Clinical Policy: Natalizumab (Tysabri), Natalizumab-sztn (Tyruko)

Reference Number: PA.CHIP.PHAR.259
Effective Date: 01/2026
Last Review Date: 10/2025

Description
Natalizumab (Tysabri®) and its biosimilar, natalizumab-sztn (Tyruko®), are integrin receptor antagonists.

FDA Approved Indication(s)
Tysabri and Tyruko are indicated:

- As monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- For 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 tumor necrosis factor-α (TNF-α)

Limitation(s) of use:

- Tysabri and Tyruko increases the risk of progressive multifocal leukoencephalopathy. When initiating and continuing treatment with Tysabri or Tyruko, physicians should consider whether the expected benefit of Tysabri or Tyruko is sufficient to offset this risk.
- In CD, Tysabri and Tyruko should not be used in combination with immunosuppressants or inhibitors of TNF-α.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that the member has met all approval criteria.

It is the policy of PA Health & Wellness® that Natalizumab (Tysabri) and Natalizumab-sztn (Tyruko) are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all)**:**

1. Diagnosis of one of the following (a, b, or c):
   a. Clinically isolated syndrome, and member is contraindicated to both, or has experienced clinically significant adverse effects to one, of the following at up to maximally indicated doses: an **interferon-beta agent** (Avonex®, Betaseron®/Extavia®†, Rebif®, or Plegridy®), **glatiramer** (Copaxone®, Glatopa®);
   b. Relapsing-remitting MS, and one of the following (i or ii):
      i. Failure of all of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated (1, 2, 3, and 4):*
         1. **Dimethyl fumarate** (generic Tecfidera®);
         2. **Teriflunomide** (generic Aubagio®);
         3. **Fingolimod** (Gilenya®);
         4. An **interferon-beta agent** (Avonex, Betaseron/Extavia, Rebif, or Plegridy) or **glatiramer** (Copaxone, Glatopa);

**Prior authorization is required for all disease modifying therapies for MS*

ii. Member has highly active MS, and failure of **fingolimod** (Gilenya) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;

c. Secondary progressive MS;

2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Tysabri and Tyruko are not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval duration: 6 months

A. Crohn's Disease (must meet all)**:**

1. Diagnosis of CD;
2. Prescribed by or in consultation with a gastroenterologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Failure of a ≥ 3 consecutive month trial of at least ONE immunomodulator (e.g., azathioprine, 6-mercaptopurine [6-MP], methotrexate [MTX]) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. Medical justification supports inability to use immunomodulators (*see Appendix E*);
5. Member meets one of the following, unless clinically significant adverse effects are experienced or all are contraindicated (a or b, *see Appendix D*):*
   a. Failure of one* adalimumab product (e.g., *Hadlima™, Simlandi®, Yusimry™, adalimumab-aaty, adalimumab-adaz, adalimumab-adbm, and adalimumab-fkjp are preferred*), used for ≥ 3 consecutive months;
   b. History of failure of two TNF blockers;

   **Prior authorization is required for adalimumab products*
6. Failure of a ≥ 3 consecutive month trial of one ustekinumab product (e.g. *Otulfi®, Pyzchiva® (branded), Steqeyma®, Yesintek™ are preferred*), unless clinically significant adverse effects are experienced or all are contraindicated;

   **Prior authorization may be required for ustekinumab products*
7. Tysabri and Tyruko are not prescribed concurrently with immunosuppressants (e.g., azathioprine, cyclosporine, 6-MP, MTX) or TNF-α inhibitors (note: aminosalicylates may be continued);
8. Dose does not exceed 300 mg (1 vial) every 4 weeks.

   Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Multiple Sclerosis (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Fidelis benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. Tysabri and Tyruko are not prescribed concurrently with other disease modifying therapies (*see Appendix D*);
4. If request is for a dose increase, new dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval duration: 12 months

B. Crohn's Disease (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Fidelis benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. Tysabri and Tyruko are not prescribed concurrently immunosuppressants (e.g., azathioprine, cyclosporine, 6-MP, MTX) or TNF-α inhibitors (note: aminosalicylates may be continued);
4. If request is for a dose increase, new dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – CP.PMN.53 for Medicaid or evidence of coverage documents;

B. Primary progressive MS.

C. Appendices/General Information

Appendix A: Abbreviation/Acronym

Key 6-MP: 6-mercaptopurine
CD: Crohn's disease
FDA: Food and Drug Administration GI: gastrointestinal
MS: multiple sclerosis
MTX: methotrexate
TNF-α: tumor necrosis factor-α

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
MS agents		
Avonex®, Rebif® (interferon beta-1a)	*Avonex*: 30 mcg IM Q week *Rebif*: 22 mcg or 44 mcg SC TIW	*Avonex*: 30 mcg/week *Rebif*: 44 mcg TIW
Betaseron®, Extavia® (interferon beta-1b)	250 mcg SC QOD	250 mg QOD
Plegridy® (peginterferon beta-1a)	125 mcg SC Q2 weeks	125 mcg/2 weeks
glatiramer acetate (Copaxone®, Glatopa®)	20 mg SC QD or 40 mg SC TIW	20 mg/day or 40 mg TIW
teriflunomide (Aubagio®)	7 mg or 14 mg PO QD	14 mg/day
fingolimod (Gilenya®)	0.5 mg PO QD	0.5 mg/day
dimethyl fumarate (Tecfidera®)	120 mg PO BID for 7 days, followed by 240 mg PO BID	480 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
CD agents		
6-mercaptopurine (Purixan®)*	50 mg PO QD or 1.5 – 2 mg/kg/day PO	2 mg/kg/day
azathioprine (Azasan®, Imuran®)*	1.5 – 2 mg/kg/day PO	2.5 mg/kg/day
corticosteroids*	prednisone 40 mg PO QD for 2 weeks or IV 50 – 100 mg Q6H for 1 week budesonide (Entocort EC®) 6 – 9 mg PO QD	Various
methotrexate (Otrexup®, Rasuvo)*	15 – 25 mg/week IM or SC	30 mg/week
Pentasa® (mesalamine)	1,000 mg PO QID	4 g/day
tacrolimus (Prograf®)*	0.27 mg/kg/day PO in divided doses or 0.15 – 0.29 mg/kg/day PO	N/A
Cimzia® (certolizumab)	Initial dose: 400 mg SC at 0, 2, and 4 weeks Maintenance dose: 400 mg SC every 4 weeks	400 mg every 4 weeks
Hadlima (adalimumab-bwwd), Simlandi (adalimumab-ryvk), Yusimry (adalimumab-aqvh), adalimumab-aaty (Yuflyma®), adalimumab-adaz (Hyrimoz®), adalimumab-fkjp (Hulio®), adalimumab-adbm (Cyltezo®)	Initial dose: 160 mg SC on Day 1, then 80 mg SC on Day 15 Maintenance dose: 40 mg SC every other week starting on Day 29	40 mg every other week
Avsola™, Renflexis™, Inflectra® (infliximab)	Initial dose: 5 mg/kg IV at weeks 0, 2 and 6 Maintenance dose: 5 mg/kg IV every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response	10 mg/kg every 8 weeks
Otulfi® (ustekinumab-aauz), Pyzchiva®	Weight based dosing IV at initial dose:	90 mg every 8 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
(ustekinumab-ttwe), Steqeyma® (ustekinumab-stba), Yesintek™ (ustekinumab-kfce)	Weight ≤ 55 kg: 260 mg Weight > 55 kg to 85 kg: 390 mg Weight > 85 kg: 520 mg <u>Maintenance dose:</u> 90 mg SC every 8 weeks	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Patients who have or have had progressive multifocal leukoencephalopathy
  - Patients who have had a hypersensitivity reaction to Tysabri or Tyruko
- Boxed warning(s): progressive multifocal leukoencephalopathy

Appendix D: General Information

- Because of the risk of progressive multifocal leukoencephalopathy, Tysabri and Tyruko are only available through a REMS program called the TOUCH® Prescribing Program.
- Disease-modifying therapies for MS are: glatiramer acetate (Copaxone®, Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plegridy®), dimethyl fumarate (Tecfidera®), diroximel fumarate (Vumerity®), monomethyl fumarate (Bafiertam™), fingolimod (Gilenya® , Tascenso ODT™), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®, and biosimilar Tyruko®), ocrelizumab (Ocrevus®), ocrelizumab/hyaluronidase-ocsq (Ocrevus Zunovo™), cladribine (Mavenclad®), siponimod (Mayzent®), ozanimod (Zeposia®), ponesimod (Ponvory™), ublituximab-xiiy (Briumvi™), and ofatumumab (Kesimpta®).
- The American Academy of Neurology 2018 MS guidelines recommend the use of Gilenya, Tysabri, Tyruko, and Lemtrada for patients with highly active MS. Definitions of highly active MS vary and can include measures of relapsing activity and MRI markers of disease activity, such as numbers of gadolinium-enhanced lesions.
- Of the disease-modifying therapies for MS that are FDA-labeled for clinically isolated syndrome, only the interferon products, glatiramer, and Aubagio have demonstrated any efficacy in decreasing the risk of conversion to MS compared to placebo. This is supported by the American Academy of Neurology 2018 MS guidelines.
- Definition of failure of MTX or DMARDs
  - Child-bearing age is not considered a contraindication for use of MTX. Each drug has risks in pregnancy. An educated patient and family planning would allow use of MTX in patients who have no intention of immediate pregnancy.
  - Social use of alcohol is not considered a contraindication for use of MTX. MTX may only be contraindicated if patients choose to drink over 14 units of alcohol per week. However, excessive alcohol drinking can lead to worsening of the condition, so

patients who are serious about clinical response to therapy should refrain from excessive alcohol consumption.

- TNF blockers:
  - Etanercept (Enbrel®), adalimumab (Humira®) and its biosimilars, infliximab (Remicade®) and its biosimilars (Avsola™, Renflexis™, Inflectra®), certolizumab pegol (Cimzia®), and golimumab (Simponi®, Simponi Aria®).

Appendix E: Medical Justification

- The following may be considered for medical justification supporting inability to use an immunomodulator for Crohn's disease:
  - Inability to induce short-term symptomatic remission with a 3-month trial of systemic glucocorticoids
  - High-risk factors for intestinal complications may include:
    - Initial extensive ileal, ileocolonic, or proximal GI involvement
    - Initial extensive perianal/severe rectal disease
    - Fistulizing disease (e.g., perianal, enterocutaneous, and rectovaginal fistulas)
    - Deep ulcerations
    - Penetrating, stricturing or stenosis disease and/or phenotype
    - Intestinal obstruction or abscess

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Relapsing MS, CD	300 mg IV every 4 weeks In CD, discontinue in patients who have not experienced therapeutic benefit by 12 weeks of induction therapy and in patients that cannot discontinue chronic concomitant steroids within six months of starting therapy	300 mg/4 weeks

V. Product Availability

Single-use vial: 300 mg/15 mL

VI. References

1. Tysabri Prescribing Information. Cambridge, MA: Biogen Inc; October 2023. Available at http://www.tysabri.com. Accessed January 23, 2025.
2. Tyruko Prescribing Information. Princeton, NJ: Sandoz Inc; August 2023. Available at www.tyruko.com. Accessed January 23, 2025.
3. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. Gastroenterology 2021; 160:2496-2508. https://doi.org/10.1053/j.gastro.2021.04.022.
4. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: Management of Crohn's disease in adults. Am J Gastroenterol. 2018;113(4):481-517. doi: 10.1038/ajg.2018.27.
5. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. Annals of Surgery. 2000; 231(1): 38-45.
6. 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(17): 777-788. Full guideline available at: https://www.aan.com/Guidelines/home/GetGuidelineContent/898. Reaffirmed on October 19, 2024

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to- date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J2323	Injection, natalizumab, 1 mg
Q5134	Injection, natalizumab-sztn (tyruko), biosimilar, 1 mg

Reviews, Revisions, and Approvals	Date
Policy created	10/2025