BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 10/27/21**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

BRIUMVI (ublituximab-xiiy)
LEMTRADA (alemtuzumab)
OCREVUS (ocrelizumab)
TYSABRI (natalizumab)

Non-Discrimination Statement is located at the end of this document.

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

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

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

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

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

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 10/27/21**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

BRIUMVI (ublituximab-xiiy)
LEMTRADA (alemtuzumab)
OCREVUS (ocrelizumab)
TYSABRI (natalizumab)

Criteria:

Refer to FDA website for current indications and dosage.

BRIUMVI (ublituximab-xiiy)
OCREVUS (ocrelizumab)

- **Criteria for initial therapy:** Briumvi (ublituximab-xiiy) or Ocrevus (ocrelizumab) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:

   - A relapsing form of multiple sclerosis (MS) including clinically isolated syndrome (CIS), relapsing-remitting disease, and active secondary progressive disease with **ALL** of the following:

     a. Clinical symptoms or attack consistent with demyelinating disease
     b. MRI of the brain and/or spinal cord was performed and meets **ONE** of the following:

        - MRI is consistent with the diagnosis of MS
        - If an MRI is insufficient for the diagnosis of MS, a CSF evaluation was done and demonstrates CSF-specific oligoclonal bands consistent with MS

     c. Individual has documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance, or not a candidate for use of **Kesimpta** (ofatumumab)
     d. Individual has documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance, or not a candidate for use of at least **ONE** of the following [Note: Criterion may be waived if individual has documented failure of Briumvi, Kesimpta, or Ocrevus due to lack of efficacy]:

        - Teriflunomide (generic or brand Aubagio)
        - Copaxone (glatiramer acetate) injection
        - Interferon beta-1a or beta-1b injection (e.g., Avonex, Plegridy, Rebif, Betaseron, Extavia)
        - Fumarate (e.g., Bafiertam, dimethyl fumarate, Tecfidera, Vumerity)

- Sphingosine 1-phosphate receptor modulator (Fingolimod, Gilenya, Mayzent, Ponvory, Tascenso ODT, Zeposia)

▪ Highly active or aggressive relapsing multiple sclerosis meeting **ALL** of the following:

a. Clinical symptoms or attack consistent with demyelinating disease
b. MRI of the brain and/or spinal cord was performed and meets **ONE** of the following:

- MRI is consistent with the diagnosis of MS
- If an MRI is insufficient for the diagnosis of MS, a CSF evaluation was done and demonstrates CSF-specific oligoclonal bands consistent with MS

c. Highly active or aggressive MS defined as **ONE** of the following:

- Demonstrated rapidly advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation severe changes in strength or coordination)
- Disabling acute relapse(s) with suboptimal response to systemic corticosteroids
- Multiple relapses (two or more) with incomplete recovery in the ongoing year
- No response to treatment with one or more disease modifying therapies for at least one year
- Magnetic resonance imaging [MRI] findings suggest highly active or aggressive multiple sclerosis (e.g., new, enlarging, or a high burden of T2 lesions, gadolinium-enhancing lesions, spinal cord lesion or brain atrophy)

d. Individual has documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance, or not a candidate for use of Kesimpta (ofatumumab)

▪ **FOR OCREVUS ONLY:** Primary progressive form of multiple sclerosis meeting **ALL** of the following:

a. Steady worsening of neurologic function (accumulation of disability) from onset of symptoms, without any distinct relapses (attacks or exacerbations) or remissions
b. Rate of progression may be variable over time with occasional plateaus or temporary improvement, but the progression is continuous
c. Has active disease on magnetic resonance imagining (MRI)

4. Individual has had all the following baseline evaluations have been completed with continued monitoring as indicated:

▪ Completion of any necessary immunizations according to current immunization guidelines 4 weeks prior to initiation
▪ Evidence of testing for hepatitis B infection prior to initiation of therapy

- Evidence that individual has received instruction on the avoidance of live vaccines until B-cell repletion
- No evidence of active infections or uncontrolled infections

5. There are **NO** contraindications, including active hepatitis B infection

6. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or myelosuppressive therapy for other conditions

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Briumvi (ublituximab-xiiy) or Ocrevus (ocrelizumab) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual's condition has responded while on therapy with response defined as achieves and maintains **TWO** of the following:

   - Stabilization or reduction in disease activity as evaluated by MRI (decrease in gadolinium enhancing lesions, decrease in number of new or enlarging T2 lesions, etc.)
   - Reduction in number of exacerbations or relapses of MS
   - Reduction in use of high dose steroids or hospitalizations for MS

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse effects that may exclude continued use such as:

   - Life-threatening infusion reactions
   - Active infections
   - Progressive multifocal leukoencephalopathy (PML)
   - For Ocrevus only: Immune mediated colitis

5. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or

myelosuppressive therapy for other conditions

Renewal duration: 12 months

- If criteria for response to therapy is not met, consider changing disease modifying therapy

- Briumvi (ublituximab-xiiy) and Ocrevus (ocrelizumab) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any one or more of the following criteria are met:

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

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

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

LEMTRADA (alemtuzumab)

- **Criteria for initial therapy:** Lemtrada (alemtuzumab) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

  2. Individual is 17 years or older

  3. Individual has a confirmed diagnosis of **ONE** of the following:

     - A relapsing form of multiple sclerosis (MS) including relapsing-remitting disease and active secondary progressive disease with **ALL** of the following:

       a. Clinical symptoms or attack consistent with demyelinating disease

b. MRI of the brain and/or spinal cord was performed and meets **ONE** of the following:

- MRI is consistent with the diagnosis of MS
- If an MRI is insufficient for the diagnosis of MS, a CSF evaluation was done and demonstrates CSF-specific oligoclonal bands consistent with MS

c. Documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance, or not a candidate for use of at least **ONE** of the following [Note: Criterion may be waived if individual has documented failure of Briumvi, Kesimpta, or Ocrevus due to lack of efficacy]:

- Teriflunomide (generic or brand Aubagio)
- Copaxone (glatiramer acetate) injection
- Interferon beta-1a or beta-1b injection (e.g., Avonex, Plegridy, Rebif, Betaseron, Extavia)
- Fumarate (e.g., Bafiertam, dimethyl fumarate, Tecfidera, Vumerity)
- Sphingosine 1-phosphate receptor modulator (Fingolimod, Gilenya, Mayzent, Ponvory, Tascenso ODT, Zeposia)

d. Individual has documented failure after a trial for at least four (4) weeks, contraindication per FDA label or intolerance to **BOTH** of the following:

- Kesimpta (ofatumumab)
- Tysabri (natalizumab)

▪ <u>Highly active or aggressive relapsing multiple sclerosis</u> meeting **ALL** of the following:

a. Clinical symptoms or attack consistent with demyelinating disease
b. MRI of the brain and/or spinal cord was performed and meets **ONE** of the following:

- MRI is consistent with the diagnosis of MS
- If an MRI is insufficient for the diagnosis of MS, a CSF evaluation was done and demonstrates CSF-specific oligoclonal bands consistent with MS

c. Highly active or aggressive MS defined as **ONE** of the following:

- Demonstrated rapidly advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation severe changes in strength or coordination)
- Disabling acute relapse(s) with suboptimal response to systemic corticosteroids
- Multiple relapses (two or more) with incomplete recovery in the ongoing year

- No response to treatment with one or more disease modifying therapies for at least one year
- Magnetic resonance imaging [MRI] findings suggest highly active or aggressive multiple sclerosis (e.g., new, enlarging, or a high burden of T2 lesions, gadolinium-enhancing lesions, spinal cord lesion or brain atrophy)

d. Individual has documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance, or not a candidate for use of **BOTH** of the following:

- Kesimpta (ofatumumab)
- Tysabri (natalizumab)

4. Individual does not have Clinically Isolated Syndrome (CIS)

5. Individual has evidence of completion of any necessary immunizations according to current immunization guidelines 6 weeks prior to initiation of Lemtrada

6. Individual has evidence of a prior history of varicella or individual has been vaccinated for the varicella zoster virus (VZV) before Lemtrada use

7. Individual has been screened for tuberculosis and individuals who test positive for tuberculosis have been treated before Lemtrada use

8. Anti-viral prophylaxis for herpetic viral infection is ongoing for the duration of treatment as per the treating provider

9. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or myelosuppressive therapy for other conditions

10. There are **NO** contraindications including:

- Active infection
- Significant viral illness such as human immunodeficiency virus

Initial approval duration: 12 mg per day on 5 consecutive days (60 mg total dose), 1-month authorization

- **Criteria for continuation of coverage (renewal request):** Lemtrada (alemtuzumab) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 10/27/21**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

BRIUMVI (ublituximab-xiiy)
LEMTRADA (alemtuzumab)
OCREVUS (ocrelizumab)
TYSABRI (natalizumab)

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual's condition has responded while on therapy with response defined as achieves and maintains **TWO** of the following:

   - Stabilization or reduction in disease activity as evaluated by MRI (decrease in gadolinium enhancing lesions, decrease in number of new or enlarging T2 lesions, etc.)
   - Reduction in number of exacerbations or relapses of MS
   - Reduction in use of high dose steroids or hospitalizations for MS

3. Individual has been adherent with the medication

4. At least 12 months have elapsed since the any previous treatment course

5. Individual has not developed any contraindications or other significant adverse effects that may exclude continued use such as:

   - Acute acalculous cholecystitis
   - Adult-Onset Still's Disease (AOSD)
   - Autoimmune conditions such as immune thrombocytopenia, anti-glomerular basement membrane disease, autoimmune encephalitis (AIE), autoimmune hepatitis, acquired hemophilia A, thrombotic thrombocytopenic purpura, and other immune cytopenias
   - Glomerular nephropathies
   - Hemophagocytic lymphohistiocytosis
   - Immune-mediated colitis
   - Life-threatening infusion reactions
   - Malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders
   - Progressive multifocal leukoencephalopathy (PML)
   - Stroke

6. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or myelosuppressive therapy for other conditions

7. There are no significant interacting drugs

Renewal duration: 12 mg per day on 3 consecutive days (36 mg total dose), 12-month authorization

- If criteria for response to therapy is not met, consider changing disease modifying therapy

BRIUMVI (ublituximab-xiiy)
LEMTRADA (alemtuzumab)
OCREVUS (ocrelizumab)
TYSABRI (natalizumab)

- Lemtrada (alemtuzumab) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any one or more of the following criteria are met:

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

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

  - Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration.

TYSABRI (natalizumab)

- **Criteria for initial therapy:** Tysabri (natalizumab) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist or Gastroenterologist depending upon indication

  2. Individual is 18 years or older

  3. Individual has a confirmed diagnosis of **ONE** of the following:

     - Moderately to severely active Crohn's disease (has a Crohn's Disease Activity Index (CDAI) score of greater than 220) with evidence of inflammation who has had an inadequate response to or is unable to tolerate conventional therapy and tumor necrosis factor (TNF) inhibitors (such as Humira (adalimumab), Cimzia (certolizumab), or infliximab product (Remicade, Unbranded Remicade, Avsola, Renflexis, Inflectra))
     - A relapsing form of multiple sclerosis (MS) including clinically isolated syndrome (CIS), relapsing-remitting disease, and active secondary progressive disease with **ALL** of the following:

       a. Clinical symptoms or attack consistent with demyelinating disease
       b. MRI of the brain and/or spinal cord was performed and meets **ONE** of the following:

- MRI is consistent with the diagnosis of MS
- If an MRI is insufficient for the diagnosis of MS, a CSF evaluation was done and demonstrates CSF-specific oligoclonal bands consistent with MS

c. Individual has documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance, or not a candidate for use of at least **ONE** of the following [Note: Criterion may be waived if individual has documented failure of Briumvi, Kesimpta, or Ocrevus due to lack of efficacy]:

- Teriflunomide (generic or brand Aubagio)
- Copaxone (glatiramer acetate) injection
- Interferon beta-1a or beta-1b injection (e.g., Avonex, Plegridy, Rebif, Betaseron, Extavia)
- Fumarate (e.g., Bafiertam, dimethyl fumarate, Tecfidera, Vumerity)
- Sphingosine 1-phosphate receptor modulator (Fingolimod, Gilenya, Mayzent, Ponvory, Tascenso ODT, Zeposia)
- Anti-CD20 monoclonal antibody (e.g., Briumvi, Kesimpta, Ocrevus)

▪ Highly active or aggressive relapsing multiple sclerosis meeting **ALL** of the following:

a. Clinical symptoms or attack consistent with demyelinating disease
b. MRI of the brain and/or spinal cord was done with and meets **ONE** of the following:

- MRI is consistent with the diagnosis of MS
- If an MRI is insufficient for the diagnosis of MS, a CSF evaluation was done and demonstrates CSF-specific oligoclonal bands consistent with MS

c. Highly active or aggressive MS defined as **ONE** of the following:

- Demonstrated rapidly advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation severe changes in strength or coordination)
- Disabling acute relapse(s) with suboptimal response to systemic corticosteroids
- Multiple relapses (two or more) with incomplete recovery in the ongoing year
- No response to treatment with one or more disease modifying therapies for at least one year
- Magnetic resonance imaging [MRI] findings suggest highly active or aggressive multiple sclerosis (e.g., new, enlarging, or a high burden of T2 lesions, gadolinium-enhancing lesions, spinal cord lesion or brain atrophy)

4. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or

myelosuppressive therapy for other conditions

5. There are **NO** contraindications including individuals who have or have had progressive multifocal leukoencephalopathy (PML)

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Tysabri (natalizumab) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist or Gastroenterologist depending upon indication

2. Individual's condition has responded while on therapy with response defined as **ONE** of the following:

   - **When used for Crohn's disease: TWO** of the following:

     a. Has experienced therapeutic benefit by 3 months of induction
     b. Is in clinical remission (a CDAI score of < 150)
     c. Has had a clinical response (reduction of CDAI score of ≥ 70 from baseline)

   - **When used for Multiple Sclerosis: TWO** of the following:

     a. Stabilization or reduction in disease activity as evaluated by MRI (decrease in gadolinium enhancing lesions, decrease in number of new or enlarging T2 lesions, etc.)
     b. Reduction in number of exacerbations or relapses of MS
     c. Reduction in use of high dose steroids or hospitalizations for MS

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse effects that may exclude continued use such as:

   - Herpes infections
   - Hepatotoxicity
   - Thrombocytopenia
   - Progressive multifocal leukoencephalopathy (PML)

5. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or myelosuppressive therapy for other conditions

Renewal duration: 12 months

- If criteria for response to therapy is not met, consider changing disease modifying therapy

- Tysabri (natalizumab) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any one or more of the following criteria are met:

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

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

- Treatment with dosing, frequency or duration outside the FDA-approved dosing, frequency or duration

Description:

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

A number of medications have been shown to modify or slow the course of MS.

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

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 10/27/21**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

BRIUMVI (ublituximab-xiiy)
LEMTRADA (alemtuzumab)
OCREVUS (ocrelizumab)
TYSABRI (natalizumab)

National Multiple Sclerosis Society 1996 Disease-Course Definitions:

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

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

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

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

National Multiple Sclerosis Society 2013 Disease-Course Revisions:

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

- Relapsing-Remitting (RRMS):
  RRMS is characterized by clearly defined attacks of new or worsening neurologic function. These attacks, often called relapses, flare-ups or exacerbations, are followed by partial or complete recovery periods (remissions). During remissions, all symptoms may disappear, or some symptoms may

continue and become permanent. However, there is no apparent progression of the disease during the periods of remission. Approximately 85 percent of people with MS are initially diagnosed with RRMS.

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

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

Definitions:

Adult: Age 18 years and older

Disease Modifying Therapy Options:

- Oral Medications:
  - Cladribine (Mavenclad)
  - Fumarates:
    - Dimethyl Fumarate (Tecfidera and generic)
    - Diroximel fumarate (Vumerity)
    - Monomethyl fumarate (Bafiertam)
  - Sphingosine-1-phosphate (S1P) receptor modulators
    - Fingolimod (Gilenya and generic, Tascenso ODT)
    - Ozanimod (Zeposia)
    - Ponesimod (Ponvory)
    - Siponimod (Mayzent)
  - Teriflunomide (Aubagio and generic)

- Injectable Medications:
  - Interferon beta-1a (Avonex (IM), Plegridy (SQ), Rebif (SQ))
  - Interferon beta-1b (Betaseron (SQ), Extavia (SQ))
  - Glatiramer acetate (Copaxone (SQ), and generic, Glatopa (SQ))
  - Monoclonal antibody Mediations:
    - Alemtuzumab (Lemtrada IV)
    - Natalizumab (Tysabri IV)
    - Ocrelizumab (Ocrevus IV)

- Ofatumumab (Kesimpta SQ)
- Ublituximab (Briumvi IV)

Moderately to severely active Crohn's disease:

Crohn's Disease Activity Index [CDAI] ≥ 220 and ≤ 450
Induction of clinical response (defined as ≥ 70-point decrease in CDAI from baseline)
Clinical remission (defined as CDAI score < 150)

Conventional Crohn's disease therapies include: Sulfasalazine, mesalamine, corticosteroids (budesonide, methylprednisolone, etc.), 6-mercaptopurine, azathioprine, methotrexate, and inhibitors of tumor necrosis factor-alpha.

Crohn's Disease Activity Index in Adults:

Patient reported stool pattern over seven days	Average number of liquid or soft stools per day	14 points per stool
	Using diphenoxylate or loperamide for diarrhea	30 points
Average abdominal pain rating over seven days	None	0 points
	Mild pain	35 points
	Moderate pain	70 points
	Severe pain	105 points
General wellbeing each day over seven days	Well	0 points
	Slightly below average	49 points
	Poor	98 points
	Very poor	147 points
	Terrible	196 points
Complications	Arthritis or arthralgia	20 points
	Iritis or uveitis	20 points
	Erythema nodosum, pyoderma gangrenosum, or aphthous stomatitis	20 points
	Anal fissure, fistula, or abscess	20 points
	Other fistula	20 points
	Temperature over 100°F (37.8°C) in the last week	20 points
Finding of an abdominal mass	No mass	0 points

	Possible mass	20 points
	Definite mass	50 points
Anemia and weight change	Absolute deviation of hematocrit* from 47 percent in males or 42 percent in females	6 points per percent deviation
	Percentage deviation from standard weight**	1 point for each percent deviation
Total criteria point count:		
0 to 149 points:	Asymptomatic remission	
150 to 220 points:	Mildly to moderately active Crohn's disease	
221 to 450 points:	Moderately to severely active Crohn's disease	
451 to 1100 points:	Severely active to fulminant disease	

Notes
* Absolute deviation of hematocrit is simply the difference in hematocrit from standard. A male patient with a hematocrit of 40 percent has an absolute deviation of 7.
** Percent deviation from standard weight is (1 - weight/standard weight) x 100, thus positive percent deviation represents weight loss, adding points to the CDAI.
Patients requiring steroids to remain asymptomatic are not considered to be in remission but are referred to as being "steroid dependent."

Risk Evaluation and Mitigation Strategies (REMS):

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

History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	08/15/24	Review with revisions: criteria (effective 10/14/24)
Pharmacy and Therapeutics Committee	02/15/24	Revisions to guideline (effective 04/16/24)
Pharmacy and Therapeutics Committee	08/17/23	Review with revisions
Pharmacy and Therapeutics Committee	02/16/23	Review with additions. New drug, additional code(s)
Pharmacy and Therapeutics Committee	08/18/22	Review with revisions
Medical Policy Panel (ad hoc)	10/27/21	Approved guideline

BRIUMVI (ublituximab-xiiy)
LEMTRADA (alemtuzumab)
OCREVUS (ocrelizumab)
TYSABRI (natalizumab)

Clinical Pharmacist	10/27/21	Development

Coding:

HCPCS: J0202, J2323, J2350, J2329

BRIUMVI (ublituximab-xiiy)
LEMTRADA (alemtuzumab)
OCREVUS (ocrelizumab)
TYSABRI (natalizumab)

Resources:

Literature reviewed 08/15/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Al Hashash J, Regueiro M. Medical management moderate to severe Crohn disease in adults. In: UpToDate, Kane SV, Robson, KM (Eds), UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated May 30, 2024. Accessed June 28, 2024.

2. Briumvi (ublituximab-xiiy). Prescribing information. TG Therapeutics, Inc 12/2022, at DailyMed https://dailymed.nlm.nih.gov/dailymed/. Accessed May 24, 2024.

3. Freedman MS, Devonshire V, Duquette P, et al. Treatment optimization in multiple sclerosis: Canadian MS Working Group recommendations. *Can J Neurol Sci*. 2020;47:437-455.

4. Lemtrada (alemtuzumab). Prescribing information. Genzyme Corporation 05/2024, at DailyMed https://dailymed.nlm.nih.gov/dailymed/. Accessed May 24, 2024.

5. Lin GA, Whittington MD, Nikitin D, et al. Treatments for Relapsing Forms of Multiple Sclerosis; Final Evidence Report. Institute for Clinical and Economic Review, February 21, 2023.

6. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med.* 2017;376(3):209-220.

7. Ocrevus (ocrelizumab). Prescribing information, Genentech, Inc. 01/2024, at DailyMed https://dailymed.nlm.nih.gov/dailymed/. Accessed May 24, 2024.

8. Olek MJ, Howard J. Management of clinically and radiologically isolated syndromes suggestive of multiple sclerosis. In: UpToDate, Mowry E, Dashe JF (Eds), UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated April 26, 2024. Accessed June 28, 2024.

9. Olek MJ, Howard J. Treatment of acute exacerbations of multiple sclerosis in adults. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated April 30, 2024. Accessed June 28, 2024.

10. Olek MJ, Mowry E. Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated November 20, 2023. Accessed June 28, 2024.

11. Olek MJ, Mowry E. Overview of disease-modifying therapies for multiple sclerosis. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated November 20, 2023. Accessed June 28, 2024.

12. Olek MJ, Mowry E. Treatment of primary progressive multiple sclerosis in adults. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated August 22, 2022. Accessed June 28, 2024.

13. Olek MJ, Mowry E. Treatment of secondary progressive multiple sclerosis in adults. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated April 12, 2023. Accessed June 28, 2024.

14. Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults. In: UpToDate, Al Hashash J, Robson, KM (Eds), UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated August 30, 2023. Accessed June 28, 2024.

15. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2018;90:777-788.

16. Steinman L, Fox E, Hartung HP, et al. Ublituximab versus teriflunomide in relapsing multiple sclerosis. *N Engl J Med*. 2022;387(8):704-714.

17. Tysabri (natalizumab). Prescribing information, Biogen, Inc. 01/2024, at DailyMed https://dailymed.nlm.nih.gov/dailymed/. Accessed May 24, 2024.

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 10/27/21**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

BRIUMVI (ublituximab-xiiy)
LEMTRADA (alemtuzumab)
OCREVUS (ocrelizumab)
TYSABRI (natalizumab)

Non-Discrimination Statement:

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

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