Multiple Sclerosis Agents
Step Therapy and Quantity Limit
Program Summary

This program is implemented on FlexRx Open, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

This is a FlexRx standard and GenRx standard step therapy program.

For KeyRx the preferred products are glatiramer (Mylan brand), Aubagio, Avonex, Betaseron, Gilenya, Rebif, Plegridy, and Tecfidera. Glatiramer agents are formulary-driven preferred agents; the formulary glatiramer agents are as follows: Mylan brand generic.

For FlexRx Open, GenRx Open, Health Insurance Marketplace and FocusRx, the preferred products are Aubagio, Avonex, Betaseron, Copaxone, Gilenya, glatiramer (Mylan brand), Rebif, Plegridy, and Tecfidera. Glatiramer agents are formulary-driven preferred agents; the formulary glatiramer agents are as follows: Mylan brand generic and Copaxone.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

This program is implemented with auto-grandfathering.

**FDA APPROVED INDICATIONS AND DOSAGE**1-11

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aubagio® (teriflunomide) tablet</td>
<td>Treatment of patients with relapsing forms of multiple sclerosis (MS)</td>
<td>7 mg or 14 mg orally once daily, with or without food</td>
</tr>
<tr>
<td>Avonex® (interferon β-1a) intramuscular injection</td>
<td>Treatment of patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS</td>
<td>May be titrated: starting with 7.5 mcg for first week, to reduce flu-like symptoms. Increase dose by 7.5 mcg each week for next 3 weeks until recommended dose of 30 mcg once weekly Maintenance dose: 30 mcg once a week</td>
</tr>
<tr>
<td>Betaseron® (interferon β-1b) subcutaneous injection</td>
<td>Treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Patients with MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS</td>
<td>Initial titration: 0.0625 mg (0.25 mL) every other day, and increase over a six-week period to 0.25 mg (1 mL) every other day Maintenance dose: 0.25 mg every other day</td>
</tr>
<tr>
<td>Copaxone® (glatiramer acetate)a</td>
<td>Treatment of patients with relapsing forms of MS</td>
<td>20 mg administered once per day or 40 mg administered three times per day</td>
</tr>
<tr>
<td>Drug</td>
<td>Description</td>
<td>Dosage</td>
</tr>
<tr>
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<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Extavia®</strong></td>
<td>Treatment of relapsing forms of MS to reduce the frequency of clinical</td>
<td>Initial titration: 0.0625 mg (0.25 mL) every other day, and increase over a six-week period to 0.25 mg (1 mL) every other day</td>
</tr>
<tr>
<td>(interferon β-1b)</td>
<td>exacerbations.</td>
<td>Maintenance dose: 0.25 mg every other day</td>
</tr>
<tr>
<td>subcutaneous injection</td>
<td>Patients with MS in whom efficacy has been demonstrated include patients</td>
<td></td>
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<tr>
<td></td>
<td>who have experienced a first clinical episode and have MRI features</td>
<td></td>
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<tr>
<td></td>
<td>consistent with MS</td>
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</tr>
<tr>
<td><strong>Gilenya®</strong></td>
<td>Treatment of relapsing forms of MS in patients 10 years of age and older</td>
<td>10 years of age and above, weighing less than or equal to 40 kg: 0.25 mg orally once daily with or without food</td>
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<tr>
<td>(fingolimod)</td>
<td></td>
<td>Adults and pediatric patients 10 years of age and older and weighing more than 40 kg: 0.5 mg orally once daily with or without food</td>
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<tr>
<td>tablet</td>
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<tr>
<td><strong>Glatopa®</strong></td>
<td>Treatment of patients with relapsing forms of MS</td>
<td>20 mg administered once daily or 40 mg administered three times per week and at least 48 hours apart</td>
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<tr>
<td>(glatiramer acetate)</td>
<td></td>
<td>(Glatopa 20mg/mL and Glatopa 40mg/mL are not interchangeable)</td>
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<tr>
<td>subcutaneous injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plegridy®</strong></td>
<td>Treatment of patients with relapsing forms of MS</td>
<td>Dose titration: 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29</td>
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<tr>
<td>(peginterferon β-1a)</td>
<td></td>
<td>Maintenance dose: 125 mcg subcutaneously every 14 days</td>
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<tr>
<td>subcutaneous injection</td>
<td></td>
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<tr>
<td><strong>Rebif®</strong></td>
<td>Treatment of patients with relapsing forms of MS to decrease the frequency</td>
<td>Titration: Generally, the starting dose should be 20% of the prescribed dose three times per week, and increased over a 4 week period to the targeted recommended dose of either 22 mcg or 44 mcg injected subcutaneously three times per week</td>
</tr>
<tr>
<td>(interferon β-1a)</td>
<td>of clinical exacerbations and delay the accumulation of physical disability</td>
<td>Maintenance dose: 22 mcg or 44 mcg injected subcutaneously three times per week</td>
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<tr>
<td>subcutaneous injection</td>
<td></td>
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</tr>
<tr>
<td><strong>Tecfidera®</strong></td>
<td>Treatment of patients with relapsing forms of MS</td>
<td>Starting dose: 120 mg orally twice daily for 7 days</td>
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<tr>
<td>(dimethyl fumerate)</td>
<td></td>
<td>Maintenance dose: 240 mg twice daily</td>
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<tr>
<td>Capsule</td>
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**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). 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. 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.

Treatment of CIS (defined as a single demyelinating event) with DMAs is recommended for patients have had a single clinical demyelinating event with 2 or more brain spinal cord lesions. These patients remain at an increased risk of a future MS diagnosis, with the highest risk incurred within 5 years of the initial event. DMAs are associated with a significant delay in second clinical relapse or new brain MRI-detected lesions in patients with a first demyelinating event who are high risk for MS on the basis of brain MRI-detected lesion. The benefit of initiating DMA has not been studied in untreated patients with CIS or RRMS who have not had relapses in 2 or more years and do not have active new MRI lesion activity. It is unknown what the risk of harm is from initiating DMAs, including adverse events and burden of taking long term medications. It is recommended that serial imaging at least annually for the first 5 years and close follow up is preferred over DMA therapy for patients with CIS or relapsing forms of MS who have not had relapses in the preceding 2 years and do not have active new MRI lesion activity.

Treatment directed at PPMS is typically more difficult than treatment of RRMS and recommendations differ between the different forms of MS. There are several effective disease modifying agents (DMAs) available for RRMS and only one DMA for PPMS. 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. DMAs reduce but do not eliminate MS relapses and MRI activity. 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.

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.\textsuperscript{12-14} Guidelines recommend initiation of treatment with DMA as soon as possible following diagnosis of RRMS or PPMS.\textsuperscript{12-15} Suggested initial treatment approach includes the following:\textsuperscript{15}

- Infusion therapy with natalizumab or ocrilizumab for patients with more active disease and for those who value effectiveness above safety and convenience. Cross-trial comparisons and clinical experience suggests natalizumab is more effective than interferons, glatiramer, or oral DMAs for patients with RRMS. Evidence from randomized trials shows that ocrilizumab is more effective than interferon beta-1a for reducing relapses. Because of its safety profile, alemtuzumab is usually reserved for patients who have had an inadequate response to two or more DMAs for 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.

The Academy of Neurology has recommended alemtuzumab, fingolimod, and natalizumab as options for patients with MS with highly active MS. Sub-analysis from phase III pivotal trials showed alemtuzumab, fingolimod, and natalizumab resulted in more favorable outcomes (reduction in relapses and MRI measures) in the patients with highly active MS compared to interferon-β therapy.\textsuperscript{14} Based on available evidence, clinicians agree that newly diagnosed patients with MS, who have clinical and radiographic markers of poor prognosis in the early stages of MS, should be treated with agents with higher efficacy from the onset, even if associated with greater risks. There lacks a consensus for what constitutes as very active MS, however.\textsuperscript{16} The National Institute for Health and Care Excellence (NICE) defines rapidly evolving severe RRMS as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.\textsuperscript{17}

Lack of response to DMAs are hard to define, as most patients with MS are not free of all disease activity. Relapses or new MRI detected lesions may develop after initiation of a DMA and before the treatment becomes effective for patients. When determining efficacy, sufficient time for the DMA therapy to take full effect and patient adherence are important to considerations. Evidence of one or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination while being treated with a DMA for a 1 year period suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.\textsuperscript{14,15} A systemic review showed that detection of gadolinium (Gd)-enhancing lesions was associated with greater predictive power for interferon treatment failure compared to the detection of new T2 lesions. However, Gd-enhancing lesions maybe more accurately detected and development of some T2 lesions might occur before full treatment effect has been achieved. Another analysis showed that clinical relapse plus 3 or more new T2 lesions during the first year of therapy was associated with both higher rates of treatment failure and disability worsening.\textsuperscript{17} 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).\textsuperscript{12}

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). 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. The benefits of combination therapies and the safety concerns associated with concurrent therapy still need further investigation.

For additional clinical information see Prime Therapeutics Formulary Chapter 9.6C Multiple Sclerosis Agents.

REFERENCES

Multiple Sclerosis Agents Step Therapy and Quantity Limit

OBJECTIVE
The intent of the Multiple Sclerosis Agents Step Therapy (ST) program is to encourage the use of preferred multiple sclerosis agents before the nonpreferred agents for patients initiating therapy. The program allows continuation of therapy with a nonpreferred MS agent when there is documentation that the patient is receiving the requested agent. The program requires the patient will not receive another MS disease modifying agent concomitantly with the requested agent. Requests for the nonpreferred agents will be reviewed when patient-specific documentation has been provided.

TARGET AGENTS
Preferred agents
Aubagio® (teriflunomide)
Avonex® (interferon β-1a)
Betaseron® (interferon β-1b)
Copaxone® (glatiramer)
Gilenya™ (fingolimod)
Glatopa™ (glatiramer)
Plegridy™ (peginterferon β-1a)
Rebif® (interferon β-1a)
Tecfidera™ (dimethyl fumarate)

Nonpreferred agents
Extavia® (interferon β-1b)

a - generic available
b - these agents are subject to duplicate therapy check only
* - for glatiramer products, preferred agents (i.e. NDC’s) as determined by formulary placement

For KeyRx the preferred products are glatiramer (Mylan brand), Aubagio, Avonex, Betaseron, Gilenya, Rebif, Plegridy, and Tecfidera. Glatiramer agents are formulary-driven preferred agents; the formulary glatiramer agents are as follows: Mylan brand generic.

For FlexRx Open, GenRx Open, Health Insurance Marketplace and FocusRx, the preferred products are Copaxone, glatiramer (Mylan brand), Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Rebif, Plegridy, and Tecfidera. Glatiramer agents are formulary-driven preferred agents; the formulary glatiramer agents are as follows: Mylan brand generic and Copaxone.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Target agent will be approved when BOTH of the following are met:
1. 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 currently being treated with the requested agent AND is at risk if therapy is changed
   OR
   c. The requested agent is a preferred agent
   OR
   d. The requested agent is a nonpreferred agent AND ONE of the following:
      i. The patient’s medication history includes the use of TWO preferred agents for MS within the past 365 days
      OR
ii. 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 for MS

**AND**

2. The patient will NOT be taking an additional disease modifying agent (DMA) for the requested indication

**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.

**NOTE:** If Quantity Limit program also applies, please refer to Quantity Limit documents.
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE

The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL

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

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
      AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient's medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria