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), and Ocrevus® (ocrelizumab) (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):
  https://www.bcbsks.com/drugs/

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; November 1, 2017; April 1, 2018; June 25, 2018
Current Effective Date: June 25, 2018

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; November 1, 2017; April 1, 2018; June 25, 2018
Current Effective Date: June 25, 2018

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.

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

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 and also the Multiple Sclerosis Agents Quantity Limit (QL) 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 Agents

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) [a]	
Gilenya® (fingolimod)	
Glatopa ® (glatiramer) [a]	
Plegridy™ (peginterferon β-1a)	
Rebif® (interferon β-1a)	
Tecfidera® (dimethyl fumarate)	

[a] generic available

FDA Approved Indications and Dosage[1-11]

Agent	Indication	Dosage and Administration
Aubagio (teriflunomide) tablet	▪ Relapsing forms of MS	7 mg or 14 mg orally once daily
Avonex (interferon β-1a) intramuscular injection	▪ Relapsing forms of MS [a]	30 mcg intramuscularly once weekly
Betaseron, Extavia (interferon β-1b) subcutaneous injection	▪ Relapsing forms of MS [a]	0.25 mg subcutaneously every other day
Copaxone [c] (glatiramer acetate) subcutaneous injection	▪ Relapsing forms of MS	20 mg subcutaneously daily or 40 mg subcutaneously three times per week at least 48 hours apart (doses are not interchangeable)
Gilenya (fingolimod) Tablet	▪ Relapsing forms of MS	0.5 mg orally once daily

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

Agent	Indication	Dosage and Administration
Glatopa (glatiramer acetate) subcutaneous injection	▪ Relapsing forms of MS	20 mg injected subcutaneously once daily (Glatopa 20mg/mL dose is not interchangeable with glatiramer acetate 40mg/mL dose)
Plegridy (peginterferon β-1a) subcutaneous injection	▪ Relapsing forms of MS	125 mcg subcutaneously every 14 days.
Rebif (interferon β-1a) subcutaneous injection	▪ Relapsing forms of MS	22 mcg or 44 mcg injected subcutaneously three times per week.
Tecfidera (dimethyl fumarate) capsule	▪ Relapsing forms of MS	Starting dose: 120 mg orally twice daily for 7 days Maintenance dose: 240 mg twice daily
Zinbryta (daclizumab) subcutaneous injection	▪ Relapsing forms of MS[b]	150 mg subcutaneously once monthly

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
c-Generic available

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 an additional disease modifying agent (DMA) for the requested indication
      OR
   b. The patient is currently being treated with an additional DMA for the requested agent AND the 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 within 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:

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

a) The patient's medication history includes the 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 prescriber is a neurologist or the prescriber has consulted with a neurologist
AND
4. The patient does NOT have any FDA labeled contraindication(s) to 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
NOTE: For agents requiring a starter dose for initial use, the starter dose will be approved per the dose table and the maintenance dose will be approved for the remainder of 12 months.

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

Renewal Evaluation

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

1. The patient has been previously approved for the requested agent through the Prime Therapeutics PA process
   AND
2. The patient has an FDA labeled indication for the requested agent
   AND
3. The patient is NOT currently being treated with an additional disease modifying agent (DMA) for the requested indication
   AND
4. The patient has had clinical benefit from treatment with the requested agent
   AND
5. The prescriber is a neurologist or the prescriber has consulted with a neurologist
   AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
7. 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

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

Dosing table for agents requiring a starter dose

<table>
<tr><th>Agent</th><th>Starting Dose</th><th>Maintenance dose</th></tr>
<tr><td>Avonex</td><td>Initial 7.5 mcg, then dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved</td><td>30 mcg intramuscularly once a week</td></tr>
<tr><td>Betaseron/ Extavia</td><td>Starting dose is 0.0625 mg (0.25 mL) subcutaneously every other day with dose increase over a 6-week period to the recommended dose of 0.25 mg (1 mL) every other day.
Week 1-2: 0.625 mg
Week 3-4: 0.125 mg
Week 5-6: 0.1875 mg
Week 7 and thereafter: 0.25 mg</td><td>0.25 mg subcutaneously every other day</td></tr>
<tr><td>Plegridy</td><td>Start 63 mcg on day 1, 94 mcg on day 15, and 125 mcg on day 29. (Requires 1 starter pen or syringe)</td><td>125 mcg every 14 days following the starting dose</td></tr>
<tr><td>Rebif</td><td>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. 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><td>22 mcg to 44 mcg three times per week</td></tr>
<tr><td>Tecfidera</td><td>Starting dose is 120 mg twice a day orally for 7 days (requires 1 starter kit). After 7 days, the dose should be increased to maintenance dose.</td><td>240 mg orally twice daily</td></tr>
</table>

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

Agent	Contraindication
Aubagio (teriflunomide)	• Severe hepatic impairment • Pregnancy • Hypersensitivity reaction to teriflunomide, leflunomide, or any of the inactive ingredients in Aubagio • Current leflunomide treatment
Avonex (interferon β-1a)	• History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation
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

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

Agent	Contraindication
Gilenya (fingolimod)	• Recent (within the last 6 months) myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with 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)	• Known hyper sensitivity to dimethyl fumerate or any of the excipients of Tecfidera
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

Examples of Agents Contraindicated as Concomitant Therapy	
Aubagio (teriflunomide)	Lemtrada (alemtuzumab)
Avonex (interferon β-1a)	Ocrevus (ocrelizumab)
Betaseron (interferon β-1b)	Plegridy (peginterferon β-1a)
Copaxone (glatiramer)	Rebif (interferon β-1a)
Extavia (interferon β-1b)	Tecfidera (dimethyl fumarate)
Gilenya (fingolimod)	Tysabri (natalizumab)
Glatopa (glatiramer)	Zinbryta (daclizumab)

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)[a]	
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)

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

Brand (generic)	Quantity Limit
Extavia (interferon β-1b)	
0.3 mg vial + syringe with diluent	15 vial/syringe units (1 box)/30 days
Gilenya (fingolimod)	
0.25 mg tablet	1 tablet/day
0.5 mg tablet	1 tablet/day
Glatopa (glatiramer) [a]	
20 mg/mL prefilled syringe	1 syringe/day (30 syringes/30 days)
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: (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

a – generic available

RATIONALE

Multiple Sclerosis

Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelization, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, visual disturbances, and elimination dysfunction), resulting in a significant impact on quality of life for patients and their families. 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: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).[12] RRMS is characterized by clearly defined relapses with either full recover or with sequelae and residual deficit upon

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

recovery. There is no or minimal disease progression during the periods between disease relapses, though individual relapses may result in severe residual disability.[13] Majority, about 85-90%, of individuals with MS demonstrate a relapsing pattern at onset, which transitions over time in the majority of untreated patients to a pattern of progressive worsening with few or no relapses or MRI activity (SPMS). SPMS begins as RRMS, but over time the disease enters a stage of steady deterioration in function, unrelated to acute attacks. Typically, when SSMS stage is reached, the relapse rate is also reduced. SPMS develops in approximately 90% of patients with RRMS after 25 years and causes the greatest amount of neurologic disability. PPMS represents only about 10 percent of MS cases and is characterized by disease progression from onset, although occasional plateaus, temporary minor improvements, and acute relapses may occur.[13]

Treatment directed at PPMS is typically more difficult than treatment of RRMS and recommendations differ between the different forms of MS. There are a number of effective disease modifying agents (DMAs) available for RRMS and only one DMA for PPMS.[13] Prior to disease modifying treatments, approximately half of patients diagnosed with relapsing MS would progress to secondary progressive MS by 10 years, and 80-90% would do so by 25 years. Approximately half of patients would no longer be able to walk unaided by 15 years.[12] Most of the treatment options for progressive types of MS involve various immunosuppressive therapies, such as azathioprine, cladribine, glucocorticosteroids, cyclophosphamide, cyclosporine, immune globulins, methotrexate, and DMAs. However, nonspecific immunosuppressants may temporarily halt a rapidly progressive course but it is difficult to employ them for more than a few months to a year or two.[13]

The goal of treatment with DMAs is to reduce early clinical and sub-clinical disease activity that is thought to contribute to long-term disability. Given the medications that are currently available – all of which primarily target inflammation – the optimal window for impacting long-term disability is during the early relapsing phase of the disease, with the goal being to slow the accumulation of lesion volume, decrease the number of relapses and prevent disability from both unresolved relapses and disease progression. Currently available therapies reduce relapse rates and MRI lesion accumulation in RRMS, in varying extents. There are few comparison trials, so information for comparative efficacy is inferential.[12-14] Guidelines recommend initiation of treatment with DMA as soon as possible following diagnosis of RRMS or PPMS.[12-15] Suggested initial treatment approach includes the following:

- Infusion therapy with natalizumab for patients with more active disease and for those who value effectiveness above safety and convenience. A cross-trial comparison and clinical experience showed natalizumab is more effective than interferons, glatiramer, or oral DMAs for patients with RRMS.
- Injection therapy (interferon or glatiramer) for patients who value safety more than effectiveness and convenience. Among these, intramuscular interferon beta-1a 30 mcg weekly or glatiramer acetate is preferred.
- Oral therapy (dimethyl fumerate, teriflunomide, or fingolimod) for patients who value convenience. Dimethyl fumerate is preferred due to being more effective and a better safety profile than the other two agents, although evidence is indirect and inconclusive. The potential teratogenicity of teriflunomide limits its use for a disease where a portion of patients are child-bearing age.[15]

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.[15]

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).[12]

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: ▪ Expanded to the current policy language from: "Non-preferred Multiple Sclerosis Agents will be approved when BOTH of the following are met: 1. ONE of the following: a. The patient is not currently being treated with a disease modifying agent (DMA) (see description) for multiple sclerosis (MS) OR b. The patient is currently being treated with a DMA for MS AND the DMA will be discontinued before starting the requested agent AND 2. ONE of the following: a. The patient's medication history indicates use of a preferred multiple sclerosis agent OR b. There is documentation that the patient is currently using the requested nonpreferred multiple sclerosis agent OR c. The prescribing physician states the patient is using the requested nonpreferred multiple sclerosis agent AND is at risk if therapy is changed OR d. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a preferred multiple sclerosis agent

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

REVISIONS	
	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: ▪ Description updated ▪ 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). ▪ Updated the FDA Approved Indication and Dosage chart including adding the drugs Aubagio® (teriflunomide) and Tecfidera (dimethyl fumarate) to the chart.
	In Policy section: ▪ Added "Through Preferred Agents" to the header. ▪ Under the Initial Evaluation portion, added "ALL of" to read "The requested agent will be approved when ALL of the following are met:" ▪ Revised 1 a and 1 b to the current language from, "The requested agent will be approved when the following are met: 1. ONE of the following: a. The patient is not currently being treated with a n additional disease modifying agent (DMA) for (MS) OR 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." ▪ Added 2 c 2) "The patient does not have any contraindications to therapy with the requested agent AND" ▪ Revised 2 c 3) and 2 c 3) a) to the current language from, 3) The requested agent is a nonpreferred agent AND ONE of the following: a) The patient's medication history indicates use of a preferred agent for MS OR ▪ In 2 c 4) relocated the following contraindications for Gilenyto a chart titled FDA Labeled Contraindications, d) Prolonged QT interval ≥ 500 ms i) Use of antineoplastic, immunosuppressive, Class Ia (e.g. disopyramide, procainamide, quinidine) or Class III (e.g. amiodarone, dronedarone, sotalol, dofetilide, ibutilide) antiarrhythmics or immune modulating therapies j) Mobitz Type II second or third-degree AV block without a functioning pacemaker k) ANY of the following in the last 6 months: i. Myocardial infarction ii. Unstable angina iii. Stroke iv. TIA v. Decompensated heart failure requiring hospitalization ▪ Added indications 5 a and 5 b, "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: 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 b the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity, to conventional CD therapy"

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

REVISIONS	
	▪ Under the Renewal Evaluation added "ALL of" to read, "The requested agent will be renewed when ALL of the following are met:" ▪ 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." ▪ 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 ▪ Added HCPCS codes: J1595, J1826, J1830, J2323 ▪ 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: ▪ Revised Title from: "Multiple Sclerosis Agents (also addresses Tysabri's use in Crohn's disease)", to: "Multiple Sclerosis Agents". ▪ Added the See also policy of "Tysabri (natalizumab)"
	In Description section: ▪ Description section updated ▪ Updated Disease Modifying Agents (DMA) chart changing Tecfidera (dimethyl fumarate) from a non-preferred to a preferred agent. ▪ Removed Tysabri (natalizumab) from the chart as it is now addressed in a stand-alone policy.
	In Policy section: ▪ In Item 2 a added look-back information In Initial Evaluation ▪ 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)" ▪ 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. ▪ In 2 c 2) added "FDA labeled" to read, "The patient does not have any FDA labeled contraindications to therapy with the requested agent" ▪ 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" ▪ 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)" ▪ Removed item 2 c 3) c) "If Gilenya, the patient's medication history indicates the use of Tysabri" ▪ 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:" ▪ Removed indications for Tysabri in 2 c: "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: 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 b) the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity, to conventional CD therapy"

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

REVISIONS	
	In Renewal Evaluation ▪ 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)" ▪ Added item 3 "The patient does not have any FDA labeled contraindications to therapy with the requested agent. AND" ▪ Updated the FDA Labeled Contraindications chart by removing Tysabri ▪ Removed the Contraindicated as Concomitant Therapy chart for Tysabri ▪ Updated the Quantity Limits chart
	Rationale section updated
	In Coding section: ▪ Removed HCPCS code: J2323
	References updated
04-01-2014	Policy posted July 15, 2014.
	Administrative Update
	In Description section: ▪ 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: ▪ Removed the Contraindicated as Concomitant Therapy chart. ▪ In the Quantity Limits chart replaced "Target Drugs" with "Disease Modifying Agents (DMA)" ▪ 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 ▪ In Item 2 b and 2 c 4) replaced "prescribing physician" with "prescriber" ▪ 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)" ▪ 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: ▪ In Initial Evaluation Item 1 revised from "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) OR b. The patient is currently being treated with a DMA AND the DMA will be discontinued before starting the requested agent. AND" to "The requested agent will be approved when ALL of the following are met: 1. The patient will not be taking an additional disease modifying agent (DMA) at the same time as the requested agent" ▪ 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" ▪ 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

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

REVISIONS	
	hypersensitivity to ALL preferred agents (i.e. Betaseron, Copaxone, Plegridy, Rebif, or Tecfidera)" ▪ In Item 2 c 4) added the following conditions: "d) Prolonged QT interval of ≥ 500 msec 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 ischemic attack, Decompensated heart failure requiring hospitalization" ▪ In Item 3 revised from "a. The prescribed dosage is within the program limit (FDA approved labeled dosage) OR 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 "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." ▪ In Renewal Evaluation Item 4 revised from "a. The prescribed dosage is within the program limit (FDA approved labeled dosage) OR 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 "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." ▪ 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:

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

REVISIONS	
	▪ In Header added "and Quantity Limit" to read "Prior Authorization and Quantity Limit Criteria for Approval" ▪ 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: 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" ▪ In Initial Evaluation Item 2 b revised "preferred" to "target" to read, "…using the target agent…" ▪ In Initial Evaluation Item 2 c removed "The patient does not have any FDA labeled contraindications to therapy with the requested agent AND" ▪ 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 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." ▪ Added Item 3 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent….AND" ▪ 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: ▪ 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: ▪ 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)". ▪ 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: ▪ Updated Contraindications chart for Gilenya (glatiramer) ▪ 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.

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

REVISIONS	
	▪ 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: ▪ Updated Contraindications chart and Quantity Limit chart to add Zinbryta (daclizumab).
	Rationale section updated
	References updated
01-01-2017	In Description section: Changed the status of Aubagio, Avonex, and Gilenya from non-preferred to preferred agents Updated the FDA Approved Indications and Dosage chart for Plegridy
	Summary of Policy section updates: ✓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. ✓Added a requirement to the renewal criteria that the patient has had clinical benefit from the requested agent. ▪ 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) ▪ These updates resulted in the following policy language changes: Initial Evaluation ▪ 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" ▪ 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)" ▪ 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." Renewal Evaluation ▪ Added Item 3 "The patient has had clinical benefit from treatment with the requested agent" ▪ Added chart titled "Dosing table for agents requiring a starter dose" Updated Contraindications and Quantity Limit charts
	References updated
04-01-2017	In Description section: ▪ Updated the FDA Approved Indications and Dosage chart
	In Policy section: ▪ 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
11-01-2017	Policy published 11-21-2017. Policy retro-effective to 11-01-2017.
	In Description section: ▪ To Target Drugs added "*" to Copaxone and in the key added "available" and removed "for Copaxone 20 mg/mL injection" to read "Generic available".

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

REVISIONS	
04-01-2018	In Description section ▪ Updated Target Agents chart and FDA Approved Indications and Dosage chart
	In Policy section: Initial Evaluation ▪ In Items 1 a, 1 b added "additional" to read "a. The patient is NOT currently being treated with an additional disease modifying agent (DMA) for the requested indication OR b. The patient is currently being treated with an additional DMA for the requested agent AND the DMA will be discontinued before starting the requested agent" ▪ In Item 2 c 2) a) removed "indicates" and added "includes the" to read "The patient's medication history includes the use of TWO preferred disease modifying agents for MS..." ▪ Added "3. The prescriber is a neurologist or the prescriber has consulted with a neurologist" Renewal Evaluation ▪ Added "2. The patient has an FDA labeled indication for the requested agent" ▪ In Item 3 added "for the requested indication" to read "3. The patient is NOT currently being treated with an additional disease modifying agent (DMA) for the requested indication" ▪ Added "5. The prescriber is a neurologist or the prescriber has consulted with a neurologist" ▪ Updated Dosing table for agents requiring a starter dose, Contraindications chart, and Quantity Limit chart, and added "Examples of Agents Contraindicated as Concomitant Therapy chart
	Rationale section updated
	References updated
06-25-2018	Policy published 07-18-2018. Policy retro-effective to 06-25-2018.
	In Policy section: ▪ Updated Quantity Limit Chart adding Gilenya 0.25mg

REFERENCES

1. Avonex prescribing information. Biogen, Inc. March 2016.
2. Betaseron prescribing information. Bayer HealthCare Pharmaceuticals, Inc. April 2016.
3. Copaxone prescribing information. Teva Neurosciences, Inc. August 2016.
4. Extavia prescribing information. Novartis Pharmaceuticals Corporation. May 2016.
5. Gilenya prescribing information. Novartis Pharmaceuticals Corporation. May 2018.
6. Rebif prescribing information. EMD Serono, Inc. November 2015.
7. Aubagio prescribing information. Genzyme Corporation. November 2016.
8. Tecfidera prescribing information. Biogen, Inc. January 2017.
9. Plegridy prescribing information. Biogen, Inc. July 2016.
10. Glatopa prescribing information. Sandoz. April 2016.
11. Zinbryta prescribing information. Biogen, Inc. August 2017.
12. Multiple Sclerosis Coalition. The Use of Disease Modifving Therapies in Multiple Sclerosis: Principals and Current Evidence. Updated March 2017. National Multple Sclerosis Society. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed 12/4/17.
13. Olek, Michael, DO., et al. Treatment of Progressive Multiple Sclerosis in Adults. UpToDate. Last Updated April 14, 2017.
14. Scolding, Neil, et. al. Association of British Neurologists: Revised (2015) Guidelines for Prescribing Disease- Modifying Treatments in Multiple Sclerosis. *Practical Neurology* 2015; 15**:** 243-243.

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information

15. Olek, Michael, DO., et al. Disease-Modifying Treatment of Relapsing-Remitting Multiple Sclerosis in Adults. UpToDate. Last updated September 22, 2017.
16. Institute for Clinical and Economic Review (ICER). Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value. November 22, 2016. Available at: https://icer-review.org/wp-content/uploads/2016/08/ICER_Draft_MS_Report_112216.pdf. Accessed 12/4/17.
17. Goodin DS, Frohman EM, Garmany GP, et al. Disease modifying therapies in multiple sclerosis. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Reaffimed October 2003 and July 2008. *Neurology* 2002;58;169-178
18. Graber J, McGraw C, Kimbrough D, Dhib-Jalbut S. Overlapping and distinct mechanisms of action of multiple sclerosis therapies. *Clinical Neurology and Neurosurgery*. 2010;112:583-591.
19. Multiple Sclerosis Therapy Consensus Group (MSTCG). Basic and escalating immunomodulatory treatments in multiple sclerosis: current therapeutic recommendations. *J Neurol*. 2008;255:1449–1463. Accessed December 2015.

Current Procedural Terminology © American Medical Association. All Rights Reserved.

Contains Public Information