Medical Policy

BlueCross BlueShield of Kansas
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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:
  http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-KS-IV-MS.pdf

  Link to Drug List (Formulary):
  https://www.bcbsks.com/drugs/

Professional	**Institutional**
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Current Effective Date: September 1, 2018	Current Effective Date: September 1, 2018

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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 who have an FDA approved indication for the agent. For the diagnosis of relapsing and remitting multiple sclerosis, one preferred agent will be required prior to use of Tysabri and two preferred agents will be required for other requested agents. The program will require patients requesting Tysabri for Crohn's disease to have tried 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 Approved Indications and Dosage [1-3]

Agent	Indication	Dosing
Lemtrada® (alemtuzumab)* intravenous infusion	▪ Relapsing forms of multiple sclerosis (RRMS)	**RRMS**: 12mg administered by intravenous infusion for 2 treatment courses: ▪ First course: 12 mg on 5 consecutive days (total of 60 mg) ▪ Second course: 12 mg on 3 consecutive days (total of 36 mg) 12 months after first initial treatment course
Ocrevus™ (ocrelizumab) intravenous infusion	▪ Relapsing forms of multiple sclerosis ▪ Primary progressive forms of multiple sclerosis (PPMS)	**PPMS/RRMS**: ¥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
Tysabri® (natalizumab) intravenous infusion	▪ Relapsing forms of multiple sclerosis ▪ Moderately to severely active Crohn's Disease	**RRMS**: 300 mg intravenously every 4 weeks **CD**: 300 mg intravenously every 4 weeks^

^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.

POLICY

Prior Authorization and Quantity Limit Criteria for Approval

Initial Evaluation

Lemtrada (alemtuzumab) will be approved when ALL of the following are met:

1. ONE of the following:
   - A. There is documentation that the patient is currently being treated with the requested agent within the past 90 days
     OR
   - B. The prescriber states that the patient is currently being treated with the requested agent AND is at risk if therapy is changed
     OR
   - C. The patient has a diagnosis of a relapsing form of multiple sclerosis (MS) and meets ONE of the following:
     - i. The patient's medication history includes the use of TWO* DMAs 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
     - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to TWO* DMAs 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
     - iii. The patient's medication history includes use of Tysabri
       OR
   - D. The patient has another FDA approved diagnosis for the requested agent

   AND
2. The patient will be receiving anti-viral prophylaxis for herpetic viral infections
   AND
3. The prescriber is a neurologist or the prescriber has consulted with a neurologist
   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 starting the requested agent

   AND

5. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
6. One of the following:
   A. The patient has NOT received treatment with the requested agent
      OR
   B. The patient has received treatment with the requested agent **AND** BOTH of the following:
      i. The patient has NOT received more than 2 treatment courses with the requested agent
         AND
      ii. The prescriber has provided the number of doses and treatment courses the patient has received

   AND
7. ONE of the following:
   A. The requested quantity (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; for the diagnosis of RRMS approve for remainder of annual dose, up to 5 doses for first treatment course and up to 3 doses for second treatment course

Initial Evaluation

Ocrevus (ocrelizumab) will be approved when ALL of the following are met:

1. ONE of the following:
   A. There is documentation that the patient is currently being treated with the requested agent within the past 90 days
   OR
   B. The prescriber states the patient is currently being treated with the requested agent AND is at risk if therapy is changed
   OR
   C. The patient has a diagnosis of a relapsing form of multiple sclerosis and ONE of the following:
      i. 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
      ii. 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
   D. The patient has a diagnosis of a primary progressive form of multiple sclerosis
   OR
   E. The patient has another FDA approved indication for the requested agent

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

   AND
3. The prescriber is a neurologist or the prescriber has consulted with a neurologist

   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 starting the requested agent

   AND
5. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

   AND

6. ONE of the following:
   A. The requested quantity (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.
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

Tysabri (natalizumab) will be approved when ALL of the following are met:
1. ONE of the following:
   A. There is documentation that the patient is currently being treated with the requested agent within the past 90 days
      OR
   B. The prescriber states the patient is currently being treated with the requested agent AND is at risk if therapy is changed
      OR
   C. The patient has a diagnosis of Crohn's Disease (CD) and ALL of the following:
      i. The requested agent will NOT be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate)
         AND
      ii. ONE of the following:
         a. The patient's medication history includes the use of ONE conventional therapy for 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 contraindications, or hypersensitivity to at least ONE conventional therapy for CD
            OR

c. The patient's medication history indicates the patient has failed ONE biologic immunomodulator FDA approved for the treatment of CD

AND

iii. ONE of the following:

a. The patient's medication history indicates use of ONE (preferred*) biologic agent for the treatment of CD (*If client has a preferred agent: Humira [adalimumab] or Stelara [ustekinumab])

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: Humira [adalimumab] or Stelara [ustekinumab])

OR

D. The patient has a diagnosis of a relapsing form of multiple sclerosis (MS) and meets ONE of the following:

i. The patient has highly active disease and is naïve to disease modifying agent therapy for MS **AND** BOTH of the following:

a. The patient has ≥2 relapses in the previous year

AND

b. The patient has ≥1 gadolinium enhancing lesion on MRI

OR

ii. ONE of the following:

a. The patient's medication history includes the use of ONE (preferred*) disease modifying agent 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 ONE (preferred*) disease modifying 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 Lemtrada

OR

E. The patient has another FDA approved indication for the requested agent

AND

2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist for the diagnosis of Crohn's Disease or neurologist for the diagnosis of MS) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

3. 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 currently being treated with an additional DMA for the requested indication and the DMA will be discontinued before starting the requested agent

   AND
4. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

   AND
5. ONE of the following:
   A. The requested quantity (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: 16 weeks for Crohn's disease and
12 months for all other FDA labeled diagnosis

Renewal Evaluation

Lemtrada (alemtuzumab), Ocrevus (ocrelizumab), or Tysabri (natalizumab) will be approved when ALL 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 an FDA approved indication for the requested agent
   AND
3. The patient has had clinical benefit from treatment with the requested agent
   AND
4. If requesting Lemtrada, then ALL of the following:
   A. The patient will be receiving anti-viral prophylaxis for herpetic viral infections
      AND
   B. The patient has NOT received more than 2 treatment courses with the requested agent
      AND
   C. The prescriber has provided the number of doses and treatment courses the patient has received
   AND
5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist for the diagnosis of Crohn's Disease or neurologist for the diagnosis of MS) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
6. 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
7. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND

8. ONE of the following:
   A. The requested quantity (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

Program Quantity Limits	
Agent	**Quantity Limit**
Lemtrada (alemtuzumab)	
12 mg/1.2 mL	5 vials/365 days
Ocrevus (ocrelizumab)	
300 mg/10 mL vial	2 vials/180 days
Tysabri (natalizumab)	
300 mg/15 mL vial	1 vial/28 days

FDA Labeled Contraindications	
Agent	**Contraindications**
Lemtrada (alemtuzumab)	Infection with Human Immunodeficiency Virus (HIV)
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.

Contraindicated Concomitant Medications	
Actemra (tocilizumab)	Orencia (abatacept)
Arcalyst (rilonacept)	Otezla (apremilast)
Aubagio (terifluonmide)	Plegridy (peginterferon beta-1a)
Avonex (interferon beta-1a)	Rebif (interferon beta-1a)
Betaseron (interferon beta-1b)	Remicade (infliximab)
Cimzia (certolizumab)	Renflexis (infliximab-abda)
Copaxone (glatiramer)	Rituxan (rituximab)
Cosentyx (secukinumab)	Rituxan Hycela (rituximab/hyaluronidase human)
Enbrel (etanercept)	Siliq (brodalumab)
Entyvio (vedolizumab)	Simponi (golimumab)

Contraindicated Concomitant Medications	
Extavia (interferon beta-1b)	Simponi ARIA (golimumab)
Gilenya (finglimod)	Stelara (ustekinumab)
Glatopa (glatiramer)	Stelara ARIA (ustekinumab)
Humira (adalimumab)	Taltz (ixekizumab)
Ilaris (canakinumab)	Tecfidera (dimethyl fumerate)
Inflectra (infliximab-dyyb)	Tremfya (quselkumab)
Kevzara (sarilumab)	Tysabri (natalizumab)
Kineret (anakinra)	Xeljanz (tofacitinib)
Lemtrada (alemtuzumab)	Xeljanz XR (tofacitinib extended release)
Ocrevus (ocrelizumab)	Zinbryta (daclizumab)
Olumiant (baricitinib)	

RATIONALE

Multiple Sclerosis

Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelization, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, visual disturbances, and elimination dysfunction), resulting in a significant impact on quality of life for patients and their families. Diagnosis of MS is primarily based on clinical presentation. The core requirement for the diagnosis is demonstration of CNS lesion dissemination and presence of symptoms such as visual loss, motor function loss, difficulty with balancing, and vertigo. There are currently four major types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).[4] RRMS is characterized by clearly defined relapses with either full recover or with sequelae and residual deficit upon recovery. There is no or minimal disease progression during the periods between disease relapses, though individual relapses may result in severe residual disability.[5] Majority, about 85-90%, of individuals with MS demonstrate a relapsing pattern at onset, which transitions over time in the majority of untreated patients to a pattern of progressive worsening with few or no relapses or MRI activity (SPMS). SPMS begins as RRMS, but over time the disease enters a stage of steady deterioration in function, unrelated to acute attacks. Typically, when SSMS stage is reached, the relapse rate is also reduced. SPMS develops in approximately 90% of patients with RRMS after 25 years and causes the greatest amount of neurologic disability. PPMS represents only about 10 percent of MS cases and is characterized by disease progression from onset, although occasional plateaus, temporary minor improvements, and acute relapses may occur.[5]

Treatment directed at PPMS is typically more difficult than treatment of RRMS and recommendations differ between the different forms of MS. There are a number of effective disease modifying agents (DMAs) available for RRMS and only one DMA for PPMS.[5] Prior to disease modifying treatments, approximately half of patients diagnosed with relapsing MS would progress to secondary progressive MS by 10 years, and 80-90% would do so by 25 years. Approximately half of patients would no longer be able to walk unaided by 15 years.[4] Most of the

treatment options for progressive types of MS involve various immunosuppressive therapies, such as azathioprine, cladribine, glucocorticosteroids, cyclophosphamide, cyclosporine, immune globulins, methotrexate, and DMAs. However, nonspecific immunosuppressants may temporarily halt a rapidly progressive course but it is difficult to employ them for more than a few months to a year or two.[5]

The goal of treatment with DMAs is to reduce early clinical and sub-clinical disease activity that is thought to contribute to long-term disability. Given the medications that are currently available – all of which primarily target inflammation – the optimal window for impacting long-term disability is during the early relapsing phase of the disease, with the goal being to slow the accumulation of lesion volume, decrease the number of relapses and prevent disability from both unresolved relapses and disease progression. Currently available therapies reduce relapse rates and MRI lesion accumulation in RRMS, in varying extents. There are few comparison trials, so information for comparative efficacy is inferential.[4-6] Guidelines recommend initiation of treatment with DMA as soon as possible following diagnosis of RRMS or PPMS.[4-7] Suggested initial treatment approach includes the following:

- Infusion therapy with natalizumab for patients with more active disease and for those who value effectiveness above safety and convenience. A cross-trial comparison and clinical experience showed natalizumab is more effective than interferons, glatiramer, or oral DMAs for patients with RRMS.
- Injection therapy (interferon or glatiramer) for patients who value safety more than effectiveness and convenience. Among these, intramuscular interferon beta-1a 30 mcg weekly or glatiramer acetate is preferred.
- Oral therapy (dimethyl fumarate, teriflunomide, or fingolimod) for patients who value convenience. Dimethyl fumarate is preferred due to being more effective and a better safety profile than the other two agents, although evidence is indirect and inconclusive. The potential teratogenicity of teriflunomide limits its use for a disease where a portion of patients are child-bearing age.[15]

When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.[7]

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).[12] The adverse effects seen with combination therapies are similar to those reported with the individual agents, but it is unclear if the risk for developing these adverse effects is higher in combination therapy. Some of the clinical effects of glatiramer may occur by entry of regulatory glatiramer-reactive cells into the central nervous system (CNS) across a disrupted blood-brain-barrier (BBB) and effects on CNS resident cells. It is possible that combining glatiramer with therapies that close the BBB like INFβ and natalizumab may limit the effectiveness of glatiramer.[12] The benefits of combination therapies and the safety concerns associated with concurrent therapy still need further investigation.

A National MS Society consensus statement recommends changing from one disease modifying therapy to another only for medically appropriate reasons (e.g. lack of efficacy, adverse effects, or if better treatments options become available).[4]

Natalizumab in relapsing remitting multiple sclerosis (RRMS)
There is growing evidence to support treatment of naïve patients with highly active RRMS with natalizumab.[15-17] Highly active relapsing MS is defined as (≥2 relapses in the year prior to therapy and ≥1 gadolinium enhancing lesion on MRI).[16,17]

There is evidence to support natalizumab as first line therapy in a subset of RRMS. Based on the literature, treatment naive 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).[15,16]

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 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.[16]

Crohn's Disease
Crohn's disease (CD) is characterized by focal, asymmetric, transmural, and occasionally, granulomatous inflammation primarily affecting the gastrointestinal (GI) tract. Therapeutic approaches for CD is to induce and maintain symptomatic control, improve quality of life, and minimize short and long term toxicity and complications. Present therapeutic approaches should be considered sequential to treat "acute disease" or "induce clinical remission," and then to "maintain response/remission." Surgery is advocated for neoplastic/preneoplastic lesions, obstructing stenoses, suppurative complications, or medically intractable disease. 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.[12]

Guidelines for CD in adults recommend treatment for mild to moderate CD with oral aminosalicylates (mesalamine and sulfasalazine), antibiotics (metronidazole or ciprofloxacin), and systemic corticosteroid treatment. For moderate to severe disease, systemic corticosteroids in combination with thiopurines such as azathioprine or 6-mercaptopurine (6-MP) are effective. 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.[12,13] Natalizumab is effective in patients who have had an inadequate response or are unable to tolerate conventional CD therapy (aminosalicylates, antibiotics, corticosteroids, immunomodulators) and anti-TNF-α monoclonal antibody therapy.[12,13]

Safety [1-3]

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

REVISIONS	
05-15-2015	Policy added to the bcbsks.com web site.
05-01-2016	Policy published 04-29-2016. Policy effective 05-01-2016.
	Description section updated
	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

REVISIONS	
	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 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)" <u>Renewal Evaluation</u> ▪ 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:

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	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
04-01-2017	The policy was updated to accomplish the following: ▪ Added Stelara to the list of preferred drugs that the patient can have tried before approval of Tysabri for treatment of Crohn's disease ▪ Updated the table of FDA labeled contraindications ▪ Addition of Inflectra, Remicade, and Silig to the list of contraindicated concomitant agents
	Updated Description section:
	In Policy section: <u>Initial Evaluation</u> ▪ 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:" ▪ In Item 3 c i added "ONE of the following:" ▪ In Item 3 c i a added "disease modifying" and "for MS" to read "The patient has highly active disease and is naïve to disease modifying agent therapy for MS and ALL of the following:" ▪ In Item 3 c i added "b. 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 c. 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 d. The patient's medication history includes use of Lemtrada" ▪ Added Item 3 d "Tysabri is prescribed AND the patient has the diagnosis of Crohn's Disease (CD), BOTH of the following: 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

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	b. The patient has a documented intolerance, FDA labeled contraindications, 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 ii. ONE of the following: a. The patient's medication history indicates use of one (preferred*) biologic agent (*If client has a preferred agent: Humira [adalimumab] or Stelara [ustekinumab]) 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: Humira [adalimumab] or Stelara [ustekinumab])" ▪ Added Item 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" ▪ 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" <u>Renewal Evaluation</u> ▪ 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
07-15-2017	Policy published 06-15-2017. Policy effective 07-15-2017.

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	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 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: ii. 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)." ▪ 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

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	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: 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

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	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" <u>Renewal Evaluation</u> ▪ 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
04-01-2018	In Description section: ▪ Updated Description ▪ Updated FDA Labeled Indication and Dosage chart
	In Policy section: <u>Initial Evaluation</u> ▪ In Lemtrada, Ocrevus, and Tysabri items 1 a and 1 b add "additional" to read "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 starting the requested agent" <u>Lemtrada</u> ▪ In Item 3 a added "within the past 30 days" to read "There is documentation that the patient is currently being treated with the requested agent within the past 30 days" ▪ In Items 3 b i and 3 b i b revised to require two disease modifying agents to read "a. The patient's medication history includes the use of TWO* DMAs for the treatment of relapsing forms of MS (*If client has preferred agent(s) the patient must try TWO of

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	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* DMAs 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)" ▪ Added "3 b ii The patient has another FDA approved diagnosis for the requested agent" ▪ In Item 4 added neurologist specialty prescriber language to read "The prescriber is a neurologist or the prescriber has consulted with a neurologist experienced in multiple sclerosis" ▪ Added "6. ONE of the following: a. The requested quantity (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" ▪ Removed "7. The prescribed dose in within the FDA approved labeled dosage" <u>Ocrevus</u> ▪ In Item 3 b removed "meets BOTH" and added "ONE" to read "The patient has a diagnosis of a relapsing form of multiple sclerosis and ONE of the following:" <u>Tysabri</u> ▪ In Item 3 b removed "meets BOTH" and added "ALL" to read "The patient has the diagnosis of Crohn's Disease (CD) and ALL of the following:" ▪ Added "3 b i. The requested agent will NOT be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate)" ▪ In Item 3 b ii 3 removed "previously", "agent indicated" and "therapy" and added "ONE", "FDA approved" and "for treatment of" to read "The patient's medication history indicates the patient has failed ONE biologic immunomodulator FDA approved for the treatment of CD" ▪ In Item 3 c removed "meets BOTH" and added "ALL" to read "The patient has a diagnosis of a relapsing form of multiple sclerosis (MS) and ALL of the following:" ▪ In Item 3 c v 1 and 3 c v 2 removed "TWO" and added "ONE" to read "1. The patient's medication history includes the use of ONE (preferred*) disease modifying agent 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 ONE TWO (preferred*) disease modifying agent for the treatment of relapsing forms of MS (*If client has preferred agents: Aubagio, Avonex, Betaseron, Copaxone, Gilenya, Glatopa, Plegridy, Rebif, or Tecfidera)" ▪ Added "3 d The patient has another FDA approved indication for the requested agent" ▪ Added "4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist for the diagnosis of Crohn's Disease or neurologist for the diagnosis of MS) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND 5. The requested dose is within FDA labeling for the requested indication" <u>Renewal Evaluation</u> ▪ Added "2. The patient has an FDA approved indication for the requested agent" and 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist for the diagnosis of Crohn's Disease or neurologist for the diagnosis of

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	MS) or the prescriber has consulted with a specialist in the area of the patient's diagnosis" ▪ Updated Contraindicated Concomitant Medications chart.
	Rationale section updated
	References updated
09-01-2018	Description section updated to include revisions to the FDA Approved Indications and Dosage chart.
	In Policy section: Summary of revisions: • Lemtrada – limit to 2 treatment courses per FDA label • Tysabri ✓Changed to require patients to either have highly active disease and is naïve to therapy OR has tried ONE preferred ✓Removal of PML risk factors check (JCV antibody positive, prior history of immunosuppressant and Tysabri used > 24 months) – REMS programs and contraindications table lists PML; duplicate requirement • Update quantity limit statements Initial Evaluation Lemtrada In Item 1 A removed "30" and added" 90" to read "...within the past 90 days" In Item 1 added "B. The prescriber states that the patient is currently being treated with the requested agent AND is at risk if therapy is changed" In Item 3 removed "experienced in multiple sclerosis" to read "...has consulted with a neurologist" In Item 6 added "A. The patient has NOT received treatment with the requested agent OR B. The patient has received treatment with the requested agent AND BOTH of the following: i. The patient has NOT received more than 2 treatment courses with the requested agent AND ii. The prescriber has provided the number of doses and treatment courses the patient has received" In Length of Approval added "for the diagnosis of RRMS approve for remainder of annual dose, up to 5 doses for first treatment course and up to 3 doses for second treatment course" to read "12 months; for the diagnosis of RRMS approve for remainder of annual dose, up to 5 doses for first treatment course and up to 3 doses for second treatment course" Ocrevus Removed "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 starting the requested agent AND 2. The patient does NOT have any FDA labeled contraindications to the requested agent" In Item 1 A added "within the past 90 days" In Item 1 added "B. The prescriber states that the patient is currently being treated with the requested agent AND is at risk if therapy is changed" In Item 1 E removed "labeled diagnosis" and added "approved indication for the requested agent" to read "The patient has another FDA approved indication for the requested agent" Added

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	"3. The prescriber is a neurologist or the prescriber has consulted with a neurologist 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 starting the requested agent AND 5. The patient does NOT have any FDA labeled contraindication(s) to the requested agent AND 6. ONE of the following: A. The requested quantity (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" <u>Tysabri</u> In Item 1 A added "within the past 90 days" In Item 1 added "B. The prescriber states the patient is currently being treated with the requested agent AND is at risk if therapy is changed" In Item 1 C iii a added "history" to read "the patient's medication history indicates..." In Item 1 D removed "ALL" and added "meets ONE" to read "The patient has a diagnosis of a relapsing form of multiple sclerosis (MS) and meets ONE of the following" In Item 1 D I added "AND BOTH of the following" Removed "If the patient is John Cunningham virus (JCV) antibody positive, they do NOT have a prior history of the use of immunosuppressants AND they have NOT used Tysabri for > 24 months" Added "5. ONE of the following: A. The requested quantity (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" Removed "The requested dose is within FDA labeling for the requested indication" <u>Renewal Evaluation</u> In Item 4 added "B. The patient has NOT received more than 2 treatment courses with the requested agent AND C. The prescriber has provided the number of doses and treatment courses the patient has received" In Item 8 removed "The requested dose is within FDA labeling for the requested indication" and added "ONE of the following: A. The requested quantity (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 the Contraindicated Concomitant Medications chart.
	Rationale section updated

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