Corporate Medical Policy: Natalizumab (Tysabri®) and Natalizumab Biosimilars **"Notification"** **POLICY EFFECTIVE JULY 1, 2026**

Restricted Product(s):

- natalizumab (Tysabri®) intravenous infusion for administration by a healthcare professional
- natalizumab-sztn (Tyruko®) intravenous infusion for administration by a healthcare professional

FDA Approved Use:

- As monotherapy, for the treatment of adults with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease
  - Limitations of use: Natalizumab increases risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing natalizumab treatment, consideration should be taken whether expected benefit is sufficient to offset risk.
- For inducing and maintaining clinical response and remission in adults 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 TNF-alpha inhibitors
  - Limitations of use: Not for use in combination with immunosuppressants or TNF-alpha inhibitors

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

Initial Criteria for Approval:

1. The patient has a diagnosis of a **relapsing form of multiple sclerosis (MS)**, to include clinically isolated syndrome, relapsing-remitting disease, or active secondary progressive disease; **AND**
   a. The patient is 18 years of age or older; **AND**
   b. The patient must still either be able to walk at least a few steps with or without aid, or alternatively must have some functional arm/ hand use consistent with performing activities of daily living; **AND**
   c. ONE of the following:
      i. The patient has highly active MS disease activity AND BOTH of the following **[medical record documentation required]**:
         1. The patient has greater than or equal to 2 relapses in the previous year; **AND**
         2. ONE of the following:
            a. The patient has greater than or equal to 1 gadolinium enhancing lesion on MRI; **OR**
            b. The patient has a significant increase in T2 lesion load compared with a previous MRI; **OR**
      ii. ONE of the following:

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1. The patient has tried and had an inadequate response to ONE of the following: dimethyl fumarate (generic Tecfidera), fingolimod (generic Gilenya), glatiramer acetate (generic Copaxone or Glatopa), or teriflunomide (generic Aubagio) **[medical record documentation required]**; **OR**
2. The patient has an intolerance or hypersensitivity to ONE of the following: dimethyl fumarate (generic Tecfidera), fingolimod (generic Gilenya), glatiramer acetate (generic Copaxone or Glatopa), or teriflunomide (generic Aubagio) **[medical record documentation required]**; **OR**
3. The patient has an FDA labeled contraindication to ALL of the following: dimethyl fumarate (generic Tecfidera), fingolimod (generic Gilenya), glatiramer acetate (generic Copaxone or Glatopa), and teriflunomide (generic Aubagio) **[medical record documentation required]**; **OR**

iii. The patient has been treated with at least three MS agents from different drug classes (see "MS Disease Modifying Agents drug classes" table below) **[medical record documentation required]**; **AND**

d. The patient is NOT receiving concurrent therapy with two or more disease-modifying drugs for multiple sclerosis, including glatiramer (Copaxone, Glatopa), interferon beta-1b (Betaseron, Extavia), interferon beta-1a (Avonex, Rebif), peginterferon beta-1a (Plegridy), fingolimod (Gilenya, Tascenso ODT), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), monomethyl fumarate (Bafiertam), ofatumumab (Kesimpta), alemtuzumab (Lemtrada), siponimod (Mayzent), cladribine (Mavenclad), ocrelizumab (Ocrevus, Ocrevus Zunovo), ponesimod (Ponvory), natalizumab (Tysabri, Tyruko), diroximel fumarate (Vumerity), ozanimod (Zeposia), and ublituximab-xiiy (Briumvi); **OR**

2. The patient has a diagnosis of moderately to severely active **Crohn's disease (CD)**; **AND**
   a. The patient is 18 years of age or older; **AND**
   b. ONE of the following:
      i. The patient has moderately to severely active disease, as evidenced by ONE of the following:
         1. The patient has BOTH of the following:
            a. Symptoms consistent with active CD (e.g., diarrhea, abdominal pain, significant weight loss, fatigue, fever, anemia, vitamin or mineral deficiencies, intermittent nausea or vomiting, etc.) **[medical record documentation required]**; **AND**
            b. Evidence of active inflammation, confirmed by ONE of the following **[medical record documentation required]**:
               i. Active inflammatory disease on cross-sectional imaging (MRE, CTE), intestinal ultrasound, or pelvic MRI for perianal disease (e.g., bowel wall thickening, ulceration, hyperenhancement, fistula, abscess); **OR**
               ii. Biomarker evidence indicative of inflammation (e.g., elevated fecal calprotectin [FC], elevated C-reactive protein [CRP], elevated erythrocyte sedimentation rate [ESR], low serum albumin); **OR**

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2. Significant extent of disease or upper GI involvement identified on radiographic or endoscopic assessment (e.g., large or deep mucosal lesions, fistulas or perianal abscesses, intestinal strictures, extensive disease [ileal involvement >40 cm or pancolitis], prior bowel resection, etc.) **[medical record documentation required]**; **OR**
3. Corticosteroid-dependence, or refractory to oral corticosteroids **[medical record documentation required]**; **OR**

ii. The patient is currently established on a biologic or systemic immunomodulator agent that is FDA approved for the treatment of CD (excluding sample use) **[medical record documentation required]**; **AND**
1. The patient has had positive clinical benefit (e.g., improvement in signs and symptoms, reduction in disease severity, etc.) from use of the biologic or systemic immunomodulator agent **[medical record documentation required]**; **AND**

c. ONE of the following:
i. The patient has tried and had an inadequate response to at least ONE of the following biologic agents for the treatment of CD used for at least 3 months: certolizumab pegol (e.g., Cimzia®), an adalimumab product, guselkumab (e.g., Tremfya®), an infliximab product (e.g., Avsola™, Inflectra®), risankizumab (e.g., Skyrizi®), an ustekinumab product, vedolizumab (Entyvio®) **[medical record documentation required]**; **OR**
ii. The patient has an intolerance or hypersensitivity to at least ONE biologic agent for the treatment of CD **[medical record documentation required]**; **OR**
iii. The patient has an FDA labeled contraindication to ALL biologic agents for the treatment of CD **[medical record documentation required]**; **AND**

d. The patient is NOT receiving the requested agent in combination with an immunomodulatory agent (e.g., TNF-alpha inhibitors, JAK inhibitors, IL-4 inhibitors) for CD; **AND**
e. The patient is NOT receiving the requested agent in combination with another immunosuppressant agent (e.g., 6-mercaptopurine, azathioprine, cyclosporine, methotrexate); **AND**

3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist for CD, neurologist for MS), or the prescriber has consulted with a specialist in the area of the patient's diagnosis; **AND**
4. The prescriber is registered through the MS TOUCH® or CD TOUCH® Prescribing Program(s), or the Tyruko MS or CD Risk Evaluation and Mitigation Strategy (REMS) Program(s); **AND**
5. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
6. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

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Continuation Criteria for Approval:

1. The patient was approved through Blue Cross NC initial criteria for approval; **OR**
2. The patient would have met initial criteria for approval at the time they started therapy; **AND**
3. The patient has had clinical benefit while receiving treatment with the requested agent (e.g., disease stability and/or improvement); **AND**
4. ONE of the following:
    a. For multiple sclerosis (MS), the patient is NOT receiving concurrent therapy with two or more disease-modifying drugs for MS, including glatiramer (Copaxone, Glatopa), interferon beta-1b (Betaseron, Extavia), interferon beta-1a (Avonex, Rebif), peginterferon beta-1a (Plegridy), fingolimod (Gilenya, Tascenso ODT), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), monomethyl fumarate (Bafiertam), ofatumumab (Kesimpta), alemtuzumab (Lemtrada), siponimod (Mayzent), cladribine (Mavenclad), ocrelizumab (Ocrevus, Ocrevus Zunovo), ponesimod (Ponvory), natalizumab (Tysabri, Tyruko), diroximel fumarate (Vumerity), ozanimod (Zeposia), and ublituximab-xiiy (Briumvi); **OR**
    b. For Crohn's disease (CD), the patient will NOT be using the requested agent in combination with an immunomodulatory agent (e.g., TNF-alpha inhibitors, JAK inhibitors, IL-4 inhibitors) for CD; **AND**
5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist for CD, neurologist for MS), or the prescriber has consulted with a specialist in the area of the patient's diagnosis; **AND**
6. The prescriber is registered through the MS TOUCH® or CD TOUCH® Prescribing Program(s), or the Tyruko MS or CD Risk Evaluation and Mitigation Strategy (REMS) Program(s); **AND**
7. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
8. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
natalizumab (Tysabri®) intravenous (IV) infusion	Relapsing forms of MS in patients ≥18 years old	IV: 300 mg every 4 weeks	J2323	3900

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FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
	Moderately to severely active CD in patients ≥18 years old	IV: 300 mg every 4 weeks; discontinue if no therapeutic benefit by 12 weeks of induction therapy and/or if unable to discontinue chronic concomitant steroids within 6 months of starting therapy		
natalizumab-sztn (Tyruko®) intravenous (IV) infusion	Relapsing forms of MS in patients ≥18 years old	IV: 300 mg every 4 weeks	Q5134	3900
	Moderately to severely active CD in patients ≥18 years old	IV: 300 mg every 4 weeks; discontinue if no therapeutic benefit by 12 weeks of induction therapy and/or if unable to discontinue chronic concomitant steroids within 6 months of starting therapy		

***Maximum units allowed for duration of approval**

***Site of Care Medical Necessity Criteria**

1. For requests for injection or infusion administration in an **inpatient setting**, the injection or infusion may be given if the above medical necessity criteria are met AND the inpatient admission is NOT for the sole purpose of administering the injection or infusion; **OR**
2. For requests for injection or infusion administration in an **outpatient hospital setting**, the injection or infusion may be given if the above medical necessity criteria are met AND ONE of the following must be met:
    a. History of a severe adverse event following the injection or infusion of the requested medication (i.e., anaphylaxis, seizure, thromboembolism, myocardial infarction, renal failure); **OR**

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b. Conditions that cause an increased risk for severe adverse event (i.e., unstable renal function, cardiopulmonary conditions, unstable vascular access); **OR**
c. History of mild adverse events that have not been successfully managed through mild pre-medication (e.g., diphenhydramine, acetaminophen, steroids, fluids, etc.); **OR**
d. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity; **OR**
e. New to therapy, defined as initial injection or infusion OR less than 3 months since initial injection or infusion; **OR**
f. Re-initiation of therapy, defined as ONE of the following:
    i. First injection or infusion after 6 months of no injections or infusions for drugs with an approved dosing interval less than 6 months duration; **OR**
    ii. First injection or infusion after at least a 1-month gap in therapy outside of the approved dosing interval for drugs requiring every 6 months dosing duration; **OR**
g. Requirement of a change in the requested restricted product formulation; **AND**

3. If the Site of Care Medical Necessity Criteria in #1 or #2 above are not met, the injection or infusion will be administered in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional.

MS Disease Modifying Agents drug classes

Drug Class	Agents
CD20 monoclonal antibody	Briumvi, Kesimpta, Ocrevus, Ocrevus Zunovo
CD52 monoclonal antibody	Lemtrada
Fumarates	Bafiertam, Tecfidera, Vumerity
Glatiramer	Copaxone, Glatopa
$IgG4_k$ monoclonal antibody	Tysabri, Tyruko
Interferons	Avonex, Betaseron, Extavia, Plegridy, Rebif
Purine antimetabolite	Mavenclad
Pyrimidine synthesis inhibitor	Aubagio
Sphingosine 1-phosphate (SIP) receptor modulator	Gilenya, Mayzent, Ponvory, Zeposia, Tascenso ODT

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References: all information referenced is from FDA package insert unless otherwise noted below.

1. Bloomingren G, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med*. 2012;366:1870-1880.
2. Lichtenstein GR, Loftus EV Jr, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol.* 2025; 120(6):1225-1264.
3. Scott FI, Ananthakrishnan AN, Click B, et al. AGA Living Clinical Practice Guideline on the Pharmacologic Management of Moderate-to-Severe Crohn's Disease. *Gastroenterology*. 2025;169(7):1397-1448.

Policy Implementation/Update Information: Criteria and treatment protocols are reviewed annually by the Blue Cross NC P&T Committee, regardless of change. This policy is reviewed in Q4 annually.

July 2026: Criteria change: For CD: Added allowance for patients currently established on a biologic or systemic immunomodulator agent that is FDA approved for treatment of the requested indication for those who have had positive clinical benefit from use of the biologic or systemic immunomodulator agent; Removed required trial and failure of conventional therapy; Replaced allowance for severely active disease with required demonstration of moderately to severely active disease by documented presence of symptoms of active disease plus evidence of active inflammation OR significant extent of disease or upper GI involvement on radiographic or endoscopic assessment OR corticosteroid-dependence or refractory to oral corticosteroids; Changes made to align with updated clinical guidelines. Other minor formatting changes made throughout policy for clarity with no change to intent. **Policy notification given 5/1/2026 for effective date 7/1/2026**.
November 2025: Criteria change: Updated Site of Care medical necessity criteria to add additional bypass for patients with a history of severe adverse events or conditions that cause an increased risk for severe adverse event to align with the Place of Service for Medical Infusions policy for clarity of intent.
August 2025: Criteria change: For CD: Updated policy to allow bypassing conventional agents for severely active Crohn's disease.
April 2025: Criteria change: For Crohn's disease indication, updated list of preferred biologic agents for trial and failure to add Tremfya and Entyvio, and to remove listed examples of adalimumab products and ustekinumab products for clarity.
October 2024: Criteria update: Updated list of disease-modifying drugs for MS not to be used concomitantly and reference table with drug classes of MS disease modifying agents for clarity.
April 2024: Coding change: Added HCPCS code Q5134 for Tyruko to dosing reference table effective 4/1/2024; deleted C9399, J3490, J3590 termed 3/31/2024.
September 2023: Criteria change: Added newly approved natalizumab biosimilar, Tyruko (natalizumab-sztn), to policy for the same FDA approved indications as Tysabri with the same coverage criteria requirements. Added drug to SOC criteria and added associated dosing and maximum units, and HCPCS codes C9399, J3490, and J3590 to FDA label reference table. Adjusted initial and continuation criteria for no combination use with two or more disease-modifying drugs for MS for clarity with no change to policy intent. Updated list of disease-

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modifying drugs for MS not to be used concomitantly and reference table with drug classes of MS disease modifying agents for clarity. Changed policy name to “Natalizumab (Tysabri®) and Natalizumab Biosimilars” from “Natalizumab (Tysabri®)”.
July 2023: Criteria update: Updated generic glatiramer acetate (generic Copaxone) to include Glatopa as an option for required trial and failure of one generic product.
July 2023: Criteria change: For MS: Adjusted requirement of trial and failure of alternative MS disease-modifying therapy to one generic product [dimethyl fumarate (generic Tecfidera), fingolimod (generic Gilenya), glatiramer acetate (generic Copaxone), or teriflunomide (generic Aubagio)] or previous treatment with at least 3 MS agents from different drug classes. Added requirement of some walking or functional arm/hand use within initial criteria. Removed requirement of no concomitant use with another chronic immunosuppressant agent for clarity. For CD: Updated list of conventional agents and biologic agents for trial and failure. For both indications, added continuation criteria and removed requirement of no significant immunocompromise. Adjusted policy formatting and added reference table with drug classes of MS disease modifying agents. **Policy notification given 5/2/2023 for effective date 7/1/2023**.
June 2021: Criteria change: CD: Medical record documentation required for trial and failure of conventional agents; removed criterion point regarding medication history indicating use of another biologic immunomodulator agent for the treatment of CD.
June 2021: Criteria change: CD: Addition of criteria for history of use of another biologic immunomodulator agent for the same indication; added requirements to be prescribed by or in consultation with a specialist; added maximum units; medical policy formatting change. **Policy notification given 4/16/2021 for effective date 6/16/2021**.
*Further historical criteria changes and updates available upon request from Medical Policy and/or Corporate Pharmacy.

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