an electrocardiogram within 6 months prior to initiating treatment."<br>▪ Added Item 3 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent….AND"<br>▪ Updated FDA Labeled Contraindications and Quantity Limits for Disease Modifying Agents (DMA) charts. |
| | Rationale section updated |
| | References updated |
| 06-26-2015 | Policy published 11-10-2015. Administrative Update retro-effective to 06-26-2015. |
| | In Description section:<br>▪ Updated Description section to include adding Glatopa TM (glatiramer) as a Preferred Agent and to the FDA Approved Indications and Dosage chart. |
| | In Policy section:<br>▪ In Initial Evaluation Item 2 c 2) b) added "Glatopa" to read "…FDA labeled contraindication, or hypersensitivity to ALL preferred agents (i.e. Betaseron, Copaxone, Glatopa, Plegridy, Rebif, or Tecfidera)".<br>▪ Updated FDA Labeled Contraindications and Quantity Limits charts adding Glatopa (glatiramer). |
| | References updated. |
| 04-15-2016 | Description section updated. FDA Approved Indications and Dosage chart updated to include removing Lemtrada (alemtuzumab) and Tysabri (natalizumab). |
| | In Policy section:<br>▪ Updated Contraindications chart for Gilenya (glatiramer)<br>▪ Updated Quantity Limit chart for Avonex (interferon β-1a) and Rebif (interferon β-1a) |
| | Rationale section updated |
| | References updated |
| 04-15-2016 | Published 05-11-2016. Retro-effective to 04-15-2016. |
| | ▪ In Quantity Limits chart corrected spelling on "Rebif Rebido" to "Rebif Rebidose". |
| 10-01-2016 | Description section updated. FDA Approved Indications and Dosage chart updated to add Zinbryta (daclizumab). |
| | In Policy section:<br>▪ Updated Contraindications chart and Quantity Limit chart to add Zinbryta (daclizumab). |
| | Rationale section updated |
| | References updated |
| 01-01-2017 | In Description section:<br>Changed the status of Aubagio, Avonex, and Gilenya from non-preferred to preferred agents<br>Updated the FDA Approved Indications and Dosage chart for Plegridy |
| | Summary of Policy section updates:<br>✓Updated the criteria to require trial of at least two preferred disease modifying agents before approval of a non-preferred agent. The previous version of this criteria required trial of one preferred agent.<br>✓Added a requirement to the renewal criteria that the patient has had clinical benefit from the requested agent.<br>▪ Added language to allow the reviewer to approve the starter dose as well as maintenance dose for those agents that require a starter dose (i.e. Plegridy, Rebif, Tecfidera)<br>▪ These updates resulted in the following policy language changes:<br>Initial Evaluation |

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| | ▪ In Item 2 c 2) a) removed "one" and added "TWO" to read "The patient's medication history indicates use of TWO preferred disease modifying agents for MS"<br>▪ In Item 2 c 2) b) added "Aubagio, Avonex, Gilenya" to read "The patient has a documented intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to ALL preferred disease modifying agents (i.e. Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)"<br>▪ In Length of Approval added "NOTE: For agents requiring a starter dose for initial use, the starter dose will approved per the dose table and the maintenance dose will be approved for the remainder of 12 months."<br>Renewal Evaluation<br>▪ Added Item 3 "The patient has had clinical benefit from treatment with the requested agent"<br>▪ Added chart titled "Dosing table for agents requiring a starter dose"<br>Updated Contraindications and Quantity Limit charts |
| | References updated |
| 04-01-2017 | In Description section:<br>▪ Updated the FDA Approved Indications and Dosage chart |
| | In Policy section:<br>▪ In Item a c 2) a) added to "(i.e. Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)" read "The patient's medication history indicates use of TWO preferred disease modifying agents for MS (i.e. Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)" |
| | Rationale section updated |
| | References updated |

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