Multiple Sclerosis Agents
Prior Authorization with Quantity Limit
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 AGENTS
NonPreferred Agent
Zinbryta™ (daclizumab)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL WITH QUANTITY LIMIT– 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:
      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 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. 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
        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 be 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 approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through 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
3. The patient has had clinical benefit from treatment with the requested agent
AND
4. The prescriber is a neurologist or the prescriber has consulted with a neurologist
AND
5. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
AND

6. 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

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
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 fumerate) 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

CLINICAL RATIONALE

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 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]

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.

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