Pharmacy Policy Bulletin

Title: Multiple Sclerosis Agents
Policy #: Rx.01.122

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, gender or quantity restrictions. Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

**Intent:**
The intent of this policy is to communicate the medical necessity criteria for interferon beta-1b (Extavia®) and interferon beta-1a (Rebif/Rebif Rebidose®), fingolimod (Gilenya), teriflunomide (Aubagio), daclizumab (Zinbryta), and dalfampridine (Ampyra) as provided under the member’s pharmacy benefit.

**Description:**
Multiple sclerosis (MS) is the most common autoimmune, inflammatory, demyelinating disease affecting the central nervous system (CNS). An unknown stimulus causes the immune system to attack the myelin sheath that protects nerves, leading to symptoms such as weakness, numbness, vision loss, and gait disturbances. More than 2.3 million people are affected by MS worldwide.

Disease modifying therapies are the standard therapy for relapsing forms of MS. These include interferon beta, glatiramer, dimethyl fumerate, teriflunomide, fingolimod, and daclizumab. While these therapies decrease the rate of relapse, they are not curative.

Interferon Beta-1b (Extavia®) is indicted for the treatment of relapsing forms of MS to decrease the frequency of clinical exacerbations.

Interferon Beta-1a (Rebif/Rebif Rebidose®) is indicted for the treatment of relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.

Interferons are cytokines that mediate antiviral, antiproliferative, and immunomodulatory activities. The mechanism of action of interferon beta 1a or 1b in the treatment of MS is unknown.
Fingolimod (Gilenya®) is indicated for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate. Fingolimod-phosphate is a sphingosine 1-phosphate receptor modulator, and binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5. Fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which fingolimod exerts therapeutic effects in MS is unknown, but may involve reduction of lymphocyte migration into the CNS.

Teriflunomide (Aubagio®) is indicated for the treatment of relapsing forms of MS.

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties, which inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is unknown but may involve a reduction in the number of activated lymphocytes in CNS.

Dalfampridine (Ampyra®) is indicated to improve walking in patients with MS.

Dalfampridine is a broad spectrum potassium channel blocker. The mechanism by which dalfampridine exerts its therapeutic effect has not been fully elucidated. In animal studies, dalfampridine has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels.

Daclizumab™ (Zinbryta) is indicated for the treatment of adult patients with relapsing forms of MS. Because of its safety profile, the use of daclizumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated in the treatment of MS.

Daclizumab is a humanized monoclonal antibody thought to modulate interleukin (IL)-2 mediates activation of lymphocytes by binding to the alpha subunits, CD25, of the IL-2 receptor. The exact mechanism of its effect in MS is unknown.

**Policy:**

Interferon beta-1b (Extavia®), interferon beta-1a (Rebif [Rebidose]®), fingolimod (Gilenya®), teriflunomide (Aubagio®), and daclizumab (Zinbryta) are approved when ONE of the following is met:

1. Documentation of a relapsing form of MS and an inadequate response or inability to tolerate TWO of the following:
   a. Interferon beta-1a (Avonex®)
   b. Interferon beta-1b (Betaseron®)
   c. Glatiramer acetate (Copaxone®/Glatopa™)
   d. Dimethyl fumarate (Tecfidera®)
   e. Peginterferon beta-1a (Plegridy™)

2. Documentation of continuous therapy with requested agent

Dalfampridine (Ampyra®) is approved when there is a diagnosis of MS.

Initial authorization: 6 months

Continuation Criteria for Ampyra® (indefinite): dalfampridine (Ampyra®) is approved when there is documentation of a 20% improvement in walking speed.
**Black Box Warning:**

**Teriflunomide (Aubagio)**

Hepatotoxicity: Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. Obtain transaminase and bilirubin levels within 6 months before initiation of Aubagio and monitor ALT levels at least monthly for six months. If drug induced liver injury is suspected, discontinue Aubagio and start accelerated elimination procedure.

Risk of Teratogenicity: Based on animal data, Aubagio may cause major birth defects if used during pregnancy. Aubagio is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during Aubagio treatment.

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**Daclizumab (Zinbryta)**

**Hepatic Injury Including Autoimmune Hepatitis**

- Zinbryta can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. Obtain transaminase and bilirubin levels before initiation of Zinbryta. Monitor and evaluate transaminase and bilirubin levels monthly and up to 6 months after the last dose.
- Zinbryta is contraindicated in patients with pre-existing hepatic disease or hepatic impairment.

**Other Immune-Mediated Disorders**

- Immune-mediated disorders including skin reactions, lymphadenopathy, non-infectious colitis, and other immune-mediated disorders can occur with Zinbryta. These conditions may require treatment with systemic corticosteroids or immunosuppressive medication.

Zinbryta is available only through a restricted distribution program called the Zinbryta REMS Program

**Guidelines:**

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the pharmacy benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

**References:**

**Applicable Drugs:**

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
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<tbody>
<tr>
<td>Extavia</td>
<td>Interferon Beta-1B</td>
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<tr>
<td>Rebif/Rebif Rebidose</td>
<td>Interferon Beta-1A</td>
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<td>Gilenya</td>
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<td>Ampyra</td>
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<td>Aubagio</td>
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<td>Zinbryta</td>
<td>Daclizumab</td>
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**Cross References:**

[4fa1-ad65-c0fd8b0ce783&type=display](Accessed November 4, 2016).

[4fa1-ad65-c0fd8b0ce783&type=display](Accessed November 4, 2016).


**Policy Version Number:** 7.00

**P&T Approval Date:** October 13, 2016

**Policy Effective Date:** December 01, 2016

**Next Required Review Date:** October 13, 2017
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