BlueCross BlueShield of Alabama

Multiple Sclerosis Agents Prior Authorization with Quantity Limit Criteria Program Summary

This program applies to Commercial and Health Insurance Marketplace formularies.

This program targets only Zinbryta for PA. Preferred agents that do NOT require PA are Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif and Tecfidera. Extavia is NDC locked out of coverage.

OBJECTIVES

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 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 DRUG
NonPreferred Agent
Zinbryta™ (daclizumab)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL WITH QUANTITY LIMIT– THROUGH PREFERRED AGENT

Initial Criteria 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
    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:
        i. The patient has an FDA labeled indication for the requested agent
        AND
        ii. If the requested agent is Zinbryta **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, and Tecfidera)

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
        i. The requested quantity (dose) is greater than the program quantity limit

        AND

        ii. The requested quantity (dose) is less than or equal to the FDA labeled dose

        AND

        iii. 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:
        i. The requested quantity (dose) is greater than the program quantity limit

        AND

        ii. The requested quantity (dose) is greater than the FDA labeled dose

        AND

        iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

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 Prime Therapeutics 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 contraindication(s) 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

i. The requested quantity (dose) is greater than the program quantity limit
AND
ii. The requested quantity (dose) is less than or equal to the FDA labeled dose
AND
iii. 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:
i. The requested quantity (dose) is greater than the program quantity limit
AND
ii. The requested quantity (dose) is greater than the FDA labeled dose
AND
iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 12 months

Agent	Contraindication
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

QUANTITY LIMITS FOR TARGET DRUGS (See QL grid for all other Quantity Limits)

Brand (generic)	GPI	Quantity Limit	Multisource Code
Zinbryta™ (daclizumab)			
150 mg/mL syringe	6240502500E520	1 syringe/30 days	M, N, O, or Y

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

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 (teriflunomide) tablet</td><td>Relapsing forms of MS</td><td>7 mg or 14 mg orally once daily</td></tr>
<tr><td>Avonex (interferon β-1a) intramuscular injection</td><td>Relapsing forms of MS[a]</td><td>30 mcg intramuscularly once weekly</td></tr>
<tr><td>Betaseron, Extavia (interferon β-1b) 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><td></td><td>Recommended Titration</td><td>Dose</td><td>Volume</td></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>
<tr><td>Copaxone (glatiramer acetate) 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 (fingolimod) Tablet</td><td>Relapsing forms of MS</td><td>0.5 mg orally once daily</td></tr>
<tr><td>Glatopa (glatiramer acetate 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 (peginterferon β-1a) 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 (interferon β-1a) 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. See recommended titration table:
<table>
<tr><td></td><td>Recommended Titration</td><td>Titration Dose for 22 mcg</td><td>Titration Dose for 44 mcg</td></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 (dimethyl fumerate) capsule</td><td>Relapsing forms of MS</td><td>Starting dose: 120 mg orally twice daily for 7 days
Maintenance dose: 240 mg twice daily</td></tr>
<tr><td>Zinbryta (daclizumab)</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

CLINICAL 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 the 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 effect of dimethyl fumarate in MS is unknown but its metabolite has been shown to active 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.

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