OBJECTIVE
The intent of the Intravenous (IV) Multiple Sclerosis Agents (MS) program is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling.

The program will approve a target agent for patients who have an FDA approved indication for the requested agent. For Tysabri and Lemtrada, the program will require patients with a relapsing form of multiple sclerosis to have failed to respond to or have an intolerance to disease modifying agents (DMAs) and/or conventional therapies used to treat these conditions. Patients must not have any FDA labeled contraindications to therapy, and must be within the appropriate FDA labeled dosing. Ocrevus will be approved for patients meeting criteria for the relapsing form of multiple sclerosis or for primary progressive multiple sclerosis. Tysabri will also be approved after conventional therapies and biologic therapy for Crohn’s disease.

TARGET AGENTS
Lemtrada™ (alemtuzumab)
Ocrevus® (ocrelizumab)
Tysabri® (natalizumab)

Initial Evaluation
Ocrevus (ocrelizumab) 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) for the requested indication
   OR
   b. The patient is currently being treated with a DMA for the requested indication AND the DMA will be discontinued before starting the requested agent

2. The patient does not have any FDA labeled contraindications to therapy with the requested agent

AND
3. ONE of the following:
   a. The patient has a diagnosis of a relapsing form of multiple sclerosis^ supported by clinical notes upon request
   OR
   b. The patient has a diagnosis of a primary progressive form of multiple sclerosis^ supported by clinical notes upon request
   OR
   c. The patient has another FDA labeled diagnosis

AND
4. The requested agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis

AND
5. If starting therapy, the patient has been tested for hepatitis B virus and determined to not have active hepatitis B viral infection

Coverage for Lemtrada is only provided when obtained through a plan's in-network pharmacy.

Precertification/Prior Authorization may be required under certain plans. Please verify each member’s benefits.

*Ocrevus indication: Relapsing Form of Multiple Sclerosis

^Diagnosis must be supported by clinical notes upon request.
AND
6. The prescribed dose is within the FDA approved labeled dosage

Length of Approval: 12 months

NOTE: For patients initiating therapy, approval will include two initial 300 mg loading doses (2 vials) and two 600 mg maintenance doses (4 vials).

Lemtrada (alemtuzumab) 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) for the requested indication
   OR
   b. The patient is currently being treated with a DMA for the requested indication AND the DMA will be discontinued before starting the requested agent

AND
2. The patient does not have any FDA labeled contraindications to therapy with the requested agent

AND
3. ONE of the following:
   a. The patient has a diagnosis of a relapsing form of MS^, supported by clinical notes upon request, AND ALL of the following:
      i. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis
      AND
      ii. ONE of the following:
          1. The patient’s medication history includes the use of at least three DMAs for the treatment of relapsing forms of MS (i.e. Aubagio, Avonex, Betaseron, Copaxone/Glatopa, Extavia, Gilenya, Ocrevus, Plegridy, Rebif, Tecfidera, Tysabri) and the following:
             a. If the patient’s medication history includes the use of Tysabri (e.g. switching from Tysabri to Lemtrada) and the patient has ONE or more of the following:
                i. Break-through attacks (worsening)^ on Tysabri
                OR
                ii. Documented intolerance, hypersensitivity, or antibodies to Tysabri
                OR
                iii. High risk patient indicated by BOTH of the following:
                    1. JCV antibody positive
                    AND
                    2. > 2 year duration of treatment on Tysabri and/or prior history of use of immunosuppressives (e.g. mitoxantrone, alemtuzumab)
                OR
                b. The patient has another FDA labeled diagnosis for the requested agent
      AND
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to three DMAs for the treatment of relapsing forms of MS

OR
4. The patient will be receiving anti-viral prophylaxis for herpetic viral infections

AND
5. The prescribed dose is within the FDA approved labeled dosage
**Length of Approval**: 3 months for MS with Lemtrada and up to 12 months for another FDA labeled indication

**Tysabri® (natalizumab)** 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) for the requested indication  
   **OR**
   b. The patient is currently being treated with a DMA for the requested indication AND the DMA will be discontinued before starting the requested agent

   **AND**

2. The patient does not have any FDA labeled contraindications to therapy with the requested agent

   **AND**

3. ONE of the following:
   a. The patient has the diagnosis of a relapsing form of MS\(^*\), supported by clinical notes upon request, AND ALL of the following:
      i. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis
      **AND**
      ii. ONE of the following:
         1. The patient has highly active or aggressive disease and ONE or more of the following:
            a. Increase in radiologic burden of disease as evidenced by MRI (e.g. new or enhancing lesions)  
            **OR**
            b. Increase in relapse activity or lack of recovery from relapse as evidenced by clinical manifestations  
            **OR**
            c. Accumulation of disability per EDSS, MSFC or clinical assessment
         **OR**
         2. The patient’s medication history includes the use of one DMA for the treatment of relapsing forms of MS (i.e. Aubagio, Avonex, Betaseron, Copaxone/Glatopa, Extavia, Gilenya, Plegridy, Rebif, Tecfidera)
         **OR**
   b. The patient’s medication history includes the use of at least one conventional therapy for the treatment of CD (e.g. aminosalicylates, metronidazole, ciprofloxacin, corticosteroids, methotrexate, or immunomodulators such as azathioprine or 6-mercaptopurine)
   **OR**
   c. The patient has a documented intolerance, FDA labeled contraindications, or hypersensitivity to a DMA for the treatment of relapsing forms of MS

   **AND**

   iii. The patient’s medication history does NOT include the use of Lemtrada

   **OR**

   b. The patient has the diagnosis of Crohn’s Disease (CD), AND BOTH of the following:
      i. ONE of the following:
         1. The patient’s medication history includes the use of at least one conventional therapy for the treatment of CD (e.g., Humira)
         **OR**
      2. The patient has a documented intolerance, FDA labeled contraindications, or hypersensitivity to conventional CD therapy

   **AND**

      ii. ONE of the following:
         1. The patient’s medication history indicates use of one biologic agent for the treatment of CD (e.g., Humira)  
         **OR**
2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one biologic agent for the treatment of CD

   OR

   c. The patient has another FDA labeled diagnosis for the requested agent

4. The prescribed dose is within the FDA approved labeled dosage

Length of Approval: 12 months for MS with Tysabri, 16 weeks for CD with Tysabri, and up to 12 months for another FDA labeled indication

^For definitions of relapsing and primary progressing forms of multiple sclerosis and break-through attacks (worsening) please see the clinical rationale section.

Renewal Evaluation

The requested agent (Ocrevus, Lemtrada, or Tysabri) will be renewed when ALL of the following are met:

1. The patient has been previously approved for the requested agent through Prime Therapeutics PA process

2. If Ocrevus or Tysabri for MS, ALL of the following:
   a. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis

3. If Ocrevus or Tysabri for MS, ALL of the following:
   a. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis
   b. The patient has shown clinical benefit (e.g. absence of disease progression or reduction in annualized relapse rate)

3. If Tysabri for Crohn’s Disease the patient has shown clinical benefit (e.g. decrease in the number of liquid or very soft stools, decrease in abdominal pain, increase in general well being)

4. If the request is for Lemtrada for a relapsing form of MS, ALL of the following:
   a. The patient will be receiving anti-viral prophylaxis for herpetic viral infections

5. The patient is NOT currently being treated with an additional disease modifying agent (DMA) for the requested indication

6. The patient has NOT received an additional disease modifying agent (DMA) for the requested indication since initiating therapy with the requested agent

7. The patient does not have any FDA labeled contraindications to therapy with the requested agent

8. The prescribed dosage is within the FDA approved labeled dosage
Length of Approval: 12 months for Ocrevus and Tysabri, 3 months for Lemtrada*

*The lifetime maximum coverage of Lemtrada is limited to 8 doses (5 doses in treatment year 1 and 3 doses in treatment year 2).

### Quantity Limit

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<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td><strong>Lemtrada (alemtuzumab)</strong></td>
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<tr>
<td>12 mg/1.2 mL</td>
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<td>M, N, O, or Y</td>
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<td>Year 2: 3 vials/90 days*</td>
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<table>
<thead>
<tr>
<th>Agent</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lemtrada (alemtuzumab)</strong></td>
<td>HIV infected patients.</td>
</tr>
</tbody>
</table>
| **Ocrevus (ocrelizumab)**  | Active hepatitis B virus infection.  
                            | History of life-threatening infusion reaction to Ocrevus.  |
| **Tysabri (natalizumab)**  | Patients who have or have had (PML). Patients who have had a hypersensitivity reaction to natalizumab. |

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members’ contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

This medical 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 medical policies are based on (i) research of current medical literature and (ii) 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.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.

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Prime Therapeutics LLC is an independent limited liability company providing pharmacy benefit management services.
## FDA APPROVED INDICATIONS AND DOSAGE1,13,22

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lemtrada®</strong> (alemtuzumab)* intravenous infusion</td>
<td>• Relapsing forms of multiple sclerosis</td>
<td><strong>RRMS</strong>: 12mg/day administered by intravenous infusion for 2 treatment courses: • 12 mg/day intravenously once daily for 5 consecutive days (total of 60 mg) 12 mg intravenously once daily for 3 consecutive days (total of 36 mg) 12 months after initial treatment course</td>
</tr>
<tr>
<td><strong>Ocrevus™</strong> (ocrelizumab) intravenous infusion</td>
<td>• Relapsing forms of multiple sclerosis • Primary progressive forms of multiple sclerosis</td>
<td><strong>PPMS/RRMS</strong>: *Initial dose: 300 mg intravenous infusion followed two weeks later by a second 300 mg intravenous infusion Maintenance dose: 600 mg intravenous infusion every 6 months</td>
</tr>
<tr>
<td><strong>Tysabri®</strong> (natalizumab) intravenous infusion</td>
<td>• Relapsing forms of multiple sclerosis • Moderately to severely active Crohn’s Disease</td>
<td><strong>RRMS</strong>: 300 mg intravenous infusion every 4 weeks <strong>CD</strong>: 300 mg intravenous infusion every 4 weeks^</td>
</tr>
</tbody>
</table>

^Discontinue if no benefit at 12 weeks. Discontinue if steroid discontinuation is not possible or if patients have to use steroids for beyond 3 months while on Tysabri.  
*Premedicate patients with corticosteroids (methylprednisolone 1,000 mg) immediately prior to therapy for the first 3 days of any treatment course. Pretreatment with antihistamines and/or antipyretics may be considered. Oral prophylaxis for herpes infection (acyclovir 200 mg twice daily) should be given to all patients on the first day of each treatment course and for a minimum of 1 month following treatment.  
^Hepatitis B virus screening is required before the first dose.

### CLINICAL RATIONALE

#### Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated inflammatory disease that affects myelinated axons in the central nervous system (CNS). Destruction of the myelin leads to varying degrees of physical disability. The mainstay of the disease is the symptomatic episodes that can occur from months to years apart (relapsing, remitting) and affect different locations in the body. Diagnosis of MS requires excluding alternative diagnoses and demonstration of dissemination of lesions in space over time.21

There are 4 different categories divided by clinical criteria which include frequency of clinical relapse, time to disease progression, and lesion development as determined by MRI. The categories are clinically isolated syndrome (CIS); relapsing-remitting (RRMS [≈85% of cases]); secondary progressive (SPMS); and primary progressive (PPMS).20

CIS referred to a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the central nervous system. CIS can be either monofocal or multifocal:  
- **Monofocal episode**: The person experiences a single neurologic sign or symptom — for example, an attack of optic neuritis — that’s caused by a single lesion.
• **Multifocal episode**: The person experiences more than one sign or symptom — for example, an attack of optic neuritis accompanied by numbness or tingling in the legs — caused by lesions in more than one place.

The episode usually has no associated fever or infection and is followed by a complete or partial recovery. Individuals who experience CIS may or may not go on to develop MS.  

RRMS – the most common disease course – is characterized by clearly defined attacks of new or increasing neurologic symptoms. These attacks – also called relapses or exacerbations – are followed by periods of partial or complete recovery (remissions). Relapses are defined as new or worsening MS symptoms that last at least 24 hours in the absence of fever or infection and have a preceding period of clinical stability lasting at least 30 days. 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.

At different points in time, RRMS can be further characterized as either **active** (with relapses and/or evidence of new MRI activity) or **not active**, as well as **worsening** (a confirmed increase in disability over a specified period of time following a relapse) or **not worsening**. An increase in disability is confirmed when the person exhibits the same level of disability at the next scheduled neurological evaluation, typically 6 to 12 months later.  

Note: Chronically present symptoms do not constitute a break-through attack.

SPMS follows an initial relapsing-remitting course. Most people 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. SPMS can be further characterized at different points in time as either **active** (with relapses and/or evidence of new MRI activity) or **not active**, as well as **with progression** (evidence of disease worsening on an objective measure of change over time, with or without relapses) or **without progression**.

PPMS is characterized by worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions. PPMS can be further characterized at different points in time as either **active** (with an occasional relapse and/or evidence of new MRI activity) or **not active**, as well as **with progression** (evidence of disease worsening on an objective measure of change over time, with or without relapse or new MRI activity) or **without progression**.

Progressive-relapsing MS (PRMS) is characterized by steadily worsening neurologic function from the beginning with occasional relapses. This disease-course definition was eliminated in the 2013 disease-course revisions. Individuals who were previously diagnosed with PRMS would now be considered PPMS: active (at the time of relapses or new MRI lesions) or not active.

Crohn’s disease (CD) is an idiopathic, chronic inflammatory disease of the gastrointestinal (GI) tract. It can affect any part of the GI tract from the mouth to the anus. Classic presentation is abdominal pain and diarrhea with periods of symptomatic relapses and remissions.

Natalizumab is a humanized monoclonal antibody that binds to integrins expressed on the surface of leukocytes and inhibits adhesion of the leukocytes to their counter-receptors. Natalizumab may further act to inhibit the interaction of leukocytes with ligands in the extracellular matrix and on parenchymal cells which in turn inhibits further recruitment and inflammatory activity of activated immune cells. The exact mechanism of this agent in the treatment of multiple sclerosis and Crohn’s disease is not fully defined. The clinical effect in MS may be secondary to blockade of the molecular interaction of integrin expressed by inflammatory cells with vascular cell adhesion molecule (VACM) on the vascular endothelial cells. In CD the interaction of an integrin with the endothelial receptor has thought to play an important contributing role in the chronic inflammation (the hallmark of the disease). The clinical effect may therefore be secondary to the blockade of the molecular interaction of integrin with the endothelial receptor.
Alemtuzumab binds to CD52 which is a cell surface antigen present in high levels on T and B lymphocytes. It is also present in lower levels on natural killer cells, monocytes, and macrophages. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis after cell surface binding to B and T lymphocytes. The exact mechanism by which alemtuzumab exerts its therapeutics effects in MS is not fully understood. Research suggests that potential immunomodulatory effects may include alterations in the number, proportion, and properties of some lymphocyte subsets after treatment.  

Ocrevus, an anti-CD20 monoclonal antibody, targets mature B-cells. Almost 95% of B-cells express the CD20 protein on their surface once they mature and do not shed them, which is what makes CD2 a potent marker for therapeutic purposes. It is believed these CD20-positive B-cells target axons and the myelin sheaths of healthy neurons, initiating a cascading series of immune reactions that lead to MS and disability in patients. Studies have shown that ocrelizumab binds to specific B-cells with CD20 markers, but not to stem cells and plasma cells, preserving vital immune functions within the host.

**Safety**

Tysabri (natalizumab) has a boxed warning for increasing the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability. The FDA MedWatch alert on February 5, 2010 notified healthcare professionals and patients that the risk of developing PML increases with the number of natalizumab infusions received. Information about the occurrence of Immune Reconstitution Inflammatory Syndrome (IRIS) in patients who have developed PML and subsequently discontinued natalizumab has also been added to the drug label. IRIS is a rare condition characterized by a severe inflammatory response that can occur during or following immune system recovery, causing an unexpected decline in a patient’s condition after return of immune function. Revisions to the drug label and patient Medication Guide, with the continued use of the TOUCH Prescribing Program, are intended to maximize the safe use of Tysabri (natalizumab) and the identification of new PML cases. Risk factors and risk stratification for the development of PML have been recommended. The risk factors identified include treatment duration with natalizumab of greater than 2 years, prior immunosuppressive use (e.g. mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil) and JCV virus seropositive. Patients with all 3 risk factors have an estimated PML risk of 11/1,000 users.

Natalizumab is contraindicated in patients who have had or who have PML and in patients with hypersensitivity to natalizumab. The most common adverse events (incidence ≥10%) in MS include headache, fatigue, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash. Common adverse events in CD include headache, upper respiratory tract infection, nausea, and fatigue.

Lemtrada (alemtuzumab) has the following boxed warnings:

- Causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals for 48 months after the last dose of Lemtrada.
- Causes serious and life threatening infusion reactions. Lemtrada must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for two hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period.
- May cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams.
- Because of the risk of autoimmunity, infusion reactions, and malignancies, Lemtrada is available only through restricted distribution under a Risk Evaluation Mitigation Strategy (REMS) Program.

Therapy with alemtuzumab is contraindicated in patients with Human Immunodeficiency Virus (HIV) infection because it causes prolonged reductions of CD4+ lymphocyte counts.
The most common adverse reactions (in approximately ≥10% of patients and greater than interferon beta [IFNB-1a] include rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paraesthesia, dizziness, abdominal pain, flushing, and vomiting.13

In controlled clinical trials, 16% of alemtuzumab-treated patients developed a herpes viral infection compared to 3% of interferon beta-1a patients. These events included oral herpes (8.8%), herpes zoster (4.2%), herpes simplex (1.8%), and genital herpes (1.3%). Serious herpetic infections in alemtuzumab-treated patients included primary varicella (0.1%), herpes zoster (0.2%), and herpes meningitis (0.1%). Antiviral agents for herpetic prophylaxis should be administered at appropriate suppressive dosing regimens starting on the first day of each treatment course and should continue for a minimum of two months following treatment with Lemtrada.13

The most common adverse events associated with ocrelizumab are upper and lower respiratory infections, infusion reactions, and skin infections. Ocrelizumab is contraindicated in patients who have history of life threatening infusion reaction to ocrelizumab as well as in patients with active hepatitis B virus as confirmed by positive results of HBsAg and anti-HB tests.22

Multiple Sclerosis
The treatment of MS is multifaceted and includes immunomodulatory therapy and symptom modification. Treatment for an acute relapse includes steroids and plasma exchange for those patients who do not respond to steroid therapy. Disease modifying therapies have been shown to slow the progression of disability and reduce the accumulation of lesions within the brain and spinal cord. There are several agents currently FDA approved to treat relapsing forms of MS. These include interferon beta-1a (Avonex, Rebif), peginterferon beta-1a (Plegridy), interferon beta-1b (Betaseron, Extavia), glatiramer acetate (Copaxone, Glatopa), natalizumab (Tysabri), mitoxantrone, fingolimod (Gilenya), teriflunomide (Aubagio), alemtuzumab (Lemtrada), dimethyl fumarate (Tecfidera)7 and ocrelizumab (Ocrevus).

Guidelines from the United States and Europe consider glatiramer and interferon beta (INFβ) as appropriate first line agents for treatment of relapsing forms of multiple sclerosis.4,5 Natalizumab is generally reserved for patients who have failed to respond to first line agents or for patients who have very progressive disease. Labeling for alemtuzumab supports its use by a neurologist experienced in RRMS after failure of interferon beta or other disease modifying therapies.13, 15, 16 Due to its safety profile FDA approved labeling advises the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to 2 or more agents approved for the treatment of RRMS.14

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).6

There is growing evidence to support treatment of naïve patients with highly active RRMS with natalizumab.17,18,19 Highly active relapsing MS is defined as (≥2 relapses in the year prior to therapy and ≥1 gadolinium enhancing lesion on MRI).18,19

There is evidence to support first line therapy in a subset of RRMS patients as first line therapy. Based on the literature, treatment naïve patients would need to be classified as highly active RRMS patients to qualify for natalizumab therapy (as defined above). Additional considerations regarding John Cunningham virus (JCV) status should also be taken into consideration when qualifying patients for natalizumab therapy.
Patients who are JCV antibody positive with a prior history of immunosuppression should not receive natalizumab as first line therapy. JCV antibody positive patients without a prior history of immunosuppression should be made aware of the increased risk of PML with increased duration of use (high risk in patients using natalizumab for >24 months). It is also recommended that patients be monitored for presymptomatic PML with MRI scans every 3-4 months as evidence has shown improved outcomes for patients that have MRI evidence of PML. Research is also showing that patient’s MRI evidence of PML often preceded symptoms by 2 to 3 months. Patients should also be monitored regularly as some patients will seroconvert (approximately 2-3% of patients).

Additional characteristics of patients that are likely to show an optimal response to natalizumab therapy include younger age at onset of therapy, less disability (EDSS of ≤4.5) or shorter disease duration (≤9.5 years), and a higher annual relapse rate (ARR) in the year prior to natalizumab initiation. Nicholas et al. defined an optimal response to natalizumab therapy as a sustained reduction in EDSS by ≥ 1 point or reduction in annualized relapse rate by more than 1 point. These parameters could help further address which patients receive natalizumab as first line therapy and support objective measures of an optimal response.

Efficacy of ocrelizumab was demonstrated in three phase III clinical studies: study 1, study 2, and study 3. Study 1 and study 2 enrolled 821 and 835 patients respectively all with a relapsing form of MS (RMS). The patients were required to have had at least 1 relapse within the previous year or 2 relapses within the previous two years. All patients were randomized to receive an initial two 300 mg doses of ocrelizumab followed by 600 mg every 24 weeks Rebif 44 mcg 3 times per week and placebo injections every 24 weeks. The primary end point of both studies was the annualized relapse rate (ARR). In both study 1 and study 2, ocrelizumab significantly lowered the ARR as well as proportion of patients with disability progression confirmed at 12 weeks after onset compared to Rebif.

Study 3 enrolled patients with a primary progressive form of MS (PPMS). The study randomized patients to receive either ocrelizumab (n=488) 600 mg or placebo (n=244) as two 300 mg injections. Both ocrelizumab and placebo were given every 24 weeks for at least 120 weeks. The time to onset of disability progression confirmed at 12 weeks after onset was significantly longer for ocrelizumab than for placebo treated patients.

Ocrevus is the first FDA-approved therapy that treats both relapsing multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS), a disease form that previously had no approved treatments. Ocrelizumab is an alternative to natalizumab and alentuzumab with a more favorable risk-benefit profile; however, long-term data on the safety and continued efficacy of ocrelizumab is necessary.

**Crohn’s Disease**

Treatment goals in CD include best control of inflammatory disease with the fewest medication side effects, normal patient function, and growth and nutritional balance in pediatric CD patients. A step wise approach for medical management is the gold standard in CD. Patients with mild disease are typically stepped-up while patients with moderate to severe disease are treated with a step-down approach.
Conventional agents include 5-aminosalicylic acid (5-ASA), antibiotics, 6-mercaptopurine, azathioprine, methotrexate, and budesonide. If patients do not respond to these agents, several biologic agents have FDA approval to treat CD. Surgical interventions are reserved for treating complications and controlling symptoms but surgical resection is not curative.

The American College of Gastroenterology (ACG) practice guidelines for CD in adults (2009) recommend treatment for mild to moderate CD with oral aminosalicylates (mesalamine and sulfasalazine), antibiotics (metronidazole or ciprofloxacin), and corticosteroid treatment (controlled-release budesonide or other conventional corticosteroids). For moderate to severe disease, azathioprine or 6-mercaptopurine (6-MP) are effective. Infliximab is recommended by ACG, the American Gastroenterological Association (AGA), and the British Society of Gastroenterology as a second-line treatment option in patients with moderately to severely active, refractory CD (including fistulizing disease). The 2009 ACG guidelines for CD state that infliximab, adalimumab, and certolizumab are all effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. Natalizumab is effective in patients who have had an inadequate response or are unable to tolerate conventional CD therapy and anti-TNF-α monoclonal antibody therapy.

References


Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members’ contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

This medical 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 medical policies are based on (i) research of current medical literature and (ii) 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.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.

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