

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

Reference Number: CP.PHAR.259

Effective Date: 08.01.16

Last Review Date: 06.25

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

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 member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Tysabri and 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*
†Betaseron is the preferred interferon beta-1b product for the Commercial and HIM lines of business
- 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:

Medicaid/HIM – 6 months

Commercial – 6 months or to the member's renewal date, whichever is longer

B. Crohn's Disease – FOR MEDICAID ONLY* (must meet all):

**Refer to CP.CPA.194 Biologic DMARDs for Commercial and HIM.PA.SP60 Biologic DMARDs for HIM*

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), *Selarsdi*[™], *Stegeyma*[®], *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

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 formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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 Centene 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:

Medicaid/HIM – 12 months

Commercial – 6 months or to the member's renewal date, whichever is longer

B. Crohn's Disease – *FOR MEDICAID ONLY (must meet all):**

**Refer to CP.CPA.194 Biologic DMARDs for commercial and HIM.PA.SP60 Biologic DMARDs for HIM*

1. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene 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: aminosaliclates 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 formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents;
- B. Primary progressive MS.

IV. 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
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)	<u>Initial dose:</u> 400 mg SC at 0, 2, and 4 weeks <u>Maintenance dose:</u> 400 mg SC every 4 weeks	400 mg every 4 weeks
Hadlima (adalimumab- bwwd), Simlandi (adalimumab-ryvk), Yusimry (adalimumab- aqvh), adalimumab-aaty (Yuflyma [®]), adalimumab-	<u>Initial dose:</u> 160 mg SC on Day 1, then 80 mg SC on Day 15 <u>Maintenance dose:</u>	40 mg every other week

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
adaz (Hyrimoz [®]), adalimumab-fkjp (Hulio [®]), adalimumab- adbm (Cyltezo [®])	40 mg SC every other week starting on Day 29	
Avsola [™] , Renflexis [™] , Inflectra [®] (infliximab)	<u>Initial dose:</u> 5 mg/kg IV at weeks 0, 2 and 6 <u>Maintenance dose:</u> 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
Otulf [®] (ustekinumab- aauz), Pyzchiva [®] (ustekinumab-ttwe), Selarsdi [™] (ustekinumab- aekn), Steqeyma [®] (ustekinumab-stba), Yesintek [™] (ustekinumab- kfce)	<u>Weight based dosing IV at initial dose:</u> 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	90 mg 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

V. 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

VI. Product Availability

Single-use vial: 300 mg/15 mL

VII. 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.

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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2021 annual review: no significant changes; references reviewed and updated.	02.08.21	05.21
Per June SDC and prior clinical guidance, modified Avsola to parity status with Inflectra and Renflexis.	06.02.21	08.21
2Q 2022 annual review: no significant changes; added Commercial and HIM lines of business (CP.CPA.82 and HIM.PA.SP17 to be retired); references reviewed and updated.	02.08.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.11.22	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Per February SDC, added Amjevita as an alternative option to Humira for CD.	02.13.23	
2Q 2023 annual review: for CD, added TNFi criteria to allow bypass if member has had history of failure of two TNF blockers; for MS, to be inclusive of members continuing therapy from a different benefit, revised Medicaid/HIM continued approval duration to reference the duration of total treatment received rather than the number of re-authorizations; references reviewed and updated.	02.21.23	05.23
Per July SDC: for CD removed criteria requiring use of Humira and Amjevita, added criteria requiring use of one adalimumab product and stating Yusimry, Hadlima, unbranded adalimumab-fkjp, and unbranded adalimumab-adaz as preferred; updated Appendix B with relevant therapeutic alternatives.	07.25.23	
Per August SDC, added generic references to Aubagio and Gilenya redirections.	08.22.23	11.23
Per December SDC, added adalimumab-adbm to listed examples of preferred adalimumab products; RT4: added Tyruko, a biosimilar, to policy.	12.06.23	02.24
Added HCPCS code [Q5134] and removed HCPCS codes [J3490, C9399]	02.22.24	
2Q 2024 annual review: no significant changes; references reviewed and updated.	01.30.24	05.24
Per June SDC: for CD, added Simlandi to listed examples of preferred adalimumab products. Per SDC: for CD, added unbranded adalimumab-aaty to listed examples of preferred adalimumab products.	07.23.24	08.24
2Q 2025 annual review: for MS, removed requirements for documentation of baseline relapses/expanded disability status score and specific measures of positive response per competitor analysis and removed notation that Extavia is the preferred interferon beta-1b product for the Medicaid line of business as it is no longer available on market per SDC; for MS continued therapy, modified HIM and Medicaid approval duration from “if member has received < 1 year of total treatment – up to a total of 12 months of treatment and if member has received ≥ 1 year of total treatment – 12 months” to “12 months”; references reviewed and updated.	02.12.25	05.25
Per April SDC: for CD, added criteria requiring use of one preferred Stelara biosimilar (Otulfi, Pyzchiva (branded), Selarsdi, Yesintek, and Steqeyma are preferred).	04.23.25	06.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted

standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

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Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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