Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCNS020.1225	**CENTRAL NERVOUS SYSTEM DRUGS** **TYRUKO®** (natalizumab-sztn intravenous solution) **TYSABRI®** (natalizumab intravenous solution)
Effective Date: 2/1/2026	**Review/Revised Date**: 04/07, 04/08, 08/09, 04/10, 04/11, 10/11, 02/12, 08/12, 08/13, 08/14, 08/15, 07/16, 09/16, 07/17, 01/18, 07/19, 11/19, 07/20, 04/21, 07/21, 06/22, 08/23, 07/24, 07/25, 12/25 (JEF)
Original Effective Date: 01/07	**P&T Committee Meeting Date**: 10/06, 04/07, 04/08, 04/09, 04/10, 04/11, 10/11, 02/12, 08/12, 08/13, 08/14, 08/15, 08/16, 10/16, 08/17, 02/18, 08/18, 08/19, 12/19, 08/20, 04/21, 08/21, 08/22, 08/24, 10/25, 12/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy for **multiple sclerosis (MS)**, all the following criteria (a-c) must be met:
    a. Must have one of the following confirmed diagnoses:
        i. Relapsing-remitting disease (RRMS)
        ii. Secondary progressive multiple sclerosis (SPMS)
        iii. Clinically isolated syndrome (CIS)
    b. Documentation of one of the following:
        i. Documentation the patient has highly active disease defined as ONE of the following:
            1) Greater than or equal to two relapses in the previous year
            2) The patient has greater than or equal to one gadolinium enhancing lesion on MRI
            3) Presence of significant T2 lesion burden defined as ONE of the following:
                a) Greater than 10 T2 lesion burden as documented with MRI
                b) Significant increase in T2 lesion load compared with a previous MRI

c) T2 lesion(s) located in spinal cord or brainstem

ii. The patient has been treated with at least three multiple sclerosis agents from different drug classes

iii. Inadequate response (after at least six months of continuous therapy) or intolerance to one of the following: generic dimethyl fumarate, generic glatiramer acetate/Glatopa®, generic fingolimod, or generic teriflunomide

iv. FDA labeled contraindication to ALL the following: generic dimethyl fumarate, generic glatiramer/Glatopa®, generic fingolimod, and generic teriflunomide

c. Negative anti-JCV antibody status **OR** if anti-JCV antibody positive, the patient must meet the following criteria:

i. Confirmation patient has not used any of the following immunosuppressants agents: mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil

ii. Medical rationale is provided for continued use despite increased risk of developing progressive multifocal leukoencephalopathy (PML)

2. For initiation of therapy for **Crohn's disease**, all the following criteria (a-c) must be met:
   a. Diagnosis of moderate to severe Crohn's disease, **AND**
   b. Documentation of trial and failure (after at least three months of therapy), intolerance, or contraindication to a preferred tumor necrosis factor (TNF) inhibitor [infliximab (Inflectra® or Renflexis®) and/or adalimumab (Hadlima®, Simlandi®, adalimumab-aaty, adalimumab-adaz)] indicated for Crohn's or vedolizumab (Entyvio®), **AND**
   c. Negative anti-JCV antibody status within the last year **OR** if anti-JCV antibody positive, the patient must meet the following criteria:
      i. Confirmation patient has not used any of the following immunosuppressants agents: mitoxantrone, azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil, **AND**
      ii. Medical rationale is provided for continued use despite increased risk of developing progressive multifocal leukoencephalopathy (PML)
3. **For patients established on therapy**: Documentation of positive clinical response to therapy must be provided

EXCLUSION CRITERIA:

1. Use of natalizumab in combination with other disease modifying therapy (DMT) to treat patients with multiple sclerosis (such as dimethyl fumarate, glatiramer)

2. Use of natalizumab in combination with immunosuppressants or TNF inhibitors (such as adalimumab).

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Prescribed by, or in consultation with, either a neurologist (for multiple sclerosis) or gastroenterologist (for Crohn's disease)

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

QUANTITY LIMIT:
Dosing and frequency must be within FDA-labeled guidelines or supported by compendia

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Natalizumab products are monoclonal antibodies that bind to integrins on the surface of leukocytes (except neutropjils). They inhibit adhesion of leukocytes to receptors, thus preventing migration of leukocytes across the endothelium into parenchyma tissue.

FDA APPROVED INDICATIONS:

- 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 remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of TNF-α
    - Limitations of use in Crohn's: Natalizumab products should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α

POSITION STATEMENT:

Boxed Warning: Progressive Multifocal Leukoencephalopathy (PML)

- Natalizumab products increase the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability
- Risk factors for the development of PML include the presence of anti-JCV antibodies, duration of therapy, and prior use of immunosuppressants. These factors should be considered in the context of expected benefit when initiating and continuing treatment
- Monitor patients, and withhold treatment immediately at the first sign or symptom suggestive of PML
- TYSABRI is available only through a special restricted distribution program called the TOUCH® Prescribing Program and must be administered only to patients enrolled in this program
- TYRUKO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TYRUKO REMS Program.

In 2010, the FDA notified healthcare professionals and patients that the risk of developing progressive multifocal leukoencephalopathy (PML) increases with the number of Tysabri infusions received. Information about the occurrence of Immune Reconstitution Inflammatory Syndrome (IRIS) in patients who have developed PML and subsequently discontinued Tysabri® has also been added to the drug label. IRIS is a rare condition characterized by a severe inflammatory response that can occur during or following immune system recovery, causing an unexpected decline in a patient's condition after return of immune function.

Guidelines for Multiple Sclerosis include the American Academy of Neurology Publication "Comprehensive Systematic Review Summary: Disease-Modifying Therapies for Adults with Multiple Sclerosis" published in 2018 and a consensus paper by the Multiple Sclerosis Coalition titled "The Use of Disease-Modifying

Therapies in Multiple Sclerosis" published in 2019. Guidelines state that initiating a disease modifying therapy (DMT) should be offered to patients as early as possible. The choice of initial DMT should be individualized to consider safety, route of administration, lifestyle, cost, efficacy, adverse effects (AEs), and tolerability. When switching therapies after failure of an agent, disease activity, adherence, AE profiles, and mechanisms of action should be considered when selecting a new agent to start. For advanced, aggressive, or highly active disease guidelines recommend fingolimod (Gilenya®), natalizumab (Tysabri®), ocrelizumab (Ocrevus®), or alemtuzumab (Lemtrada®). Additionally, guidelines state categorize DMT therapies for evidence for lowering relapse rate (see Table 1).[5]

Table 1. DMT Evidence for Lowering Relapse Rate[5]

Very Low	Low	Moderate	Strong
Immunoglobulins	Cyclophosphamide	Azathioprine	Alemtuzumab
Methotrexate	Mycophenolate Mofetil	Interferon beta-1b	Cladribine
Rituximab			Dimethyl Fumarate†
Corticosteroids			Fingolimod†
			Glatiramer Acetate†
			Interferon beta-1a
			Mitoxantrone
			Natalizumab
			Ocrelizumab
			Pegylated Interferon
			Teriflunomide†

† Generic Available

Table 2: Billing Guidelines and Coding Information

CODES◊		
HCPCS code	**Coding Description**	**Brand Name**
J2323	Injection, natalizumab, 1 mg	Tysabri
Q5134	Injection, natalizumab-sztn (tyruko), biosimilar, 1 mg	Tyruko
ADMINISTRATION◊		

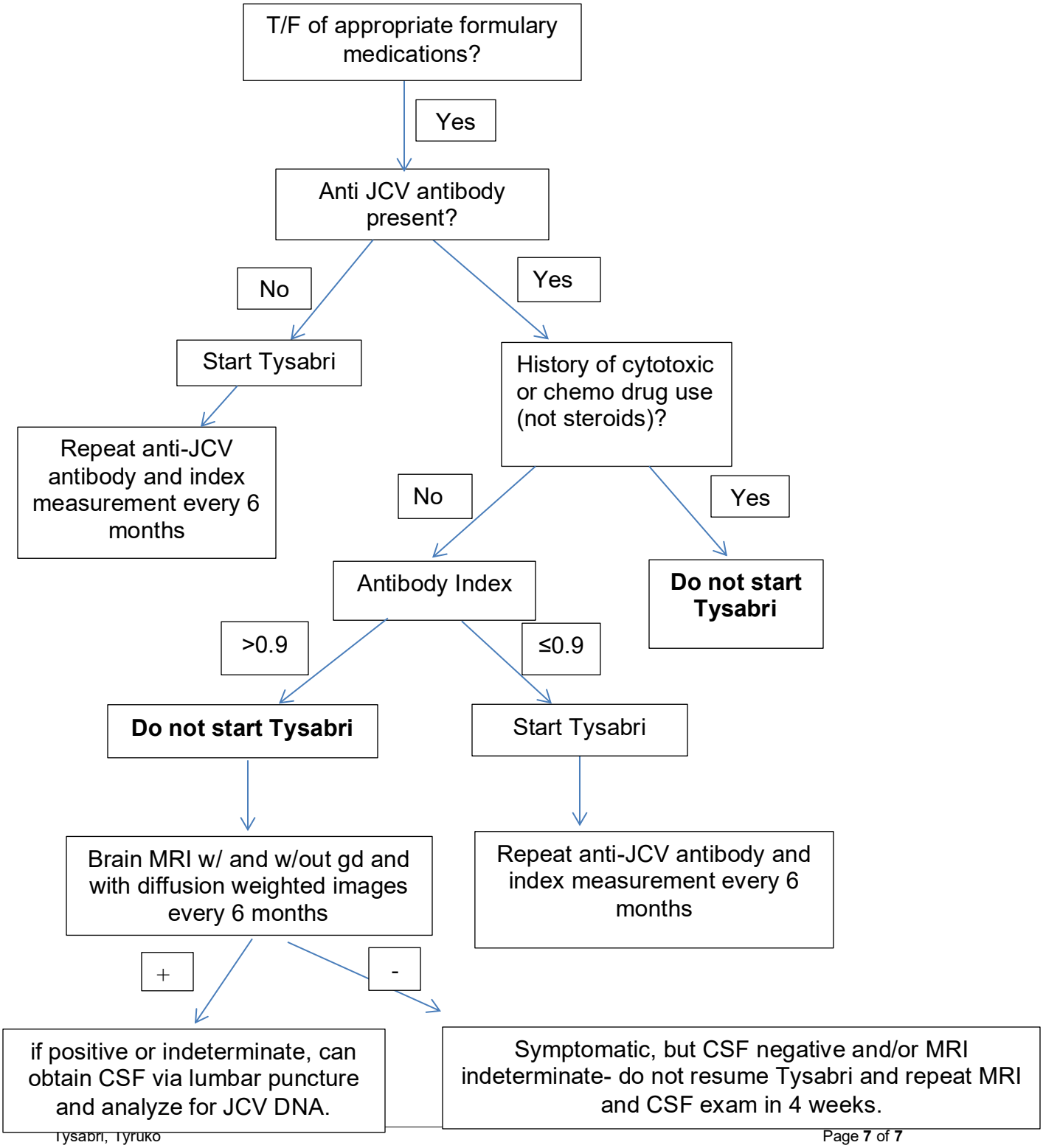
96365	Ther/proph/diag iv inf init	
96413	Chemo iv infusion 1 hr	

◊ Coding/Administration Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCE/RESOURCES:

1. Tysabri® package insert. Cambridge, MA: Biogen Idec Inc.; 2025 March.
2. Gorelik L, Lerner, M, Bixler S, et al. Anti-JC Virus Antibodies: Implications for PML Risk Stratification. *Ann Neurol* 2010;68:295-303.
3. Yousry TA, Habil DM, Major EO, et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. *N Engl J Med 2006*;354:924-33.
4. Yousry TA, Habil DM, Major EO, et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. N Engl J Med 2006;354:924-33.
5. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Neurology 2018;90:777–788.
6. Tyruko® package insert. Princeton, NJ. Sandoz Inc.; 2025 October.

APPENDIX


T/F of appropriate formulary medications?
Yes
Anti JCV antibody present?
No
Yes
Start Tysabri
History of cytotoxic or chemo drug use (not steroids)?
Repeat anti-JCV antibody and index measurement every 6 months
No
Yes
Antibody Index
Do not start Tysabri
>0.9
≤0.9
Do not start Tysabri
Start Tysabri
Brain MRI w/ and w/out gd and with diffusion weighted images every 6 months
Repeat anti-JCV antibody and index measurement every 6 months
+
-
if positive or indeterminate, can obtain CSF via lumbar puncture and analyze for JCV DNA.
Symptomatic, but CSF negative and/or MRI indeterminate- do not resume Tysabri and repeat MRI and CSF exam in 4 weeks.