Medical Policy

Title:  Tysabri® (natalizumab), Lemtrada™ (alemtuzumab), and Ocrevus® (ocrelizumab) (IV Multiple Sclerosis Agents)

See Also:  Multiple Sclerosis Agents

Prime Therapeutics will review Prior Authorization requests

Prior Authorization Form:

Link to Drug List (Formulary):

Professional
Original Effective Date:  May 15, 2015
Revision Date(s):  May 15, 2015;
May 1, 2016; April 1, 2017; July 15, 2017
Current Effective Date:  July 15, 2017

Institutional
Original Effective Date:  May 15, 2015
Revision Date(s):  May 15, 2015;
May 1, 2016; April 1, 2017; July 15, 2017
Current Effective Date:  July 15, 2017

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The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.
DESCRIPTION
The intent of the Intravenous (IV) Multiple Sclerosis (MS) Agents medical drug criteria 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 with an FDA approved indication for the requested agent. The program will require patients with a relapsing form of multiple sclerosis to have failed to respond to or have intolerance to two preferred disease modifying agents. The program will also approve Tysabri or Lemtrada for MS for patients who have failed Lemtrada or Tysabri respectively. Patients requesting Tysabri for Crohn's disease will be required to have failed conventional therapies and biologic therapy for Crohn's disease. The program will require the requested dose is within FDA labeling.

Target Agents
- Lemtrada™ (alemtuzumab)
- Ocrevus® (ocrelizumab)
- Tysabri® (natalizumab)

FDA Labeled Dosage

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Dosing</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lemtrada™</strong> (alemtuzumab)*</td>
<td>12 mg intravenously once daily for 5 consecutive days (total of 60 mg) then 12 mg intravenously once daily for 3 consecutive days (total of 36 mg) 12 months after initial treatment course</td>
<td>Relapsing forms of multiple sclerosis</td>
</tr>
<tr>
<td><strong>Ocrevus®</strong> (ocrelizumab)</td>
<td>Starting dose: 300 mg intravenously followed by a second infusion of 300 mg two weeks later Maintenance dose: 600 mg intravenously every 6 months</td>
<td>Relapsing forms of multiple sclerosis Primary progressive forms of multiple sclerosis</td>
</tr>
<tr>
<td><strong>Tysabri®</strong> (natalizumab)</td>
<td>300 mg intravenously every 4 weeks</td>
<td>Relapsing forms of multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>300 mg intravenously every 4 weeks^</td>
<td>Crohn's Disease</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.
POLICY

Prior Authorization and Quantity Limit Criteria for Approval

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

3. ONE of the following:
   a. There is documentation that the patient is currently being treated with the requested agent
   OR
   b. The patient has a diagnosis of a relapsing form of multiple sclerosis and meets BOTH of the following:
      i. ONE of the following:
         1. The patient’s medication history includes the use of TWO (preferred*) disease modifying agents for the treatment of relapsing forms of MS
            (*If client has preferred disease modifying agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)
         OR
         2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to TWO (preferred*) disease modifying agents for the treatment of relapsing forms of MS
            (*If client has preferred agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)
      AND
      ii. The requested agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis
   OR
c. The patient has a diagnosis of a primary progressive form of multiple sclerosis and meets the following:
   i. The requested agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis

   **OR**

d. The patient has another FDA labeled diagnosis

   **AND**

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

   **AND**

5. The prescribed dose is within the FDA approved labeling

**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).

**Initial Evaluation**

**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. There is documentation that the patient is currently being treated with the requested agent
   **OR**
   b. The patient has a diagnosis of a relapsing form of multiple sclerosis and meets BOTH of the following:
      i. **ONE** of the following:
         a. The patient's medication history includes the use of TWO preferred* agents for the treatment of relapsing forms of MS (*If client has preferred agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)
         **OR**
b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a preferred agent for the treatment of relapsing forms of MS
   (*If client has preferred agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)
   OR
c. The patient’s medication history includes the use of Tysabri
   AND
   ii. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis
   AND
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:** 12 months

**Initial Evaluation**

**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. There is documentation that the patient is currently being treated with the requested agent
   OR
   b. The patient has the diagnosis of Crohn’s Disease (CD) and meets 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. aminosalicylates, metronidazole, ciprofloxacin, corticosteroids, methotrexate, or immunomodulators such as azathioprine or 6-mercaptopurine)
         OR
2. The patient has a documented intolerance, FDA labeled contraindications, or hypersensitivity to at least one conventional CD therapy
   OR
3. The patient’s medication history indicates the patient has previously failed a biologic immunomodulator agent indicated for CD therapy
   AND
   ii. ONE of the following:
      1. The patient's medication indicates use of one (preferred*) biologic agent
         (*If client has a preferred agent: adalimumab [Humira] or Stelara [ustekinumab]) for the treatment of CD
         OR
      2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one (preferred*) biologic agent for the treatment of CD
         (*If client has a preferred agent: adalimumab [Humira] or Stelara [ustekinumab])
         OR
   c. The patient has a diagnosis of a relapsing form of multiple sclerosis (MS) and meets BOTH of the following:
      i. ONE of the following:
         1. The patient has highly active disease and is naïve to disease modifying agent therapy for MS and meets ALL of the following:
            a. ≥2 relapses in the previous year
            AND
            b. ≥1 gadolinium enhancing lesion on MRI
            AND
            c. If the patient is John Cunningham virus (JCV) antibody positive, they do NOT have a prior history of use of immunosuppressives
            AND they have NOT used Tysabri for > 24 months
            OR
      2. ONE of the following:
         a. The patient’s medication history includes the use of TWO (preferred*) disease modifying agents for the treatment of relapsing forms of MS
            (*If client has preferred disease modifying agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)
            OR
b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to TWO (preferred*) disease modifying agents for the treatment of relapsing forms of MS
   (*If client has preferred agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebi, or Tecfidera)
   OR

  c. The patient’s medication history includes use of Lemtrada

    AND

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

    AND

  4. The prescribed dose is within FDA labeling

**Length of approval:** 16 weeks for Crohn’s disease and 12 months for all other FDA labeled diagnosis

**Renewal Evaluation**

**Ocrevus (ocrelizumab), Tysabri (natalizumab) or Lemtrada (alemtuzumab)** 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.

   AND

2. The patient has had clinical benefit from treatment with the requested agent

   AND

3. If requesting Lemtrada, the patient will be receiving anti-viral prophylaxis for herpetic viral infections

   AND

4. ONE of the following:
   
   a. The patient is not currently being treated with an additional disease modifying agent (DMA) for the requested indication

   OR

   b. The patient is currently being treated with an additional DMA for the requested indication AND the DMA will be discontinued before continuing with the requested agent

   AND

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

   AND

6. The prescribed dose is within FDA labeling

**Length of Approval:** 12 months
## Program Quantity Limits

<table>
<thead>
<tr>
<th>Agent</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lemtrada</strong> (alemtuzumab)</td>
<td>12 mg/1.2 mL 5 vials/365 days</td>
</tr>
<tr>
<td><strong>Ocrevus</strong> (ocrelizumab)</td>
<td>300 mg/10 mL vial 2 vials/180 days</td>
</tr>
<tr>
<td><strong>Tysabri</strong> (natalizumab)</td>
<td>300 mg/15 mL vial 1 vial/28 days</td>
</tr>
</tbody>
</table>

## Contraindications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lemtrada</strong> (alemtuzumab)</td>
<td>Infection with Human Immunodeficiency Virus (HIV)</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. |

## Table 3: Contraindicated Concomitant Medications

<table>
<thead>
<tr>
<th>Lemtrada, Ocrevus, or Tysabri</th>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriflunomide</td>
<td>Aubagio</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Actemra</td>
<td></td>
</tr>
<tr>
<td>Alefacept</td>
<td>Amevive</td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Cinzia</td>
<td></td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Cosentyx</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td></td>
</tr>
<tr>
<td>Anakinra</td>
<td>Kineret</td>
<td></td>
</tr>
<tr>
<td>Abatacept</td>
<td>Orencia</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Rituxan</td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>Simponi</td>
<td></td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Stelara</td>
<td></td>
</tr>
<tr>
<td>Rilonacept</td>
<td>Arcalyst</td>
<td></td>
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<tr>
<td>Canakinumab</td>
<td>Ilaris</td>
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<tr>
<td>Interferon beta-1a</td>
<td>Avonex</td>
<td></td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td>Betaseron</td>
<td></td>
</tr>
<tr>
<td>Peginterferon beta-1a</td>
<td>Plegidy</td>
<td></td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Tecfidera</td>
<td></td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td>Extavia</td>
<td></td>
</tr>
<tr>
<td>Glatiramer</td>
<td>Copaxone</td>
<td></td>
</tr>
<tr>
<td>Glatiramer</td>
<td>Glatopa</td>
<td></td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Gilenya</td>
<td></td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>Rebif</td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Zinbryta</td>
<td></td>
</tr>
<tr>
<td>ocrelizumab</td>
<td>Ocrevus</td>
<td></td>
</tr>
</tbody>
</table>
RATIONALE

Multiple Sclerosis
Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system. It is characterized by demyelination of nerves leading to decreased or improper nerve function. MS affects an estimated 2.3 million people worldwide, is more common among women than men, and has a mean age of onset of 28 to 31 years. MS is categorized into three different types depending on disease presentation.

Types of Multiple Sclerosis

<table>
<thead>
<tr>
<th>Types of MS</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Relapsing-Remitting MS (RRMS) | • Patients experience defined periods of disease relapses followed by full recovery or recovery with sequelae and residual deficit after recovery.  
• RRMS is the most common type of MS accounting for 80% – 90% of MS patients. |
| Secondary-Progressive MS (SPMS) | • Initial disease course is similar to RRMS followed by gradual disease worsening with or without periods of relapses or remission.  
• Transition from RRMS to SPMS usually takes 10 to 20 years from disease onset. |
| Primary progressive MS (PPMS) | • Characterized by worsening of neurologic function from disease onset without early relapses or remissions.  
• PPMS is further categorized into active PPMS in patients who experience occasional relapses or inactive in patients without relapses.  
• PPMS Accounts for about 10% of patients with MS |

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. These include 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), dimethyl fumarate (Tecfidera) and Zinbryta (daclizumab).

Guidelines from the United States and Europe consider glatiramer or interferon beta (INFβ) as appropriate first line agents for treatment of relapsing remitting multiple sclerosis. 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. The manufacturer 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.

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).
Tysabri, (natalizumab), Lemtrada (alemtuzumab), and Ocrevus (ocrelizumab)

Safety 1,13
Tysabri (natalizumab) has a boxed warning for increasing the risk of PML and is contraindicated in patients who have had or who have PML. It is also contraindicated 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.1

Lemtrada (alemtuzumab) has boxed warnings for serious (including fatal) autoimmune conditions, serious and life-threatening infusion site reactions, and increased risk of malignancies. Alemtuzumab is contraindicated in patients with HIV infection.

The most common adverse reactions (in approximately ≥10% of patients and greater than interferon beta [IFNB-1a]) include headache, rash, pyrexia, nasopharyngitis, nausea, fatigue, urinary tract infection, urticaria, insomnia, pruritus, upper respiratory tract infection, pain in extremity, arthralgia, back pain, paraesthesia, diarrhea, oropharyngeal pain, sinusitis, vomiting, dizziness, confusion, chills and flushing. Most were reported as infusion associated reactions.

Crohn’s Disease (CD)
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.8

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-aminosalicyclic 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.

The American College of Gastroenterology (ACG) practice guidelines for CD in adults (2009)9 recommend treatment for mild to moderate CD with oral aminosalicylates (mesalamine and sulfasalazine), antibiotics (metronidazole or ciprofloxacin), and corticosteroid treatment.9,10 For moderate to severe disease, systemic corticosteroids in combination with thiopurines such as azathioprine or 6-mercaptopurine (6-MP) are effective.9 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).9,11,12 The 2009 ACG guidelines for CD9 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.9
There is growing evidence to support treatment of naïve patients with highly active RRMS with natalizumab.\textsuperscript{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).\textsuperscript{18,19}

There is evidence to support natalizumab 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).\textsuperscript{18,19} 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.\textsuperscript{2} Patients should also be monitored regularly as some patients will seroconvert (approximately 2-3% of patients).\textsuperscript{17,18}

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.\textsuperscript{18}

**Ocrevus (ocrelizumab) for treatment of multiple sclerosis**

**Safety\textsuperscript{20}**

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.

**Efficacy\textsuperscript{20}**

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.
therapy for the treatment of CD (e.g. aminosalicylates, metronidazole, ciprofloxacin, corticosteroids, methotrexate, or immunomodulators such as azathioprine or 6-mercapto purine) OR
b) The patient has a documented intolerance, FDA labeled contraindications, or hypersensitivity to conventional CD therapy AND
2) One of the following:
a) The patient’s medication indicates use of one (preferred*) biologic agent (*If client has a preferred agent: adalimumab [Humira]) for the treatment of CD OR
b) The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one (preferred*) biologic agent for the treatment of CD (*If client has a preferred agent: adalimumab [Humira]) AND
iii. If Tysabri AND relapsing forms of MS, ONE of the following:
1) The patient’s medication history includes the use of at least 2 (preferred*) agents for the treatment of relapsing forms of MS (*If client has preferred agents: Betaseron, Copaxone, Plegridy, Rebif, or Tecfidera) OR
2) The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to two (preferred*) agents for the treatment of relapsing forms of MS (*If client has preferred agents: Betaseron, Copaxone, Plegridy, Rebif, or Tecfidera)” Renewal Evaluation
\[\text{Added Items 2, 2 a, and 2 b:}\]
“2. If Tysabri for MS, ALL of the following:
a. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis
b. ONE of the following:”
\[\text{In Item 2 b i added “a sustained reduction from BASELINE EDSS by ≥1” and removed shown clinical benefit with the requested agent” to read “The patient has a sustained reduction from BASELINE EDSS by ≥1”}\]
\[\text{Added Item 2 b ii “The patient has had a reduction > 1 point from BASELINE in annualized relapse rate”}\]
\[\text{Added Item 3}\]
“3. If the request is for Lemtrada, ALL of the following:
a. The patient will be receiving anti-viral prophylaxis for herpetic viral infections AND
b. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis AND
c. ONE of the following:
i. The patient has a sustained reduction from BASELINE EDSS by ≥1 OR
ii. The patient has had a reduction > 1 point from BASELINE in annualized relapse rate”
\[\text{Removed “If the request is for Lemtrada, the patient will be receiving anti-viral prophylaxis for herpetic viral infections”}\]
\[\text{In Item 4 added “with the requested agent” to read “The patient does not have any FDA labeled contraindications to therapy with the requested agent”}\]

Rationale section updated
References updated

04-01-2017 The policy was updated to accomplish the following:
\[\text{Added Stelara to the list of preferred drugs that the patient can have tried before approval of Tysabri for treatment of Crohn’s disease}\]
\[\text{Updated the table of FDA labeled contraindications}\]
\[\text{Addition of Inflectra, Remicade, and Silig to the list of contraindicated concomitant agents}\]

Updated Description section:
In Policy section:
### REVISIONS

**Initial Evaluation**
- In Item 2 removed "therapy with" to read "The patient does not have any FDA labeled contraindications with the requested agent"
- In Item 3 b ii added "ONE of the following:
  a. The patient's medication history includes the use of TWO* agents for the treatment of relapsing forms of multiple sclerosis (MS) (*If client has preferred agent(s), the patient must try TWO of the following: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera) OR
  b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to TWO* agents for the treatment of relapsing forms of MS (*If client has preferred agent(s), the patient must try TWO of the following: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera) OR
  c. The patient’s medication history includes the use of Tysabri"
- In Items 3 b iii and 3 c ii added "requested" to read "The requested agent…"
- In Item 3 c added "BOTH" and removed "ALL" to read "Tysabri is prescribed AND the patient has a diagnosis of a relapsing form of MS, BOTH of the following:"  
  a. The patient has highly active disease and is naïve to disease modifying agent therapy for MS and ALL of the following:
  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)  
  ii. ONE of the following:
    a. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least one conventional CD therapy OR
    b. The patient’s medication history indicates the patient has previously failed a biologic immunomodulator agent indicated for CD AND
  
  i. ONE of the following:
    a. 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
    b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least one conventional CD therapy OR
    c. The patient’s medication history indicates the patient has previously failed a biologic immunomodulator agent indicated for CD AND
REVISIONS

iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit‘
   • In Length of Approval "removed "MS with Tysabri or Lemtrada" and added "for any other FDA labeled diagnosis" to read "12 months for any other FDA labeled diagnosis"
   • Revised Items 2 and 3 from: "2. If Tysabri for MS, ALL of the following:
     a. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis AND
     b. ONE of the following:
        i. The patient has a sustained reduction from BASELINE EDSS by ≥1 OR
        ii. The patient has had a reduction > 1 point from BASELINE in annualized relapse rate
        AND
     3. If the request is for Lemtrada, ALL of the following:
        a. The patient will be receiving anti-viral prophylaxis for herpetic viral infections AND
        b. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis AND
        c. ONE of the following:
           i. The patient has a sustained reduction from BASELINE EDSS by ≥1 OR
           ii. The patient has had a reduction > 1 point from BASELINE in annualized relapse rate" to "2. The patient has had clinical benefit from treatment with the requested agent AND
     3. If requesting Lemtrada, the patient will be receiving anti-viral prophylaxis for herpetic viral infections"
   • Added Item 5 "ONE of the following:
     a. The quantity requested (dose) is less than or equal to the program quantity limit OR
     b. ALL of the following:
        i. The requested quantity (dose) is greater than the program quantity limit AND
        ii. The requested quantity (dose) is less than or equal to the FDA labeled dose AND
        iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit"
   • Updated Contraindications chart
   • Added Contraindicated Concomitant Medications chart.

Rationale section updated
References updated


Title updated to include Ocrevus (ocrelizumab) to read "Tysabri (natalizumab), Lemtrada (alemtuzumab), and Ocrevus (ocrelizumab) (IV Multiple Sclerosis Agents)"

Description section updated

In Policy section:
   • Added Ocrevus criteria of:
     "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 AND
     2. The patient does not have any FDA labeled contraindications to therapy with the requested agent AND
     3. ONE of the following:
        a. There is documentation that the patient is currently being treated with the requested agent OR
<table>
<thead>
<tr>
<th>REVISIONS</th>
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<tr>
<td>b. The patient has a diagnosis of a relapsing form of multiple sclerosis and meets BOTH of the following:</td>
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<tr>
<td>i. ONE of the following:</td>
</tr>
<tr>
<td>1) The patient’s medication history includes the use of TWO (preferred*) disease modifying agents for the treatment of relapsing forms of MS (*If client has preferred disease modifying agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera) OR</td>
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<tr>
<td>2) The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to TWO (preferred*) disease modifying agents for the treatment of relapsing forms of MS (*If client has preferred agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera) AND</td>
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<tr>
<td>ii. The requested agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis OR</td>
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<td>c. The patient has a diagnosis of a primary progressive form of multiple sclerosis and meets the following:</td>
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<tr>
<td>ii. The requested agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis OR</td>
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<td>d. The patient has another FDA labeled diagnosis AND</td>
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<td>4. If starting therapy, the patient has been tested for hepatitis B virus and determined to not have active hepatitis B viral infection AND</td>
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<td>5. The prescribed dose is within the FDA approved labeling Length of approval: 12 months.</td>
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<td>NOTE: For patients initiating therapy, approval will include two initial 300 mg loading doses (2 vials) and two 600 mg maintenance doses (4 vials).</td>
</tr>
</tbody>
</table>

- Removed Tysabri from the following Tysabri or Lemtrada criteria to reflect only Lemtrada criteria (see policy): |
  "Tysabri® (natalizumab) or Lemtrada™ (alemtuzumab) 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. AND |
  2. The patient has had clinical benefit from treatment with the requested agent AND |
  3. If requesting Lemtrada, the patient will be receiving anti-viral prophylaxis for herpetic viral infections AND |
  4. ONE of the following: |
  a. The patient is not currently being treated with an additional disease modifying agent (DMA) for the requested indication OR |
  b. The patient is currently being treated with an additional DMA for the requested indication AND the DMA will be discontinued before continuing with the requested agent AND |
  3. The patient does not have any FDA labeled contraindications to the requested agent AND |
  4. ONE of the following: |
  a. The quantity requested (dose) is less than or equal to the program quantity limit OR |
  b. ALL of the following: |
  i. The requested quantity (dose) is greater than the program quantity limit AND |
  ii. The requested quantity (dose) is less than or equal to the FDA labeled dose AND |
  iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit Length of Approval: 12 months* |

- Added the following stand-alone Tysabri criteria: |
  "Tysabri® (natalizumab) will be approved when ALL of the following are met: |
  1. ONE of the following:
### REVISIONS

| 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. | There is documentation that the patient is currently being treated with the requested agent OR |
| b. | The patient has the diagnosis of Crohn’s Disease (CD) and meets 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. aminosalicylates, metronidazole, ciprofloxacin, corticosteroids, methotrexate, or immunomodulators such as azathioprine or 6-mercaptopurine) OR |
| 2. | The patient has a documented intolerance, FDA labeled contraindications, or hypersensitivity to at least one conventional CD therapy OR |
| 3. | The patient’s medication history indicates the patient has previously failed a biologic immunomodulator agent indicated for CD therapy AND |
| ii. | ONE of the following: |
| 1. | The patient’s medication indicates use of one (preferred*) biologic agent (*If client has a preferred agent: adalimumab [Humira] or Stelara [ustekinumab]) for the treatment of CD OR |
| 2. | The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one (preferred*) biologic agent for the treatment of CD (*If client has a preferred agent: adalimumab [Humira] or Stelara [ustekinumab]) OR |
| c. | The patient has a diagnosis of a relapsing form of multiple sclerosis (MS) and meets BOTH of the following: |
| i. | ONE of the following: |
| 1. | The patient has highly active disease and is naïve to disease modifying agent therapy for MS and meets ALL of the following: |
| a. | ≥2 relapses in the previous year AND |
| b. | ≥1 gadolinium enhancing lesion on MRI AND |
| c. | If the patient is John Cunningham virus (JCV) antibody positive, they do NOT have a prior history of use of immunosuppressives AND they have NOT used Tysabri for > 24 months OR |
| 2. | ONE of the following: |
| a. | The patient’s medication history includes the use of TWO (preferred*) disease modifying agents for the treatment of relapsing forms of MS (*If client has preferred disease modifying agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera) OR |
| b. | The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to TWO (preferred*) disease modifying agents for the treatment of relapsing forms of MS (*If client has preferred agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera) OR |
| c. | The patient’s medication history includes use of Lemtrada AND |
| ii. | The requested agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis AND |
| 4. | The prescribed dose is within FDA labeling |

Length of approval: 16 weeks for Crohn’s disease and 12 months for all other FDA labeled diagnosis
REVISIONS

Renewal Evaluation

- Added "Ocrevus (ocrelizumab) to read "Ocrevus (ocrelizumab), Tysabri® (natalizumab) or Lemtrada™ (alemtuzumab) will be renewed when ALL of the following are met:" 
- In Item 6 added "The prescribed dose is within FDA labeling"
- Removed "ONE of the following:
  a. The quantity requested (dose) is less than or equal to the program quantity limit OR
  b. ALL of the following:
     i. The requested quantity (dose) is greater than the program quantity limit AND
     ii. The requested quantity (dose) is less than or equal to the FDA labeled dose AND
     iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit"
- Added Ocrevus to the Program Quantity Limits, Contraindications and Contraindicated Concomitant Medications tables
- Updated the Contraindicated Concomitant Medications chart
- Rationale section updated
- References updated

REFERENCES

2. Deleted.
3. Deleted.
8. Deleted.
14. Deleted