Department:	Pharmacy Management	**Original Approval:**	01/20/2016
Policy #:	PM126	**Last Approval:**	06/14/2018
Title:	Natalizumab (Tysabri®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Natalizumab (Tysabri): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Age - Medication list (current and past) to include start and end dates of previous trials for all biologics and disease-modifying agents -Prescribed by or in consultation with a neurologist, gastroenterologist or specialist as indicated -Labs/diagnostics -Dosing and duration requested.

BACKGROUND

Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS).[1] Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing treatment with Tysabri, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that usually leads to death or severe disability. The efficacy of Tysabri beyond 6 years duration is unknown. Efficacy of Tysabri in relapsing MS was established in two pivotal clinical trials.[2-3]

Tysabri is also indicated for inducing and maintaining clinical response and 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 tumor necrosis factor (TNF)-α, for example, an infliximab product (such as Remicade® [infliximab for intravenous {IV} infusion] or Inflectra™ [infliximab-dyyb IV infusion]), Humira® (adalimumab for subcutaneous [SC] injection), Cimzia® (certolizumab pegol for SC injection).[1,4-6] Tysabri should not be used in combination with immunosuppressants (e.g., azathioprine, 6-mercaptopurine, cyclosporine, methotrexate [MTX]) or inhibitors of TNFα. Aminosalicylates may be continued during therapy with Tysabri.

The recommended dose of Tysabri is 300 mg by IV infusion over approximately 1 hour every 4 weeks.[1] Tysabri is available as a preservative-free solution in single-use vials containing 300 mg of Tysabri in 15 mL (20 mg/mL). This concentrated solution must be diluted before IV administration in 100 mL of 0.9% sodium chloride injection. It should not be given IV push or by bolus injection.

Risk Evaluation and Mitigation Strategy (REMS)

Tysabri is available only through a special restricted distribution program called the TOUCH® Prescribing Program, which requires registration by the prescribers, patients, infusion centers, and pharmacies

associated with infusion centers.[1] Tysabri must be administered only to patients enrolled in and who meet all the conditions of the TOUCH Prescribing Program. Tysabri's MS indication is for monotherapy because it is unknown how combination use with other immune modifying drugs could impact its safety.[1,7]

Table 1. Estimated US Incidence of PML Stratified by Risk Factor.[1*]

Anti-JCV Antibody Negative[‡]	Tysabri Exposure[†]	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
< 1/1,00	1 to 24 months	< 1/1,000	1/1,000
	25 to 48 months	3/1,000	12/1,000
	49 to 72 months	6/1,000	13/1,000

PML – Progressive multifocal leukoencephalopathy; *The risk estimates are based on post-marketing data in the US from about 69,000 Tysabri exposed patients; JCV – John Cunningham virus; [‡] The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%; [†] Data beyond 6 years of treatment are limited.

Each of the following risk factors is associated with an increased risk of PML.[1] These factors should be considered in the context of expected benefit when Tysabri is started and continued.

- Treatment duration, especially greater than 2 years. There is limited experience using Tysabri for greater than 6 years; OR
- Prior immunosuppressant use (e.g., mitoxantrone, azathioprine, MTX, cyclophosphamide, mycophenolate mofetil); OR

Presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk of developing PML.

For Crohn's disease, Tysabri should not be used with concomitant immunosuppressants or TNFα inhibitors.[1] Also in Crohn's disease, the drug should be discontinued if the patient has not had therapeutic benefit by 12 weeks of induction therapy. For patients with Crohn's disease who start Tysabri while on chronic oral corticosteroids, steroid tapering should be started as soon as a therapeutic benefit of Tysabri has occurred. If these patients cannot be tapered off oral corticosteroids within 6 months of starting Tysabri, Tysabri must be discontinued. Prescribers should also consider discontinuing Tysabri in patients who require additional steroid use > 3 months in a calendar year to control their Crohn's disease.

Multiple Sclerosis (MS)

MS is a chronic demyelinating, disabling disease of the central nervous system (CNS) characterized by recurrent and progressive neurologic dysfunction.[8] MS lesions occur in many different parts of the CNS and the symptoms and clinical course of the disease are highly variable. Some common signs and symptoms of the disease include vision problems (e.g., nystagmus), ambulation problems, pain, fatigue, spasticity, cognitive dysfunction, depression, ataxia, sensory loss, bladder disturbances, bowel dysfunction, dizziness, and vertigo. Most people with MS are diagnosed between the ages of 20 and 50 years, but MS can manifest in young children and older adults. Approximately 400,000 people are living with MS in the US and approximately 200 people are newly diagnosed weekly.

Four different clinical courses of MS have been delineated.[8] A relapse is defined as the development of new or recurring symptoms lasting at least 24 hours and separated from a previous attack by at least 1 month. *Relapsing-remitting MS (RRMS)* is characterized by acute attacks usually followed by almost complete recovery with limited progression. Disease progression is minimal between attacks. Approximately 85% of people are initially diagnosed with RRMS. *Secondary progressive MS (SPMS)* begins as relapsing-remitting course but the disease transitions in many patients to a steadily progressive form with increased loss of function. Of the 85% of patients who initially have RRMS, more than 50% will develop SPMS within 10 years and 90% within 25 years. *Primary progressive MS (PPMS)* is noted by a steady decline in function from the onset without noted relapses. Around 10% of patients are diagnosed with PPMS. *Progressive-relapsing MS (PRMS)* starts with disease progression at onset with occasional acute relapses and continued disease progression. Only a small minority of patients (< 5%) have PRMS. About 10% of the MS population has a benign disease course, which is generally determined retrospectively. Among those with relapsing forms of MS, the severity, duration, and frequency of relapses vary widely among patients. The Expanded Disability Scale Score (EDSS) is the scale most often used to assess neurologic disability and evaluates cerebellar, pyramidal, brainstem, sensory, bowel, bladder, visual, and mental functional systems on a scale that ranges from 0 (normal neurologic examination) to 10 (death due to MS). Magnetic resonance imaging (MRI) evaluations are used to assess current MS disease activity, as well as to monitor for permanent neurologic damage.

Other Disease-Modifying Drug Therapies for Multiple Sclerosis

Interferon beta therapies indicated for use in relapsing forms of MS include Avonex® (interferon beta-1a for intramuscular [IM] injection), Plegridy™ (peginterferon beta-1a SC injection), Rebif® (interferon beta-1a for SC injection), and Betaseron®/Extavia® (interferon beta-1b for SC injection).[9-13] Another self-injectable MS therapy is Copaxone® (glatiramer acetate injection for SC use), which can be dosed SC either once daily (QD) [20 mg/mL] or three times weekly (TIW) [40 mg/mL].[14] Generics are available for both strengths (20 mg/mL and 40 mg/mL).[15-16] Glatopa™ (glatiramer acetate injection for SC use) is also a generic for Copaxone but is available in the 20 mg/mL dose only.[17] Although some differences in efficacy have been observed in clinical trials among the interferon beta products, in general, these self-injectable MS therapies appear to reduce the annualized response rate by approximately one-third.[18] Zinbryta® (daclizumab injection for SC use), an interleukin-2 receptor blocking antibody, is indicated for the treatment of patients with relapsing forms of multiple sclerosis.[19] Patients can self-administer Zinbryta with proper training.[19] Oral disease-modifying therapies indicated in relapsing forms of MS include Aubagio® (teriflunomide tablets), Gilenya® (fingolimod capsules), and Tecfidera® (dimethyl fumarate delayed-release capsules).[20-22] These therapies have also demonstrated benefits in patients with MS.[23] Other infused therapies are available. Lemtrada® (alemtuzumab injection for IV use), a CD52-directed cytolytic monoclonal antibody, is indicated for the treatment of patients with relapsing forms of MS.[24] Mitoxantrone injection is given by IV infusion, but due to toxicities, its role is limited to carefully-selected patients who have not responded to other therapies.[25] Ocrevus™ (ocrelizumab injection for IV use) is a CD20-directed cytolytic antibody indicated for the treatment of adult patients with relapsing or primary progressive forms of MS.[26]

Starting treatment with an FDA-approved disease-modifying treatment is recommended as soon as possible after a diagnosis of relapsing MS regardless of the patient's age; for patients with a first clinical event and MRI features consistent with MS when other possible causes have been excluded; and for

patients with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity.[23] Treatment with a disease-modifying agent should be continued indefinitely unless one of the following occurs: sub-optimal treatment response; intolerable side effects; inadequate adherence to the treatment regimen; or availability of a more appropriate treatment.

Crohn's Disease, Adults

According to 2008 American College of Gastroenterology (ACG) guidelines on management of Crohn's disease in adults, patients with moderate-severe Crohn's disease are treated with prednisone 40 to 60 mg/day until symptoms are resolved or weight gain is resumed (usually 7 to 28 days).[24] Infection or abscess is treated with antibiotics or drainage. For maintenance therapy, azathioprine or 6-mercaptopurine have been beneficial after induction therapy with corticosteroids. Parenteral MTX 25 mg/week is effective for steroid-dependent and steroid-refractory Crohn's disease. The TNFα antagonists, Cimzia, Humira, and an infliximab product (e.g., Remicade, Inflectra), are effective for moderate to severe active Crohn's disease in those who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. Monotherapy with an infliximab product or an infliximab product plus azathioprine is more effective than azathioprine in patients with mild to moderate Crohn's disease who do not respond to first-line therapy with mesalamine and/or corticosteroids. Humira has been effective in patients who have not received other biologics and in those who lost response to an infliximab product (e.g., Remicade, Inflectra). Cimzia, Humira, and an infliximab product may be used as alternatives to steroids in selected patients with Crohn's disease who have contraindications to corticosteroids or who not desire steroid therapy. Tysabri is effective in moderate to severe active Crohn's disease and active inflammation (e.g., elevated C-reactive protein level) who have an inadequate response or are unable to tolerate conventional Crohn's disease therapies and TNF antagonists. The 2013 ACG guidelines on use of thiopurines, MTX, and TNFα antagonists biologics in Crohn's disease do not address use of Tysabri.[25] These guidelines have not been updated since the approvals of Entyvio and Stelara for bowel conditions.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicade Members	***Tysabri is not considered for approval for Relapsing Forms of Multiple Sclerosis unless member has tried and failed TWO preferred products, including: Avonex, Betaseron, Copaxone, Gilenya, Rebif, Tecfidera. Tysabri is included in the WA HCA Single Preferred drug list.*** *Document if member meets this criteria, which medications were tried, and deny if criteria is not met. Otherwise, continue to clinical criteria below.*
Medicare Members	***Continue to criteria for approval below.*** ***Step-utilization of Part D drugs not required.***

Coverage of Tysabri is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Relapsing Form of Multiple Sclerosis (MS) in an Adult.

Criteria. *The patient must meet the following criteria (A, B, C, AND D)*:

- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient has a relapsing form of MS (relapsing forms of MS are RRMS, SPMS with relapses, and PRMS); AND
- **C)** The patient meets ONE of the following (i or ii):
  - **i.** According to the prescribing physician the patient has had an inadequate response, or is unable to tolerate, ONE disease-modifying agent used for MS (e.g., Avonex [interferon beta-1a for intramuscular {IM} injection], Rebif [interferon beta-1a for subcutaneous {SC} injection], Betaseron [interferon beta-1b for SC injection], Extavia [interferon beta-1b for SC injection], Copaxone [glatiramer acetate injection for SC use], Glatopa [glatiramer acetate injection for SC use], Plegridy [peginterferon beta-1a SC injection], Gilenya [fingolimod capsules], Aubagio [teriflunomide tablets], Tecfidera [dimethyl fumarate delayed-release capsules], or Lemtrada [alemtuzumab injection for intravenous use]); OR
  - **ii.** The patient has highly active or aggressive disease according to the prescribing physician; AND
- **D)** Tysabri is prescribed by, or in consultation with, a physician who specializes in the treatment of multiple sclerosis (MS) and/or a neurologist.

Tysabri is indicated for the treatment of adults with relapsing forms of MS.[1] Tysabri therapy is considered by some experts for rapidly worsening MS.[26] There are no data on the use of Tysabri in patients with rapidly worsening MS and only one Phase II trial included patients with SPMS. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in Multiple Sclerosis (MS) in Adults.

Dosing must meet the following: 300 mg IV infusion over 1 hour every 4 weeks.[1]

The approved dose of Tysabri in MS is 300 mg IV infusion over 1 hour every 4 weeks.[1] In one retrospective review conducted in nine multiple sclerosis centers, various extended interval regimens were compared to the standard interval dosing every 4 weeks.[33] The extended interval dosing (EID) regimens used were early extended dosing (EED; n=249) every 4 weeks 3 days to 6 weeks 6 days; late extended dosing (LED; n=274) every 7 weeks to 8 weeks 5 days; and variable extended dosing (n=382) alternating between EED and LED. These groups were compared to patients on standard interval dosing (n=1093) every 4 weeks. No evidence of clinical or radiographic disease activity was observed in 62% of patients on standard interval dosing and 61% of patients on EID (P = 0.83). The authors concluded that dosing intervals up to 8 weeks 5 days did not diminish effectiveness of therapy with Tysabri. No cases of PML were observed in the patients receiving EID compared to four cases in the standard interval dosing cohort. In one Phase IV single center trial, 50 patients with MS who had been receiving Tysabri for at least 24 months and were considering discontinuing Tysabri were enrolled to study immediate cessation

vs. tapering down.[34] Patients were randomized to either the immediate discontinuation group (IDG) where Tysabri was discontinued at once and another disease modifying drug therapy was started or to the tapered group (TG) where two more Tysabri doses were given at 6 and 8 weeks before starting another disease modifying drug. MRI testing was done at baseline and 6 and 12 months after the last Tysabri infusion. There was a higher relapse rate in the IDG (n = 28) vs the TG (n = 8) over 12 months from the last infusion (P = 0.007). Most relapses occurred within 3 months of discontinuing Tysabri (20 vs. 7 relapses, P = 0.012). The IDG had a higher number of new T2 lesions within 6 to 12 months of discontinuation (P = 0.025), a higher mean absolute T2-lesion volume change from 0 to 12 months (1.1 mL vs. 0.1 mL, P = 0.024) and a higher number of new T1-hypointense lesions over 0 to 12 months (P = 0.005) and also from baseline to 6 months (P = 0.026) compared to the TG.

Initial Approval/Extended Approval.

- **A)** *Initial Approval*. Initial approval is for 12 months.
- **B)** *Extended Approval*. Approve at additional 12-month intervals in patients with relapsing forms of MS.

Duration of Therapy in Multiple Sclerosis (MS): Indefinite.

It is thought that the incidence of PML increases with increasing duration of therapy and most patients receive natalizumab for 2 to 3 years.

Labs/Diagnostics. None required.

2. Crohn's Disease in an Adult.

Criteria. *The patient must meet the following criteria (A, B, C, AND D):*

- **A)** The patient is ≥ 18 years of age; AND
- **B)** Patient has moderately to severely active Crohn's disease with evidence of inflammation, that is, has an elevated C-reactive protein; AND
- **C)** Patient has tried at least TWO of the following agents for Crohn's disease: Humira (adalimumab for subcutaneous [SC] injection], Cimzia (certolizumab pegol for SC injection), an infliximab product (for example, Remicade [infliximab for intravenous {IV} infusion], Inflectra [infliximab-dyyb IV infusion]), Entyvio™ (vedolizumab injection for IV use), or Stelara® (ustekinzumab for SC injection or for IV infusion) for at least 2 months each and had an inadequate response or was intolerant to these agents; AND
- **D)** Tysabri is prescribed by or in consultation with a gastroenterologist.

Tysabri is indicated for reducing and maintaining clinical response and 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.[1]

Dosing in Crohn's Disease in Adults.
Dosing must meet the following: 300 mg IV infusion over one hour every 4 weeks.[1]

The approved dose of Tysabri in Crohn's disease is a 300 mg IV infusion over one hour every 4 weeks.[1] If the patient has not experienced therapeutic benefit by 12 weeks of induction, then Tysabri should be discontinued. In patients with Crohn's disease who start Tysabri while on chronic oral corticosteroids, steroids should be tapered as soon as there is a therapeutic benefit from Tysabri. If the patient cannot be tapered off of oral corticosteroids within 6 months of starting Tysabri, then Tysabri should be discontinued. Also, consideration should be given to discontinuing Tysabri in patients who require additional steroid therapy in excess of 3 months in a calendar year to control their Crohn's disease.

Initial Approval/Extended Approval.

A) *Initial Approval.* Initial approval is for 3 months (3 doses given at Weeks 0, 4 and 8).

B) *Extended Approval.* Approve for an additional 12 months of therapy if the patient received 3 doses of Tysabri and had a response (e.g., reduced number of liquid/soft stools, reduced abdominal pain, less use of antidiarrheal agents) as determined by the prescribing physician. Continue to approve at 12-month intervals.

Duration of Therapy in Crohn's Disease. Indefinite.

Labs/Diagnostics. None required.

3. Patient has been Started on Tysabri. Approve if the patient meets the conditions for coverage required for **Dosing, Extended Approval, Duration of Therapy,** and **Labs/Diagnostics** for an approved use in this *Tysabri Utilization Review* policy.

Waste Management for All Indications.
The dose in adults is 300 mg every 4 weeks.

Conditions Not Recommended for Approval
Tysabri has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Children with Multiple Sclerosis (MS) or Crohn's disease.** Tysabri is not indicated in pediatric patients with MS or Crohn's disease who are < 18 years of age.[1] There have been case series reports of use of Tysabri in adolescents aged 12 to 17 years with RRMS who were refractory to other agents.[27-28] Long-term risks of using Tysabri in children are not known. Interferon beta and Copaxone are the two most frequently used disease modifying therapies used in pediatric patients with RRMS in the US.[29] Limited information is available on use of Tysabri in adolescents with Crohn's disease.[30]

2. **Concurrent Use of Tysabri with an Immunosuppressant Agent in Patients with Crohn's Disease.** Tysabri should not be given in combination with an immunosuppressant agent (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or MTX) or with a TNFα inhibitor (e.g., an infliximab

product [such as Remicade, Inflectra], Humira, Cimzia).[1] Tysabri is not indicated in combination with Entyvio or Stelara. Ordinarily, patients who are receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune function should not take Tysabri.[1] Aminosalicylates may be continued during therapy with Tysabri. Tysabri can be started in patients on chronic oral corticosteroids, but patients should be tapered off corticosteroids.

3. **Current Use of Tysabri with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS) or with an Immunosuppressant in Patients with MS.** Tysabri should not be given in combination with other disease-modifying agents used for MS (e.g., Betaseron/Extavia, Rebif, Copaxone/Glatopa, Avonex, Lemtrada, Plegridy, Zinbryta, Gilenya, Aubagio, Tecfidera) or with an immunosuppressant such as mitoxantrone, cyclophosphamide, Ocrevus (ocrelizumab injection for IV use), Rituxan® (rituximab injection for IV infusion), Campath® (alemtuzumab injection for IV infusion), azathioprine, MTX, or mycophenolate mofetil. Tysabri is only indicated as monotherapy due to an increased risk of PML.[1] Ordinarily, patients with MS who are receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune function should not take Tysabri.

4. **Immune Compromised Patients with Multiple Sclerosis (MS) or Crohn's Disease.** Patients with a medical condition that results in significantly compromised immune system function such as human immunodeficiency virus (HIV) infection, leukemia, lymphoma, or organ transplant should not ordinarily be treated with Tysabri.[1]

5. **Primary Progressive (Chronic Progressive) Multiple Sclerosis (MS).** The safety and efficacy of Tysabri have not been studied in patients with primary progressive (chronic progressive) MS. Tysabri is indicated in patients with relapsing forms of MS.[1]

6. **Ulcerative Colitis.** Efficacy data with use of this product are limited.[31]

7. Coverage is not recommended for circumstances *not* listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

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CFR		
WAC	WAC 284-43-2050	
RCW		
Contract Citation	☒ WAH	
	☒ IMC	
	☒ MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
01/13/2016	New	Kelly Force; Yusuf Rashid, RPh
01/20/2016	Approval	MMLT
01/12/2017	No revisions	Fran McGaugh
01/13/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM137 to PM126	Cindy Bush
05/22/2018	Updated, added LOB box	Gary Deng, Pharmacy Student

		Catherine Vu, PharmD
06/14/2018	Approval	UM Committee