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

See Also: Multiple Sclerosis Agents

Prime Therapeutics will review Prior Authorization requests

Prior Authorization Form:

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

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

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

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

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 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 Tysabri or Lemtrada for patients with MS who have failed to respond to or have intolerance to preferred first line and/or conventional therapies used to treat these conditions, who do not have any FDA labeled contraindications to therapy, and with appropriate FDA labeled dosing. The program will also approve Tysabri or Lemtrada for MS for patients who have failed Lemtrada or Tysabri respectively. Tysabri will also be approved after conventional therapies and biologic therapy for Crohn’s disease.

Agents
- **Tysabri®** (natalizumab)
- **Lemtrada™** (alemtuzumab)

FDA Labeled Dosing

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Dosing</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemtrada™ (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>Multiple sclerosis</td>
</tr>
<tr>
<td>Tysabri® (natalizumab)</td>
<td>300 mg intravenously every 4 weeks</td>
<td>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.
POLICY

Initial Criteria

Tysabri or Lemtrada 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. Lemtrada (alemtuzumab) is prescribed AND the patient has a diagnosis of a relapsing form of MS, ALL of the following:
      i. The patient will be receiving anti-viral prophylaxis for herpetic viral infections
      AND
      ii. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis
   OR
   c. Tysabri is prescribed AND the patient has the diagnosis of a relapsing form of MS, ALL of the following:
      i. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis
      AND
      ii. The patient has highly active disease and is naïve to therapy and ALL of the following:
         a) \( \geq 2 \) relapses in the previous year
         AND
         b) \( \geq 1 \) 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
   d. The patient has another FDA labeled diagnosis for the requested agent

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

**Length of Approval:** 12 months for MS with Tysabri or Lemtrada and
16 weeks for CD with Tysabri

**Renewal Evaluation**

**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. 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
   
      **AND**

4. ONE of the following:
   - The patient is not currently being treated with an additional disease modifying agent (DMA) for the requested indication
   
     **OR**
   - 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**
4. The patient does not have any FDA labeled contraindications to therapy with the requested agent

AND

5. The prescribed dosage is within the FDA approved labeled dosage

**Length of Approval:** 12 months

### FDA Labeled Contraindications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemtrada (alemtuzumab)</td>
<td>Patients with hypersensitivity reactions, HIV infected patients, patients with active or latent tuberculosis, patients with severe active infections, active malignancies, patients on antineoplastic or immunosuppressive therapies, and patients with a history of progressive multifocal leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>Tysabri (natalizumab)</td>
<td>Patients who have or have had (PML). Patients who have had a hypersensitivity reaction to natalizumab.</td>
</tr>
</tbody>
</table>

### Program Quantity Limits

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemtrada (alemtuzumab)</td>
<td>12 mg/1.2 mL</td>
</tr>
<tr>
<td>Tysabri (natalizumab)</td>
<td>300 mg/15 mL vial</td>
</tr>
</tbody>
</table>

**RATIONALE**

**Description**

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. 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 relapsing-remitting (RRMS [≈85% of cases]); secondary progressive (SPMS); primary progressive (PPMS); and progressive-relapsing (PRMS).

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.1

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.13

Safety

**Natalizumab and Progressive Multifocal Leukoencephalopathy (PML)**

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.2 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.2 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.3

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.1

**Alemtuzumab and Progressive Multifocal Leukoencephalopathy (PML)**

Lemtrada (alemtuzumab) has a boxed warning for PML. It has been reported in B-cell chronic lymphocytic leukemia (B-CLL) patients with or without alemtuzumab treatment. The frequency is no greater than background frequency. Alemtuzumab has additional boxed warnings for serious (including fatal) autoimmune conditions such immune thrombocytopenic purpura and anti-glomerular basement membrane disease and opportunistic infections including serious and
Tysabri, (natalizumab) and Lemtrada (alemtuzumab) and sometimes fatal viral, bacterial, protozoan, and fungal infections. These infections have been reported in non-MS patients at a higher and more frequent dose than used in the treatment of MS. Antiviral prophylaxis for herpes is strongly recommended.

Contraindications to therapy with alemtuzumab include hypersensitivity reactions, HIV infected patients, patients with active or latent tuberculosis, patients with severe active infections, active malignancies, patients on antineoplastic or immunosuppressive therapies, and patients with a history of PML.13

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, contusion, chills and flushing. Most were reported as infusion associated reactions.

**FDA Labeled Indication (Category A, B or C)**

Pivotal clinical trial data for each of the products can be accessed in the prescribing information.

**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), and dimethyl fumarate (Tecfidera).7

Guidelines from the United States and Europe consider glatiramer and interferon beta (INF β) 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 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.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

**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
Tysabri, (natalizumab) and Lemtrada (alemtuzumab) and 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. Surgical interventions are reserved for treating complications and controlling symptoms but surgical resection is not curative.\(^8\)

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 (controlled-release budesonide or other conventional corticosteroids).\(^9,10\) For moderate to severe disease, 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 CD\(^9\) 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-\(\alpha\) monoclonal antibody therapy.\(^9\)

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).\(^18,19\) 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.\(^2\) Patients should also be monitored regularly as some patients will seroconvert (approximately 2-3% of patients).\(^17,18\)

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.\(^18\)
REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>05-15-2015</td>
<td>Policy added to the bcbsks.com web site.</td>
</tr>
<tr>
<td>05-01-2016</td>
<td>Policy published 04-29-2016. Policy effective 05-01-2016.</td>
</tr>
<tr>
<td></td>
<td>Description section updated</td>
</tr>
</tbody>
</table>

In Policy Section:

Initial Evaluation

- In Item 3 b added “is prescribed” and “the patient has a diagnosis of a” to read “Lemtrada (alemtuzumab) is prescribed AND the patient has a diagnosis of a relapsing form of MS, ALL of the following:”
- Added Item 3 c “Tysabri is prescribed AND the patient has the diagnosis of a relapsing form of MS, ALL of the following:
  i. The agent is prescribed by or in consultation with a neurologist experienced in multiple sclerosis AND
  ii. The patient has highly active disease and is naïve to therapy and 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”
- Removed the following criteria related to use of preferred medications before use of Tysabri or Lemtrada:
  “3) ONE of the following:
   a) 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
   b) 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) AND
   ii. If Tysabri AND CD, ALL of the following:
      1) 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 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
• 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:”
• 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”
• Added Item 2 b ii “The patient has had a reduction > 1 point from BASELINE in
  annualized relapse rate”
• 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”
• Removed “If the request is for Lemtrada, the patient will be receiving anti-viral
  prophylaxis for herpetic viral infections”
• 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

REFERENCES
1. Tysabri prescribing information. Accessed November 2015. Available at:
   4f3323ea2962.
2. FDA Medwatch. Natalizumab MedWatch Alert. 2/5/2010. Available at:
3. FDA Medwatch. New risk factor for Progressive Multifocal Leukoencephalopathy (PML)
   associated with Tysabri (natalizumab). Available at:
   10/23/12.
   sclerosis. Report of the Therapeutics and Technology Assessment Subcommittee of the
   American Academy of Neurology and the MS Council for Clinical Practice Guidelines.
   Reaffirmed 9/24/2010. Neurology 2002;58;169-178 Available at:
5. National Multiple Sclerosis Society Disease Management Consensus Statement-
   Recommendations from the MS Information Sourcebook; 2007 Update. National Multiple
   Sclerosis Society. Available at: http://www.nationalmssociety.org/for-professionals/


