Medicare Part B Healthcare Administered Multiple Sclerosis Prior Authorization

FDA APPROVED INDICATIONS AND DOSAGE[1-3]

Agent(s)	Indication(s)	Dosage
Lemtrada® (alemtuzumab) Injection for intravenous use	• Treatment of relapsing forms of multiple sclerosis (MS) to include relapsing-remitting disease and active secondary progressive disease, in adults Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS Limitations of use: Lemtrada is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile	**Relapsing forms of MS:** 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) administered 12 months after first treatment course

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Agent(s)	Indication(s)	Dosage
Ocrevus® (ocrelizumab) Injection for intravenous use	• Treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults • Primary progressive (PPMS) forms of multiple sclerosis, in adults	**Relapsing forms of Multiple Sclerosis:** 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 **PPMS:** 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

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Agent(s)	Indication(s)	Dosage
Tysabri® (natalizumab) Injection for intravenous use	• Monotherapy for the treatment of patients with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults • Inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's Disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate conventional CD therapies and inhibitors of TNF-α Important Limitations: In CD Tysabri should not be used in combination with immunosuppressants or inhibitors of TNF- α	**Relapsing forms of Multiple Sclerosis:** 300 mg intravenous infusion every 4 weeks **CD:** 300 mg intravenous infusion every 4 weeks. If the patient with CD has not experienced therapeutic benefit by 12 weeks of corticosteroids, commence induction therapy, discontinue Tysabri. For patients with Crohn's disease who start Tysabri while on chronic oral steroid tapering as soon as a therapeutic benefit of Tysabri has occurred; if the patient with CD cannot be tapered off oral corticosteroids within 6 months of starting Tysabri, discontinue Tysabri. Other than the initial six-month taper, prescribers should consider discontinuing Tysabri for patients who require additional steroid use that exceeds three months in a calendar year to control their CD

CLINICAL 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. While traditionally viewed as a disease solely of CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.[4]

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

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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).[11]

Clinically isolated syndrome
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. When CIS is accompanied by lesions on a brain MRI that are similar to those seen in MS, the person has a high likelihood of a second episode of neurologic symptoms and diagnosis of relapsing-remitting MS. When CIS is not accompanied by MS-like lesions on brain MRI, the person has a much lower likelihood of developing MS.[11] When caused by an acute inflammatory demyelinating event, approximately 85% of all patients subsequently develop MS. The relationship between conventional brain MRI features and the short-term risk of CIS patients developing definite MS has been assessed by several studies and allows for the diagnosis of MS based on the 2017 McDonald criteria. However, in CIS patients with initial multifocal clinical symptom presentation the abnormal MRI did not stratify the risk for clinically definite disease conversion.[15]

CIS cohort studies spanning 7 through 20 years of follow-up investigated the long-term risk of MS development and found conversions rates of 65-80% for patients with an abnormal conventional MRI and 8-20% for those with an inconspicuous baseline MRI.[15]

Relapsing remitting multiple sclerosis (RRMS)
RRMS is characterized by clearly defined attacks (relapses) of new or increasing neurologic symptoms. These relapses are followed by periods of partial or complete recovery. There is no or minimal disease progression during the periods between disease relapses, though individual relapses may result in severe residual disability. The course of MS varies, however, 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.[11]

Secondary progressive multiple sclerosis (SPMS)
SPMS begins as RRMS, but over time the disease enters a stage of steady deterioration in function, unrelated to acute attacks. Typically, when SPMS stage is reached, the relapse rate is also reduced. Prior to the era of disease-modifying agents (DMAs), approximately half of patients diagnosed with relapsing MS would progress to SPMS by 10 years, and 80-90% would do so by 25 years.[11]

Primary progressive multiple sclerosis (PPMS)
PPMS is characterized by worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions.[11] Currently ocrelizumab is the only DMA FDA approved for PPMS. A 2016 Institute for Clinical and Economic Review (ICER) report included rituximab as treatment for both relapsing forms and progressive forms of MS based on feedback from practicing clinicians, specialty societies, manufacturers, and payors. The results of the ICER evaluation on the use of rituximab for MS showed that the

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evidence is promising and recommend rituximab as an option for treating multiple forms of MS.[5]

2017 McDonald Criteria for the diagnosis of Multiple Sclerosis:
Diagnostic criteria for multiple sclerosis combining clinical, imaging, and laboratory evidence have evolved over time. The increasing incorporation of paraclinical assessments, especially imaging, to supplement clinical findings has allowed earlier, more sensitive, and more specific diagnosis.[9,10]

The diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time.[9]

Misdiagnosis of multiple sclerosis remains an issue in clinical practice, and several factors that potentially increase this risk have been identified. Multiple sclerosis has heterogeneous clinical and imaging manifestations, which differ between patients over time. There is no single pathognomonic clinical feature or diagnostic test; diagnosis of multiple sclerosis relies on the integration of clinical, imaging, and laboratory findings. MRI abnormalities associated with other diseases and non-specific MRI findings, which are common in the general population, can be mistaken for multiple sclerosis. The increasingly strong focus on timely diagnosis to alleviate uncertainty for patients and allow initiation of disease-modifying therapies might also increase the risk of misdiagnosis.[9]

With increasing availability and use of MRI, incidental T2 hyperintensities on brain imaging are common, the subset of individuals with MRI findings that are strongly suggestive of multiple sclerosis lesions but with no neurological manifestations or other clear-cut explanation are said to have radiologically isolated syndrome. There is no consensus on whether patients with radiologically isolated syndrome will develop MS. Some practitioners argue that these patients have a high likelihood of developing MS while others argue that up to two-thirds of these patients will not receive a diagnosis of MS in 5 years. A consensus panel decided to require clinical manifestations to make the diagnosis of MS (2017 McDonald Criteria for the diagnosis of Multiple Sclerosis).[9]

The 2017 McDonald criteria to diagnose MS is shown in the chart below.[9,10]

Clinical Presentation	**Additional Data needed to make MS diagnosis**
In a person with a typical attack/CIS at onset	
Greater than or equal to 2 attacks and objective clinical evidence of greater than or equal to 2 lesions OR Greater than or equal to 2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space[a] and dissemination in time[b] have been met

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Clinical Presentation	Additional Data needed to make MS diagnosis
Greater than or equal to 2 attacks and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional clinical attack implicating different CNS site OR Greater than or equal to 1 symptomatic or asymptomatic MS-typical T2 lesions in greater than or equal to 2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial, or spinal cord
1 attack and objective clinical evidence of greater than or equal to 2 lesions	**ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR New T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) OR CSF specific (i.e., not in serum) oligoclonal bands
1 attack and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional attack implicating different CNS site OR Greater than or equal to 1 MS-Typical symptomatic or asymptomatic T2 lesions in greater than or equal to 2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial, or spinal cord **AND** **ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR New T2 enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) OR CSF-specific (i.e., not in serum) oligoclonal bands
In a person with progression of disability from onset	

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Clinical Presentation	Additional Data needed to make MS diagnosis
Progression from onset	1 year of disability progression (retrospective or prospective) **AND** **TWO** of these criteria: Greater than or equal to 1 symptomatic or asymptomatic MS-typical T2 lesions (periventricular, juxtacortical/cortical, or infratentorial) **OR** Greater than or equal to 2 T2 spinal cord lesions **OR** CSF-specific (i.e., not in serum) oligoclonal bands

a - Dissemination in space is defined as one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in 2 or more of four areas of the CNS (periventricular, cortical or juxtacortical, and infratentorial brain regions, and the spinal cord) demonstrated by an additional clinical attack implicating a different CNS site or by MRI.[9]

b - Dissemination in time is defined as simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI. The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.[9]

Treatment of MS

Both the Multiple Sclerosis Coalition and the American Academy of Neurology recommend initiating treatment with a DMA FDA approved for the patient's phenotype as soon as possible following the diagnosis of multiple sclerosis. There are several DMAs with at least 10 mechanisms of action available to people with MS. The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the individual and the treating clinician.[4,7]

The Multiple Sclerosis Coalition recommends that clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, natalizumab or ocrelizumab for newly diagnosed individuals with highly active MS. Clinicians should also consider prescribing a high efficacy medication for individuals who have breakthrough activity on another DMA regardless of the number of previously used agents.[4] The American Academy of Neurology has recommended alemtuzumab, fingolimod, and natalizumab as options for patients with MS with highly active MS. There lacks a consensus for what constitutes as highly active MS, however.[7] The National Institute for Health and Care Excellence (NICE) defines rapidly evolving severe RRMS as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.[8]

Lack of response to DMAs is hard to define, as most patients with MS are not free of all disease activity. Relapses or new MRI detected lesions may develop after initiation of a DMA and before the treatment becomes effective for patients. When determining efficacy, sufficient time for the DMA therapy to take full effect and patient adherence are important considerations. Evidence of one or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination while being treated with a DMA for a 1 year period suggests a sub-optimal response, an alternative regimen (e.g., different

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mechanism of action) should be considered to optimize therapeutic benefit.[6] 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]

Existing MS therapies are partly effective in halting ongoing inflammatory tissue damage and clinical progression. MS pathogenesis is complex and probably heterogeneous among patient, suggesting that combination therapy strategies that target a range of disease mechanisms might be more effective than medications used as monotherapy. Although preliminary studies have provided favorable results, however, several subsequent large, randomized, controlled trials have had negative of conflicting results. There also may be more adverse reactions associated with combination therapies due to the additive effect.[13]

In 2020 a Canadian MS working group published recommendations on optimal therapy in relapsing forms of MS. This group notes that there are few studies that have directly compared injectable and oral DMTs. A recent network meta-analysis suggested that pegylated interferon-β-1a and dimethyl fumarate have superior efficacy to other base therapies, there are insufficient data to demonstrate that one base injectable or oral DMT is superior to another. As a result, the choice of initial treatment will need to be individualized according to disease activity, severity, and comorbidities.[14]

In addition to base therapies, the working group considers 5 DMTs to be of higher efficacy which although can be used as initial therapy, they are generally reserved for patients with a poor response or tolerability with a base therapy. Patients presenting with high disease activity or aggressive/rapidly evolving MS at onset could be considered to initiate therapy with one of these more effective therapies, but the most common treatment initiation is to start on a base therapy with the view of switching within 6 -12 months. The 5 agents considered to be of higher efficacy are:[14]

- Oral agents
    - Fingolimod
    - Cladribine
- Monoclonal antibodies
    - Natalizumab
    - Ocrelizumab
    - Alemtuzumab

The MS working group discussed the criteria for switching therapies in RRMS and recommends a change in DMT is indicated for patients who meet any of the Major criteria below:[14]

	Minor	**Major**
Relapse rate	• One relapse in first 2 years of treatment	• ≥ 2 relapses in first year of treatment
Severity	• Mild • No functional impairment (school, work, daily activities, etc.) • No motor/cerebellar/brain stem /sphincter involvement	• Moderate to severe • Functional impairment • Motor/cerebellar/brain stem/sphincter involvement
Recovery	• Full recovery at 6 months	• Incomplete recovery

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	• No functional impairment • EDSS change from baseline ≤ 1 point at 6 months unless baseline EDSS >5.5	• Functional impairment • If EDSS at baseline was 0 then > 1.5 point change from baseline • If EDSS > 0 but less than 5.5 at baseline then > 1 point change at 6 months • If EDSS > 5.5 any change would be a major concern
MRI	• One new lesion	• ≥ 3 new lesions during treatment excluding spinal cord lesions • > 1 spinal cord lesion

The workgroup does note that on-treatment relapses should only be performed once the drug has achieved a full clinical effect (typically 2-6 months after drug initiation). Relapses that occur before the maximal efficacy of the drug has been reached should be given less weight, but major criteria should take precedence regardless of timing.[14]

For patients with SPMS the workgroup states that is generally advised to continue with the current DMT after onset of SPMS since many patients will have ongoing inflammatory disease and subclinical disease activity may worsen if treatment is withdrawn. A change in treatment may be warranted in patients with active SPMS who continue to have relapses or new MRI lesions, with the caveat that there is insufficient evidence to identify criteria for a suboptimal response in patients with SPMS.[14]

For patients with primary progressive MS clinicians should offer ocrelizumab to patients with active disease provided the benefits outweigh the risks. Caution is recommended when considering treatment for PPMS subgroups that are less likely to benefit from treatment, such as older patients, those with long-standing stable disease, and/or significant neurological deficits, since the limited benefits may not justify the risk associated with treatment. Rituximab may be considered as an alternative therapy for PPMS in regions that permit off-label use in MS due to cost or other considerations.[14]

Crohn's Disease
Crohn's Disease (CD) is an inflammatory condition that can affect any portion of the gastrointestinal tract from the mouth to the perianal area. Choice of therapy is dependent on the anatomic location of disease, the severity of disease, and whether the treatment goal is to induce remission or maintain remission.[12,16]

The American Gastroenterological Association (AGA) 2021 guideline recommends the following:[16]

- Biologic therapy:
  - The AGA suggest early introduction with a biologic, with or without an immunomodulator, rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids
  - Anti-TNF (i.e., infliximab or adalimumab) and ustekinumab are recommended over no treatment for the induction and maintenance of remission

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- Vedolizumab is suggested over no treatment for the induction and maintenance of remission
- AGA suggests against the use of natalizumab over no treatment for the induction and maintenance of remission
- Patients naïve to biologic therapy, the AGA recommends infliximab, adalimumab, or ustekinumab over certolizumab pegol and suggests the use of vedolizumab over certolizumab pegol for the induction of remission
- Patients with primary non-response to anti-TNF, the AGA recommends ustekinumab and suggests vedolizumab for induction of remission
- Patients with secondary non-response to infliximab, the AGA recommends use of adalimumab or ustekinumab and suggests the use of vedolizumab for the induction of remission (if adalimumab was the first line drug, there is indirect evidence to suggest using infliximab as a second-line agent)

- DMARD therapy:
  - Corticosteroids are suggested over no treatment for the induction of remission, and are recommended against for maintenance of remission
  - Patients in corticosteroid induced remission or with quiescent moderate to severe CD, the AGA suggests thiopurines for maintenance of remission
  - Subcutaneous or intramuscular methotrexate are suggested over no treatment for the induction and maintenance of remission
  - The AGA recommends against the use of 5-aminosalicylates or sulfasalazine over no treatment for the induction or maintenance of remission
  - The AGA suggests against the use of thiopurines over no treatment for achieving remission and recommends biologic drug monotherapy over thiopurine monotherapy for induction of remission
  - The AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission

- Combination therapy:
  - Patients that are naïve to biologics and immunomodulators, the AGA suggest use of infliximab in combination with thiopurines over infliximab monotherapy for the induction and maintenance of remission (combination infliximab with methotrexate may be more effective over infliximab monotherapy)
  - Patients that are naïve to biologics and immunomodulators, the AGA suggest use of adalimumab in combination with thiopurines over adalimumab monotherapy for the induction and maintenance of remission (combination adalimumab with methotrexate may be more effective over adalimumab monotherapy)
  - No recommendations are being made regarding the use of ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic monotherapy for induction or maintenance or remission

The 2018 American College of Gastroenterology (ACG) guideline recommends the following:[12]

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- Mild to moderately severe disease/low risk disease:
    - Sulfasalazine (in doses of 3-6 grams daily) is effective in colonic and/or ileocolonic CD, but not those with isolated small bowel disease
    - 5-aminosalicylic (ASA) suppositories and enema preparations are effective for induction and maintenance of remission in rectal and sigmoid disease
    - Conventional corticosteroids are primarily used for the treatment of flares, and are often used as a bridge until immunomodulators and/or biologic agents become effective
    - Controlled ileal release budesonide is effective for induction of remission in ileocecal disease
- Moderate to severe disease/moderate to high risk disease
    - Corticosteroids are effective for short-term use in alleviating signs and symptoms of moderate to severely active CD, but do not induce mucosal healing and should be used sparingly
    - Azathioprine, 6-mercaptopurine, or MTX (15 mg once weekly) may be used in treatment of active disease and as adjunctive therapy for reducing immunogenicity against biologic therapy
    - TNF inhibitors should be used to treat CD that is resistant to treatment with corticosteroids and that is refractory to thiopurines or MTX
    - Natalizumab should be considered for induction of symptomatic response and remission in patients with active Crohn's disease
- Maintenance therapy:
    - Thiopurines or methotrexate should be considered once remission is induced with corticosteroids
    - TNF inhibitors, specifically infliximab, adalimumab, and certolizumab pegol, should be used in combination with azathioprine, MTX, or 6-mercaptopurine to maintain remission of TNF induced remission
    - Natalizumab should be used for maintenance of natalizumab-induced remission of Crohn's disease only if serum antibody to John Cunningham virus (JCV) is negative. Testing for anti-JCV antibody should be repeated every 6 months and treatment stopped if the result is positive

Safety[1-3]

- **Tysabri** (natalizumab) has a boxed warning for increasing the risk of progressive multifocal leukoencephalopathy (PML) and is contraindicated in patients who have had or who have PML. Tysabri is also contraindicated in patients with hypersensitivity to natalizumab.[1]

- **Lemtrada** (alemtuzumab) has boxed warnings for serious (including fatal) autoimmune conditions, serious and life-threatening infusion site reactions, and increased risk of malignancies. Lemtrada is contraindicated in patients with HIV infection.[2]

- **Ocrevus** (ocrelizumab) is contraindicated in patients who have history of life threatening infusion reaction to ocrelizumab as well as in patients with active hepatitis B virus as confirmed by positive results of HBsAg and anti-HB tests.[3]

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Document History
Original Prime Standard Part B criteria, approved by P&T UM Committee 12/2021

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Medicare Part B Healthcare Administered Multiple Sclerosis Prior Authorization

Coverage and policy application are contingent on National Coverage Determinations (NCD) and Local Coverage Determinations (LCD). An NCD or LCD that is applicable to the drug or product must be used in lieu of applicable medical necessity criteria. Also, please note that Prior Authorization criteria cannot be stricter than an NCD or LCD with specified step therapy requirements.

TARGET PREFERRED AGENT(S)	TARGET NON-PREFERRED AGENT(S)
Target preferred and non-preferred agent(s) to be determined client	Target preferred and non-preferred agent(s) to be determined client
Lemtrada® (alemtuzumab) **Ocrevus®** (ocrelizumab) **Tysabri®** (natalizumab)	

Brand (generic)	GPI	Multisource Code	HCPCS/J Code
Lemtrada (alemtuzumab)			
12 mg/1.2 mL Single dose vial	62405010002020	M, N, O, or Y	J0202
Ocrevus (ocrelizumab)			
300 mg/10 mL Single dose vial	62405060002020	M, N, O, or Y	J2350
Tysabri (natalizumab)			
300 mg/15 mL Single dose vial	62405050001320	M, N, O, or Y	J2323

CRITERIA FOR APPROVAL
Evaluation
Target Agent(s) will be approved when ALL of the following are met:

1. The requested agent is being used for ONE of the following:
    a. An FDA approved indication
    OR
    b. An indication in CMS approved compendia

    AND
2. If the client has preferred agents, then ONE of the following:
    a. The requested agent is the preferred agent
    OR
    b. Information has been provided that indicates the patient has been treated with the requested agent in the past 365 days
    OR
    c. There is documentation that the patient has had an ineffective treatment response to the active ingredient(s) of ALL preferred agent(s)
    OR
    d. The patient has a documented intolerance, hypersensitivity, or FDA labeled contraindication to the active ingredient(s) of ALL preferred agent(s)
    OR

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e. The prescriber has submitted documentation indicating ALL preferred agent(s) are likely to be ineffective or are likely to cause an adverse reaction or other harm to the patient

AND

3. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
4. The requested quantity (dose) is within FDA labeled dosing or supported in compendia for the requested indication

Length of Approval: up to 12 months

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