MULTIPLE SCLEROSIS INJECTABLE THERAPY

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Description:

Multiple sclerosis (MS) is an unpredictable and potentially disabling disease of the central nervous system, which interrupts the flow of information within the brain, and between the brain and body. The disease is thought to be triggered in a genetically susceptible individual by a combination of one or more environmental factors. In MS, the immune system attacks tissue and cells within the central nervous system (CNS) and causes damage to nerve connections resulting in neurological symptoms. Although MS is not curable, there is much an individual can do to manage the disease and symptoms it can cause. A number of medications have been shown to modify or slow the course of MS.

MS is categorized into four types. As the understanding of the disease process in MS advances, the definitions have evolved:

**National Multiple Sclerosis Society 1996 Disease-Course Definitions**

- **Primary Progressive (PPMS):**
  PPMS is characterized by steady worsening of neurologic functioning, without any distinct relapses (also called attacks or exacerbations) or periods of remission. Rate of progression may vary over time with occasional plateaus or temporary improvement but the progression is continuous.

- **Progressive-Relapsing (PRMS):**
  PRMS is the least common of the four disease courses. Similar to PPMS, individuals with PRMS experience steadily worsening neurologic function and disease progression from the very beginning, in addition to occasional relapses like those experienced with RRMS. Because PRMS is progressive from onset, it may be initially diagnosed as PPMS, and then subsequently changed to PRMS when a relapse occurs. Although this disease course is progressive from the outset, each individual’s symptoms and rate of progression will be different.

- **Relapsing-Remitting (RRMS):**
  RRMS is characterized by clearly defined attacks of worsening neurologic function. These attacks, often called relapses, flare-ups or exacerbations, are followed by partial or complete recovery periods (remissions), during which symptoms improve partially or completely and there is no apparent progression of disease. RRMS is the most common disease course at the time of diagnosis. Approximately 85 percent of individuals are initially diagnosed with RRMS, compared to 10-15 percent with progressive forms of the disease.
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Description: (cont.)

National Multiple Sclerosis Society 1996 Disease-Course Definitions (cont.)

- Secondary Progressive (SPMS): SPMS follows after the relapsing-remitting disease course (RRMS). Of the 85 percent of individuals who are initially diagnosed with RRMS, most will eventually transition to SPMS, which means that after a period of time in which they experience relapses and remissions, the disease will begin to progress more steadily (although not necessarily more quickly), with or without any relapses (also called attacks or exacerbations).

National Multiple Sclerosis Society 2013 Disease-Course Revisions

- Clinically Isolated Syndrome (CIS): CIS is a first episode of neurologic symptoms caused by inflammation and demyelination in the central nervous system. The episode, which by definition must last for at least 24 hours, is characteristic of multiple sclerosis but does not yet meet the criteria for a diagnosis of MS because people who experience a CIS may or may not go on to develop MS.

- Relapsing-Remitting (RRMS): RRMS is characterized by clearly defined attacks of new or worsening neurologic function. These attacks, often called relapses, flare-ups or exacerbations, are followed by partial or complete recovery periods (remissions). During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. However, there is no apparent progression of the disease during the periods of remission. Approximately 85 percent of people with MS are initially diagnosed with RRMS.

- Primary Progressive (PPMS): PPMS is characterized by worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions. Approximately 15 percent of people with MS are diagnosed with PPMS.

- Secondary Progressive (SPMS): SPMS follows after the relapsing-remitting disease course (RRMS). Most individuals who are diagnosed with RRMS will eventually transition to a secondary progressive course in which there is a progressive worsening of neurologic function (accumulation of disability) over time.
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Definitions:

Preferred Multiple Sclerosis Therapy Medications:
- Aubagio® (oral medication)
- Avonex®
- Copaxone®
- Extavia®
- Gilenya® (oral medication)
- Plegridy®
- Rebif®
- Tecfidera® (oral medication)

Risk Evaluation and Mitigation Strategies (REMS):
Use of Lemtrada®, and Tysabri® is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

Criteria:

See Resources section for FDA-approved dosage

Avonex (interferon beta-1a) or Rebif (interferon beta-1a):

- Avonex or Rebif for the treatment of multiple sclerosis is considered medically necessary with documentation of ALL of the following:

  1. ONE of the following:
     - Individual has been diagnosed with a relapsing form of multiple sclerosis
     - Individual has experienced a first clinical episode and has MRI features consistent with multiple sclerosis

  2. No evidence of a history or hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation

  3. Treatment of multiple sclerosis is not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

- Avonex or Rebif for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:
- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Betaseron® (interferon beta-1b):

- Betaseron for the treatment of multiple sclerosis is considered medically necessary with documentation of ALL of the following:
  1. ONE of the following:
     - Individual has been diagnosed with a relapsing form of multiple sclerosis
     - Individual has experienced a first clinical episode and has MRI features consistent with multiple sclerosis
  2. Failed response to the preferred multiple sclerosis therapy medications Aubagio AND Avonex AND Copaxone AND Extavia AND Gilenya AND Pledridy AND Rebif AND Tecfidera (unless otherwise contraindicated or not labeled for the indication being prescribed with documentation of ANY of the following:
     - Individual’s condition has not improved or has worsened
     - Individual experienced a significant adverse drug event to the preferred MS medications
     - Individual is intolerant to the preferred MS medications
  3. No evidence of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol
  4. Treatment of multiple sclerosis is not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

- Betaseron for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting

These indications include, but are not limited to:

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Copaxone (glatiramer) or Glatopa® (glatiramer):

- Copaxone or Glatopa for the treatment of multiple sclerosis is considered medically necessary with documentation of ALL of the following:
  1. ONE of the following:
     - Individual has been diagnosed with a relapsing form of multiple sclerosis
     - Individual has experienced a first clinical episode and has MRI features consistent with multiple sclerosis
  2. No evidence of hypersensitivity to glatiramer acetate or mannitol
  3. Treatment of multiple sclerosis is not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

- Copaxone or Glatopa for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Extavia (interferon beta-1b):

- Extavia for the treatment of multiple sclerosis is considered medically necessary with documentation of ALL of the following:
  1. ONE of the following:
     - Individual has been diagnosed with a relapsing form of multiple sclerosis
     - Individual has experienced a first clinical episode and has MRI features consistent with multiple sclerosis
  2. No evidence of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol
  3. Treatment of multiple sclerosis is not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

**Extavia (interferon beta-1b):** (cont.)

- Extavia for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to*:

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

Lemtrada (alemtuzumab):

LEMTRADA IS AVAILABLE ONLY THROUGH RESTRICTED DISTRIBUTION UNDER A RISK EVALUATION AND MITIGATION STRATEGY (REMS) PROGRAM CALLED LEMTRADA REMS PROGRAM.

- Lemtrada for the treatment of multiple sclerosis is considered medically necessary with documentation of ALL the following:
  1. Individual has a relapsing form of multiple sclerosis and has a failed response to two or more drugs indicated for the treatment of relapsing forms of multiple sclerosis
  2. Evidence of completion of any necessary immunizations according to current immunization guidelines 6 weeks prior to initiation of Lemtrada
  3. Evidence of a prior history of varicella or individual has been vaccinated for the varicella zoster virus (VZV) before Lemtrada use
  4. Screen for tuberculosis before Lemtrada use and treat individuals who test positive for tuberculosis before Lemtrada use
  5. Evidence that individual has received instruction on avoiding potential sources of Listeria monocytogenes and instruction on the avoidance of live vaccines following Lemtrada therapy
  6. Anti-viral prophylaxis for herpetic viral infection is ongoing for the duration of treatment as per the treating provider
  7. No evidence of the Human Immunodeficiency Virus (HIV)
  8. No evidence of active infections or uncontrolled infections
  9. Treatment of multiple sclerosis is not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)
  10. The number of approvable infusions will be ONE of the following:
      - Lemtrada for initial regimen for relapsing MS: 8 infusions
      - Lemtrada for recurrent relapses of MS after initial regimen: 3 infusions per year
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

**Lemtrada (alemtuzumab):** (cont.)

- Lemtrada for all other indications not previously listed or if above criteria is not met is considered *experimental or investigational* based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to*:

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

Mitoxantrone:

- Mitoxantrone is considered medically necessary for individuals who have been diagnosed with ALL of the following:
  1. ONE of the following:
     - Individual has experienced a first clinical episode and has MRI features consistent with multiple sclerosis
     - Progressive-relapsing multiple sclerosis (PRMS)
     - Worsening relapsing-remitting multiple sclerosis (RRMS)
     - Secondary progressive multiple sclerosis (SPMS)
  2. No evidence of hypersensitivity to Mitoxantrone
  3. Treatment of multiple sclerosis is not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)

- Mitoxantrone for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Primary progressive multiple sclerosis (PPMS)
- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

Ocrevus™ (ocrelizumab):

- Ocrevus for the treatment of multiple sclerosis is considered **medically necessary** with documentation of ALL of the following:
  1. **ONE** of the following:
     - Individual has a relapsing form of multiple sclerosis and has a failed response to two or more drugs indicated for the treatment of relapsing forms of multiple sclerosis
     - Individual has been diagnosed with a primary progressive form of multiple sclerosis
  2. Evidence of completion of any necessary immunizations according to current immunization guidelines 6 weeks prior to initiation of Ocrevus
  3. Evidence of testing for hepatitis B infection prior to initiation of therapy
  4. No evidence of active infections or uncontrolled infections
  5. Evidence that individual has received instruction on the avoidance of live vaccines following Ocrevus therapy until B-cell repletion
  6. Absence of **ALL** of the following contraindications:
     - Active hepatitis B infection
     - History of life-threatening infusion reaction to Ocrevus
  7. Treatment of multiple sclerosis is not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)

- Ocrevus for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

Plegridy (peginterferon beta-1a):

- Plegridy for the treatment of multiple sclerosis is considered medically necessary with documentation of ALL of the following:
  1. **ONE** of the following:
     - Individual has been diagnosed with a relapsing form of multiple sclerosis
     - Individual has experienced a first clinical episode and has MRI features consistent with multiple sclerosis
  2. No evidence of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation
  3. Treatment of multiple sclerosis is not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)

- Plegridy for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

**Tysabri (natalizumab):**

For Tysabri for treatment of Crohn’s disease, see BCBSAZ Medical Coverage Guideline #O930, “Tysabri for Crohn’s Disease”.

**TYSABRI IS AVAILABLE ONLY THROUGH A RESTRICTED PROGRAM UNDER A RISK EVALUATION AND MITIGATION STRATEGY (REMS) CALLED THE TOUCH® PRESCRIBING PROGRAM.**

- Tysabri is considered *medically necessary* as monotherapy with documentation of **ALL** of the following:
  1. **ONE** of the following:
     - Individual has been diagnosed with a relapsing form of multiple sclerosis
     - Individual has experienced a first clinical episode and has MRI features consistent with multiple sclerosis
  2. No evidence of previous hypersensitivity reaction to Tysabri
  3. Treatment of multiple sclerosis is not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)

- Tysabri for all other indications not previously listed or if above criteria not met is considered *experimental or investigational* based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to*:

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Criteria: (cont.)

- Continuation of ALL agents listed above (except Lemtrada) is considered *medically necessary* with documentation of ALL of the following:

  1. **THREE** of the following:
     - Mild/minimal to no functional neurologic (pyramidal, cerebellar, brainstem, sensory) disabilities
     - Ambulatory without need for assistance
     - Reduction in number of exacerbations or relapses of MS
     - Prolonged time to exacerbation or relapses of MS
     - Reduction in hospitalizations for MS

  2. Not used concurrently with other injectable or oral medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression)

  3. No unacceptable drug toxicity

Resources:

Literature reviewed 08/27/18. We do not include marketing materials, poster boards and non-published literature in our review.


MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Resources: (cont.)


Avonex Package Insert. 12/22/2015:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex is an interferon beta indicated for the treatment of patients with</td>
<td>For intramuscular use only.</td>
</tr>
<tr>
<td>relapsing forms of multiple sclerosis to slow the accumulation of physical</td>
<td>Recommended dose: 30 micrograms once a week.</td>
</tr>
<tr>
<td>disability and decrease the frequency of clinical exacerbations. Patients</td>
<td>Avonex may be titrated, starting with 7.5 micrograms for first week,</td>
</tr>
<tr>
<td>with multiple sclerosis in whom efficacy has been demonstrated include</td>
<td>to reduce flu-like symptoms. Increase dose by 7.5 micrograms each week</td>
</tr>
<tr>
<td>patients who have experienced a first clinical episode and have MRI</td>
<td>for next 3 weeks until recommended dose of 30 micrograms.</td>
</tr>
<tr>
<td>features consistent with multiple sclerosis.</td>
<td>Week 1 7.5 micrograms 1/4 dose</td>
</tr>
<tr>
<td></td>
<td>Week 2 15 micrograms 1/2 dose</td>
</tr>
<tr>
<td></td>
<td>Week 3 22.5 micrograms 3/4 dose</td>
</tr>
<tr>
<td></td>
<td>Week 4+ 30 micrograms full dose</td>
</tr>
</tbody>
</table>

Safety and effectiveness of Avonex has not been established in pediatric patients.
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Resources: (cont.)

Betaseron Package Insert. 04/19/2016:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betaseron is an interferon beta indicated for the treatment of relapsing</td>
<td>For subcutaneous use only.</td>
</tr>
<tr>
<td>forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.</td>
<td>Recommended dose: 0.25 mg every other day.</td>
</tr>
<tr>
<td></td>
<td>Generally, start at 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></td>
<td>Weeks 1-2: 0.0625 mg 1/4 dose</td>
</tr>
<tr>
<td></td>
<td>Weeks 3-4: 0.125 mg 1/2 dose</td>
</tr>
<tr>
<td></td>
<td>Weeks 5-6: 0.1875 mg 3/4 dose</td>
</tr>
<tr>
<td></td>
<td>Week 7+: 0.25 mg full dose</td>
</tr>
</tbody>
</table>

Safety and effectiveness of Betaseron has not been established in pediatric patients.

Copaxone Package Insert. 01/23/2018:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copaxone is indicated for the treatment of patients with relapsing-forms of multiple sclerosis.</td>
<td>For subcutaneous injection only, doses are not interchangeable.</td>
</tr>
<tr>
<td></td>
<td>Recommended dose: 20 mg/mL per day or 40 mg/mL three times per week and at least 48 hours apart. Copaxone 20 mg/mL and Copaxone 40 mg/mL are not interchangeable.</td>
</tr>
<tr>
<td></td>
<td>Safety and effectiveness of Copaxone has not been established in pediatric patients.</td>
</tr>
</tbody>
</table>
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Resources: (cont.)

Extavia Package Insert. 05/12/2016:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extavia is an interferon beta indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.</td>
<td>For subcutaneous use only. Recommended dose: 0.25 mg injected subcutaneously every other day. Generally, start at 0.0625 mg (0.25 mL) subcutaneously every other day and increase over a six-week period to 0.25 mg (1 mL) every other day. Weeks 1-2: 0.0625 mg 1/4 dose Weeks 3-4: 0.125 mg 1/2 dose Weeks 5-6: 0.1875 mg 3/4 dose Week 7+: 0.25 mg full dose Safety and effectiveness of Extavia has not been established in pediatric patients.</td>
</tr>
</tbody>
</table>

Glatopa Package Insert. 04/16/2015:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatopa is indicated for the treatment of patients with relapsing-forms of multiple sclerosis.</td>
<td>For subcutaneous injection only. Do not administer intravenously. Recommended dose: 20 mg/mL: administer once per day. Glatopa 20 mg per mL and glatiramer acetate injection 40 mg per mL are not interchangeable. Safety and effectiveness of Glatopa has not been established in pediatric patients.</td>
</tr>
</tbody>
</table>
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

**Resources:** (cont.)

Lemtrada Package Insert. 12/13/2017:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
</table>
| Lemtrada is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. | Only prescribers certified with the Lemtrada REMS Program may prescribe Zinbryta for multiple sclerosis.  
For intravenous infusion.  
Recommended dosage: 12 mg/day by intravenous infusion over 4 hours for 2 treatment courses.  
First course: 12mg/day on 5 consecutive days (60 mg total dose)  
Second course: 12mg/day on 3 consecutive days (36 mg total dose) administered 12 months after first treatment course.  
Safety and effectiveness of Lemtrada in pediatric patients less than 17 years of age has not been established. |
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Resources: (cont.)

Mitoxantrone Package Insert:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated in the treatment of patients with primary progressive multiple sclerosis.</td>
<td>For intravenous infusion.</td>
</tr>
<tr>
<td>Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated in the treatment of patients with primary progressive multiple sclerosis.</td>
<td>Recommended dosage: 12 mg/m² given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months.</td>
</tr>
<tr>
<td>Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated in the treatment of patients with primary progressive multiple sclerosis.</td>
<td>Left ventricular ejection fraction (LVEF) should be evaluated by echocardiogram or MUGA prior to administration of the initial dose of Mitoxantrone and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop at any time during treatment. Mitoxantrone should not be administered to multiple sclerosis patients with an LVEF &lt;50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of ≥140 mg/m². Complete blood counts, including platelets, should be monitored prior to each course of Mitoxantrone and in the event that signs or symptoms of infection develop. Mitoxantrone generally should not be administered to multiple sclerosis patients with neutrophil counts less than 1500 cells/mm³. Liver function tests should also be monitored prior to each course. Mitoxantrone therapy in multiple sclerosis patients with abnormal liver function tests is not recommended because Mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments. Women with multiple sclerosis who are biologically capable of becoming pregnant, even if they are using birth control, should have a pregnancy test, and the results should be known, before receiving each dose of Mitoxantrone. Safety and effectiveness of Mitoxantrone has not been established in pediatric patients.</td>
</tr>
</tbody>
</table>
Ocrevus Package Insert. 03/28/2017:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis.</td>
<td>Administer Ocrevus under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion reactions. Initial dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion. Subsequent doses: single 600 mg intravenous infusion every 6 months. If a planned infusion of Ocrevus is missed, administer Ocrevus as soon as possible; do not wait until the next scheduled dose. Reset the dose schedule to administer the next sequential dose 6 months after the missed dose is administered. Doses of Ocrevus must be separated by at least 5 months. Dose modifications in response to infusion reactions depends on severity. Life-threatening Infusion Reactions Immediately stop and permanently discontinue Ocrevus if there are signs of a life-threatening or disabling infusion reaction. Provide appropriate supportive treatment. Severe Infusion Reactions Immediately interrupt the infusion and administer appropriate supportive treatment, as necessary. Restart the infusion only after all symptoms have resolved. When restarting, begin at half the infusion rate at the time of onset of the infusion reaction. If this rate is tolerated, increase the rate as described in Table 1. This change in rate will increase the total duration of the infusion but not the total dose. Mild to Moderate Infusion Reactions Reduce the infusion rate to half the rate of at the onset of the infusion reaction and maintain the reduced rate for at least 30 minutes. If this rate is tolerated, increase the rate as described in Table 1. This change in rate will increase that total duration of the infusion but not the total dose. Observe the patient for at least one hour after the completion of the infusion. Safety and effectiveness of Ocrevus has not been established in pediatric patients.</td>
</tr>
</tbody>
</table>
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Resources: (cont.)

Ocrevus Package Insert: (cont.)

- FDA-approved indication and dosage: (cont.)

<table>
<thead>
<tr>
<th>Indication</th>
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<td>Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis.</td>
<td></td>
</tr>
</tbody>
</table>

| Table 1 Recommended Dose, Infusion Rate, and Infusion Duration for RMS and PPMS |
|---|---|---|
| Amount and Volume | Infusion Rate and Duration |
| Initial Dose (two infusions) | Infusion 1 | 300 mg in 250 mL |
| | Infusion Rate | 3 |
| | Duration | 2.5 hours or longer |
| | Infusion 2 (2 weeks later) | 300 mg in 250 mL |
| | Infusion Rate | 3 |
| | Duration | 2.5 hours or longer |
| Subsequent Doses (one infusion) | One infusion every 6 months | 600 mg in 500 mL |
| | Infusion Rate | 3 |
| | Duration | 3.5 hours or longer |

1 Solutions of Ocrevus for IV infusion are prepared by dilution of the drug product into an infusion bag containing 0.9% Sodium Chloride Injection, to a final drug concentration of approximately 1.2 mg/mL.
2 Administer the first Subsequent Dose 6 months after Infusion 1 of the Initial Dose.
3 Infusion time may take longer if the infusion is interrupted or slowed.
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Resources: (cont.)

Plegridy Package Insert. 07/14/2016:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
</table>
| Plegridy is an interferon beta indicated for the treatment of patients with relapsing forms of multiple sclerosis. | For subcutaneous use only.  
Recommended dose: 125 micrograms every 14 days.  
Plegridy dose should be titrated, starting with 63 micrograms.  
Day 1: 63 micrograms  
Day 15: 94 micrograms  
Day 29 and every 14 days thereafter: 125 micrograms  
Safety and effectiveness of Plegridy has not been established in pediatric patients. |

Rebif Package Insert. 09/27/2016:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
</table>
| Rebif is an interferon beta indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. | For subcutaneous injection only.  
Recommended dose: 22 mcg or 44 mcg injected subcutaneously three times per week.  
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.  
Safety and effectiveness of Rebif has not been established in pediatric patients. |
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Resources: (cont.)

Tysabri Package Insert. 04/18/2018:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. Tysabri increases the risk of PML. When initiating and continuing treatment with Tysabri, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk.</td>
<td>Only prescribers registered in the MS TOUCH® Prescribing Program may prescribe Tysabri for multiple sclerosis. Recommended dose: 300 mg intravenous infusion over one hour every four weeks. Safety and effectiveness of Tysabri is not indicated in pediatric patients below the age of 18 years of age.</td>
</tr>
</tbody>
</table>

Initial Approval Duration for ALL agents: 6 months

Renewal Approval Duration for ALL agents: 12 months
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Dii kwe’ é atah nílínígii Blue Cross Blue Shield of Arizona haada yit’éego bina’ííldiikgo éi doodago Háida bíjá aniyyeeéíígíí t’áadoo le’é yiina’ííldiikgo bee hahaz’áanii hólo díí t’áa hazaad’k’ehi háká a’oowolgo bee hah’á a dóó baq’éña ilínígód. Ata’ halne’éídí kójí bich’éjí’ hodilíinh 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thể thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thống dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعد أسلحة بخصوصية بالضرورة يبلغكم من دون أية تكلفة. للتحدث مع مرجم التصل ب 877-475-4799.
MULTIPLE SCLEROSIS INJECTABLE THERAPY (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang ibang tinituunan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makuasa ang isang tagsalog, tumawag sa 877-475-4799.

Korean: 만약 치유 또는 치유가 필요한 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 치유는 그러한 도움과 정보를 치유의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 동 역시와 얘기하기 위해서는 877-475-4799로 전화하십시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizonaについてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799までお電話ください。

Farsi: اگر شما یکی از شرک‌ها با‌کم می‌باشید ، سوال‌های مربوط به آموزش کمک‌های بیماری مزمن، به‌مشکلات آنها یا نیازهای آنها را به‌طور رایگان در دو همراهی با کمک‌کننده‌های 877-475-4799 می‌توانید دریافت کنید.

Assyrian: گذشته‌ها، یکی از شرک‌ها با‌کم شده‌اید، سوال‌های مربوط به آموزش کمک‌های بیماری مزمن، به‌مشکلات آنها یا نیازهای آنها را به‌طور رایگان در دو همراهی با کمک‌کننده‌های 877-475-4799 می‌توانید دریافت کنید.

Serbo-Croatian: Ukoiko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือคนที่คุณช่วยเหลอมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสมควรจะได้รับความช่วยเหลอมและข้อมูลภาษา ของคนโดยไม่เสียค่าใช้จ่าย โปรดโทรมาที่ 877-475-4799.