***Sample Letter of Medical Necessity for a Treatment-Naïve Patient***

**Note:** **the sample letter below is for your reference only and is intended to be customized for individual patients starting treatment for relapsing multiple sclerosis (RMS) based upon your independent clinical evaluation and medical judgment. The Important Safety Information does not need to be included as part of your letter.**

**INDICATION**

TYSABRI® (natalizumab) is indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. TYSABRI increases the risk of PML. When initiating and continuing treatment with TYSABRI, physicians should consider whether the expected benefit of TYSABRI is sufficient to offset this risk.

**IMPORTANT SAFETY INFORMATION**

**WARNING: Progressive Multifocal Leukoencephalopathy (PML)**

**TYSABRI® (natalizumab) increases the risk of 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 with TYSABRI.**

**Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.**

**Because of the risk of PML, TYSABRI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH® Prescribing Program.**

* Infection by the JC Virus (JCV) is required for the development of PML
* There are no known interventions that can reliably prevent PML or that can adequately treat PML if it occurs
* Postmarketing data suggest that the risk of developing PML may be associated with relative levels of serum
anti-JCV antibody compared to a calibrator as measured by ELISA (often described as an anti-JCV antibody
index value)
* MRI findings may be apparent before clinical signs or symptoms suggestive of PML. Monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Consider monitoring patients at high risk for PML more frequently. Lower PML-related mortality and morbidity have been reported following TYSABRI discontinuation in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis
* PML has been reported after discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation. Patients should continue to be monitored for any new signs or symptoms that may be suggestive of PML for at least 6 months after discontinuation of TYSABRI
* Adverse events that may occur during plasma exchange (PLEX) include clearance of other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema. Although PLEX has not been prospectively studied in TYSABRI-treated patients with PML, it has been used in such patients in the postmarketing setting to remove TYSABRI more quickly from the circulation. There is no evidence that PLEX has any benefit in the treatment of opportunistic infections such as PML
* JCV infection of granule cell neurons in the cerebellum, i.e., JCV granule cell neuronopathy (GCN), with symptoms similar to PML, has been reported in patients treated with TYSABRI. JCV GCN can occur with or without concomitant PML and can cause cerebellar dysfunction. Diagnosis and management of JCV GCN should follow guidance provided for PML
* Immune reconstitution inflammatory syndrome (IRIS) has been reported in the majority of TYSABRI-treated patients who developed PML and subsequently discontinued TYSABRI. In almost all cases, IRIS occurred after PLEX was used to eliminate circulating TYSABRI. It presents as a clinical decline in the patient’s condition after TYSABRI removal (and, in some cases, after apparent clinical improvement) that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes in the MRI. TYSABRI has not been associated with IRIS in patients discontinuing treatment with TYSABRI for reasons unrelated to PML. In TYSABRI-treated patients with PML, IRIS has been reported within days to several weeks after PLEX. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken

**Contraindications**

* TYSABRI is contraindicated in patients who have or have had PML
* TYSABRI is contraindicated in patients who have had a hypersensitivity reaction to TYSABRI

**TYSABRI TOUCH Prescribing Program**

* Because of the risk of PML, TYSABRI is available only through a restricted distribution program under a REMS called the TOUCH® Prescribing Program
* Patients must be enrolled in the TOUCH Prescribing Program, read the Medication Guide, understand the risks associated with TYSABRI, and complete and sign the Patient Enrollment Form

**Herpes Infections – Encephalitis, Meningitis and Acute Retinal Necrosis**

* TYSABRI increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses
* Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving TYSABRI
* The duration of treatment with TYSABRI prior to onset ranged from a few months to several years
* Monitor patients receiving TYSABRI for signs and symptoms of meningitis and encephalitis. If herpes encephalitis or meningitis occurs, TYSABRI should be discontinued, and appropriate treatment for herpes encephalitis/meningitis should be administered
* Patients being administered TYSABRI are at a higher risk of acute retinal necrosis (ARN), a fulminant viral infection of the retina caused by the family of herpes viruses. Patients with eye symptoms such as decreased visual acuity, redness or eye pain should be referred for retinal screening as serious cases of ARN can lead to blindness of one or both eyes

Please see Important Safety Information continued on next page and full [**Prescribing Information**](https://www.tysabrihcp.com/content/dam/commercial/tysabri/hcp/en_us/pdf/tysabri_prescribing_information.pdf), including **Boxed Warning**.

* Following clinical diagnosis of ARN, consider discontinuation of TYSABRI

**Hepatotoxicity**

* Clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with TYSABRI in the postmarketing setting
* Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred
as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses
* TYSABRI should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence)

**Hypersensitivity/Antibody Formation**

* Hypersensitivity reactions have occurred in patients receiving TYSABRI, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%
* Reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain
* If a hypersensitivity reaction occurs, discontinue administration of TYSABRI and initiate appropriate therapy. Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI
* Hypersensitivity reactions were more frequent in patients with antibodies to TYSABRI compared with patients who did not develop antibodies to TYSABRI in both MS and CD studies
* Patients who receive TYSABRI for a short exposure (1 to 2 infusions) followed by an extended period without treatment are at higher risk of developing anti-natalizumab antibodies and/or hypersensitivity reactions on re-exposure, compared to patients who received regularly scheduled treatment

**Immunosuppression/Infections**

* The immune system effects of TYSABRI may increase the risk for infections
* In Study MS1, certain types of infections—including pneumonias and urinary tract infections (including serious cases), gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections—occurred more often in TYSABRI-treated patients than in placebo-treated patients. One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received TYSABRI in Study MS1
* In Studies MS1 and MS2, an increase in infections was seen in patients concurrently receiving short courses of corticosteroids. However, the increase in infections in TYSABRI-treated patients who received steroids was similar to the increase in placebo-treated patients who received steroids
* In a long-term safety study of patients, opportunistic infections (pulmonary mycobacterium avium intracellular, aspergilloma, cryptococcal fungemia and meningitis, and Candida pneumonia) have been observed in <1% of TYSABRI-treated patients
* Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections over the risk observed with use of TYSABRI alone
* In Studies MS1 and MS2, the rate of any type of infection was approximately 1.5 per patient-year in both TYSABRI-treated patients and placebo-treated patients
* In Study MS1, the incidence of serious infections was approximately 3% in TYSABRI-treated patients and in placebo-treated patients. Most patients did not interrupt treatment with TYSABRI during infections

**Laboratory Test Abnormalities**

* In clinical trials, TYSABRI was observed to induce increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persisted during TYSABRI exposure, but were reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils were not observed. TYSABRI induces mild decreases in hemoglobin levels (mean decrease of 0.6 g/dL) that are frequently transient

**Thrombocytopenia**

* Cases of thrombocytopenia, including immune thrombocytopenic purpura (ITP), have been reported with the use of TYSABRI in the postmarketing setting. Symptoms of thrombocytopenia may include easy bruising, abnormal bleeding, and petechiae. Delay in the diagnosis and treatment of thrombocytopenia may lead to serious and life-threatening sequelae. If thrombocytopenia is suspected, TYSABRI should be discontinued
* Cases of neonatal thrombocytopenia, at times associated with anemia, have been reported in newborns with
*in utero* exposure to TYSABRI. A CBC should be obtained in neonates with *in utero* exposure to TYSABRI

**Adverse Reactions**

* The most common adverse reactions reported at an incidence of ≥10% with TYSABRI and ≥2% difference with placebo were headache (38% vs 33%), fatigue (27% vs 21%), infusion reactions (24% vs 18%), urinary tract infections (21% vs 17%), arthralgia (19% vs 14%), depression (19% vs 16%), pain in extremity (16% vs 14%),
rash (12% vs 9%), gastroenteritis (11% vs 9%), and vaginitis (10% vs 6%)
* The most frequently reported serious adverse reactions in Study MS1 were infections (3.2% vs 2.6% placebo), including urinary tract infection (0.8% vs 0.3%) and pneumonia (0.6% vs 0%), acute hypersensitivity reactions (1.1% vs 0.3%, including anaphylaxis/anaphylactoid reaction [0.8% vs 0%]), depression (1.0% vs 1.0%, including suicidal ideation or attempt [0.6% vs 0.3%]), and cholelithiasis (1.0% vs 0.3%)
* Based on animal data, TYSABRI may cause fetal harm. TYSABRI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Please see full [**Prescribing Information**](https://www.tysabrihcp.com/content/dam/commercial/tysabri/hcp/en_us/pdf/tysabri_prescribing_information.pdf), including **Boxed Warning.**

This sample letter is for informational purposes only, providing an example of language that may be required or helpful when responding to a request from a patient’s health plan. Use of this information does not constitute medical or legal advice and does not guarantee reimbursement for coverage. It is not intended to be a substitute for, or an influence on, the independent clinical decision of the prescribing healthcare professional.

[Insert Date]

[ATTN: Health Plan Contant Name]

[Health Plan Name]

[Address]

[Patient Name]

[Patient Insurance ID Number]

[Patient Date of Birth]

[Reference Number]

 **RE: Request for My Patient to Start on TYSABRI® (natalizumab) for Relapsing Multiple Sclerosis (RMS)**

Dear [Health Plan Contact Name]:

I am writing this letter of medical necessity on behalf of [Patient Name] to request coverage of TYSABRI® (natalizumab), a United States Food and Drug Administration (FDA)-approved therapy for the treatment of patients with relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.1

I am a board-certified [field of certification] and have been treating [Patient Name] for [XX] [months/years]. In my clinical opinion, [Patient Name] should receive TYSABRI for the following reasons:

* [HCP to summarize reasons the preferred drugs on formulary are not appropriate]

Please see below for [Patient Name]’s medical history and prognosis, and the rationale for treatment with TYSABRI.

**PATIENT MEDICAL SUMMARY**

* [Date of diagnosis and ICD-10 code(s)]
* [Magnetic resonance imaging (MRI) data]
* [Physical disability, including description and related test results]
* [History of relapse(s), including dates and symptoms]
* [Pertinent laboratory values]
* [Clinical data indicating response to TYSABRI treatment]

**TREATMENT RATIONALE**

* [HCP to insert reason(s) for recommending TYSABRI based on medical history and comorbidities, breakthrough disease activity, EDSS history, medication intolerance, contraindications/allergies, or changes in MS QoL assessment]
* [HCP to insert other relevant clinical data specific to their patient such as:]

|  |  |
| --- | --- |
| **SHORT-TERM****& LONG-TERM****EFFICACY** | * *In the 2-year AFFIRM trial, more than 80% of people treated with TYSABRI had no progression of disability, compared to 71% taking placebo.2*
	+ *Nearly 70% of people treated with TYSABRI had remained relapse free, compared to 41% taking**placebo.2*
	+ *97% of people treated with TYSABRI had no new Gd+ lesions that showed disease activity on an MRI, compared with 72% taking placebo2*
* *In the TOP trial, TYSABRI reduced relapses by 88% in Year 1 with low ARRs (<0.20) sustained out to 15 years.2*
	+ *Additionally, the median EDSS scores were stable across 10 years with TYSABRI4*
* *Efficacy was seen as early as Day 42 in a post-hoc analysis of AFFIRM data, with patients treated with TYSBARI having a 5.4% risk of relapse, compared with 9.3% with placebo (HR: 0.56, 95% CI: 0.34-0.93)3*
* *TYSABRI has more than 15 years of clinical trial and real-world experience across 1 million+ patient-years, supporting its use as an effective treatment for my patient*
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| **LONG-TERM****SAFETY** | * *Results from the 15-year TOP trial evaluating TYSABRI's long-term safety showed real world data consistent with AFFIRM data and no new safety concerns were identified.4*
* *In the 5-year TYGRIS trial, rates of opportunistic infections and malignancies in patients taking TYSABRI were low, and rates of malignancies were similar to the general population5*
* *The risk of developing PML while on treatment is <1% regardless of JCV antibody status. Active infection by JCV is required for the development of PML.1,4*
	+ *PML risk in patients who are positive for anti-JCV antibodies can be further stratified by treatment duration and prior immunosuppressant use.1*
	+ *There is no restriction on duration of treatment specifically regarding PML risk with TYSABRI1*
 |
| **RISK MANAGEMENT** | * *The STRATIFY JCV™ Antibody Test is the only FDA-approved test validated specifically for TYSABRI to aid in risk stratification for PML for use in conjunction with other clinical data to support the safe use of TYSABRI*
	+ *Since 2012, over 2 million STRATIFY JCV™ tests have been performed to support neurologists as a clinical decision-making tool for patients on or considering TYSABRI*
* *The TOUCH Prescribing Program is the required REMS program that has been supporting HCPs and patients in the safe administration of TYSABRI since 2006.*
	+ *It helps facilitate appropriate use by allowing enrolled patients to obtain TYSABRI through certified prescribers, pharmacies, and infusion centers. The program informs about the risk of PML associated with TYSABRI and promotes early diagnosis of PML and timely discontinuation of TYSABRI in the event of suspected PML.*
* *The TOUCH Prescribing Program enabled Biogen to create the PML risk stratification table specific to TYSABRI that is based on data from 100,000 TYSABRI-exposed patients. The risk stratification table facilitates PML vs. benefit comparisons of TYSABRI and inform treatment decisions.1*
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**SITE OF CARE ALTERNATIVE TO HOME INFUSION**

Consistency in the site of TYSABRI administration can help patients adhere to treatment and ultimately achieve their care goals. I am requesting for my patient to start on TYSABRI at [Name of Site-of-Care] rather than home infusion because:

* [HCP to insert reasons for recommendation to use an alternative Site-of-Care to home infusion, such as
	+ Patient has experienced trouble following verbal or written instructions
	+ Patient has an EDSS score of [>6], indicating deficiencies in their fine motor skills
	+ Patient requires/requests follow-up, monitoring, and high touch evaluation provided by an infusion site with access to emergency medications, equipment, and personnel
	+ Patient cannot accommodate the space and consistency needed for home infusion]

**ENCLOSURES/ATTACHMENTS:** [TYSABRI Prescribing Information, Medication history and/or chart notes describing previous therapies and specific outcomes;MRI data; Patient’s history of relapses (i.e., relevant clinical chart notes)**;** EDSS history**;** Supporting literature (i.e., clinical guidelines, recent clinical trials, compendia, peer reviewed publications, etc.)]

In summary, based on the patient’s current condition and the clinical data available to date, treatment with TYSABRI for [Patient Name] is medically appropriate and necessary.

Please call my office at [telephone number] for any additional information. I look forward to your response.

Sincerely,

[Prescriber Signature]

**References:** **1.** TYSABRI Prescribing Information. Cambridge, MA: Biogen. **2.** Polman CH, et al. *N Engl J Med.* 2006;354(9):899-910. **3.** Kappos L, et al. *J Neurol.* 2013;260:1388-1395. **4**. Butzkueven H, et al. *Neurol Neurosurg Psychiatry.* 2020;91:660-668. **5.** Foley J, et al; TYGRIS investigators. *Mult Scler Relat Disord.* 2020;39:101863. **6.** Hersh CM, Kieseier B, de Moor C, et al. *Mult Scler J Exp Transl Clin.* 2021;7(2): 20552173211004634 **7.** TYSABRI Cumulative Post-Market & Clinical Trial Patient Exposure. Data on file. Biogen, Cambridge, MA.