TYSABRI® (natalizumab)

COVERAGE AND REIMBURSEMENT

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.

DECISIVE ACTION MATTERS
TYSABRI (natalizumab)

COVERAGE AND REIMBURSEMENT

Biogen is committed to providing support on behalf of patients with relapsing multiple sclerosis (RMS) who are prescribed TYSABRI® therapy. This document is designed to provide information materials that can help practice administrators and other key practice staff understand the various aspects of the administrative needs and reimbursement process for TYSABRI. In addition, this document contains links to sample forms that illustrate how to meet specific health plan requirements.

HOW TO USE YOUR TYSABRI COVERAGE AND REIMBURSEMENT GUIDE

1. The main sections are listed across the top of the document and enable you to move from one section to the next.

2. On the main page of each section, you will find a list of the contents that that section comprises. You can simply click on the information you wish to view and go right to that page.

Additional information or support material can be found through the www.TYSABRIHCP.com site. To find this information, links with this symbol # will take you there.

The information is intended for informational purposes only and does not represent legal or billing advice. For specific guidance in this area, consult your own legal/billing advisor and billing/coding specialist, because it remains your responsibility to ensure the accuracy of the claims your office submits. The content here is based on information current as of January 2016 and may have changed. Any product, ancillary supplies, or services received free of charge cannot be billed to third-party payers, because doing so could be a violation of federal and/or state laws and/or third-party-payer requirements.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
TYSABRI (natalizumab) COVERAGE AND REIMBURSEMENT (CONT’D)

Additional Help:

FINANCIAL & INSURANCE SUPPORT

IS AVAILABLE TO HELP WITH QUESTIONS REGARDING A PATIENT’S HEALTH PLAN COVERAGE FOR TYSABRI® AND CAN CONNECT YOU WITH AN ACCESS AND REIMBURSEMENT MANAGER, WHEN NEEDED:

1-800-456-2255
PREScribing Tysabri (natalizumab)

The TOUCH® Prescribing Program and Enrollment Process

Understanding Insurance Coverage for Tysabri®

Completing a Prior Authorization or Pre-Certification

Requesting a Medical Exception

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
THE TOUCH PRESCRIBING PROGRAM

Due to the risk of progressive multifocal leukoencephalopathy (PML), TYSABRI® (natalizumab) is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH® Prescribing Program, which stands for TYSABRI Outreach: Unified Commitment to Health. Prescribers should educate patients on the benefits and risks of treatment with TYSABRI, ensure that patients receive the Medication Guide, and encourage them to ask questions.

The TOUCH Prescribing Program restricts the availability of TYSABRI to certified prescribers, infusion sites, pharmacies, and patients enrolled in the program.

Remember, patients can receive TYSABRI through only a TOUCH-authorized infusion site. For a comprehensive list of TOUCH-authorized sites, click here Infusion Site Locator. The Biogen Access and Reimbursement Manager team will work with you to locate additional TOUCH-authorized sites so that your patients have options. The Access and Reimbursement Manager team can potentially train and authorize the site based upon established criteria.

Inform
prescribers, infusion sites, and patients about the risk of PML associated with TYSABRI, including the increased risk of PML with longer treatment duration, prior immunosuppressant use, and the presence of John Cunningham virus (JCV) antibodies

Warn
against concurrent use with antineoplastic, immunosuppressant, or immunomodulating agents and in patients who are immunocompromised

Promote
early diagnosis of PML and timely discontinuation of TYSABRI in the event of suspected PML

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
THE TOUCH PRESCRIBING PROGRAM
ENROLLMENT PROCESS

Getting Started in the TOUCH Prescribing Program

The first step to getting a patient started on TYSABRI® (natalizumab) is to review, complete, and sign the TOUCH® Prescribing Program Prescriber/Patient Enrollment Form pictured below. To learn more about enrolling in the TOUCH Prescribing Program, contact a Support Coordinator from Above MS™ at Biogen, by calling toll free: 1-800-456-2255.

If your office has questions about the TOUCH Prescribing Program Prescriber/Patient Enrollment form, please contact a Support Coordinator from Above MS at 1-800-456-2255 Monday through Friday from 8:30 AM to 8:00 PM (ET).

For more information on the TOUCH Prescribing Program, please click below to visit TOUCH On-Line.

TOUCH Prescribing Program

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
THE TOUCH PRESCRIBING PROGRAM
ENROLLMENT PROCESS (CONT’D)

Your office and the patient will receive a Notice of Patient Authorization (pictured to the right) to confirm enrollment in the TOUCH® Prescribing Program. This is specific to the TOUCH Prescribing Program and is NOT an indication of insurance coverage.

Upon completing the FIRST TOUCH Prescribing Program Prescriber/Patient Enrollment Form, a provider will receive a TOUCH ID. This alphanumeric code is your unique identifier as a participant in the TOUCH Prescribing Program, and it may be referenced by Biogen or pharmacies as part of communication about program compliance or ordering TYSABRI® (natalizumab).

Each patient will also be assigned a unique TOUCH ID as part of enrollment in the TOUCH Prescribing Program. This alphanumeric code will be on the Notice of Patient Authorization that notifies providers that a patient is authorized to receive TYSABRI. Only authorized patients may receive TYSABRI, and TYSABRI may be administered only at TOUCH-authorized infusion sites.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
UNDERSTANDING INSURANCE COVERAGE

Benefit Investigation

Once your office and the patient are enrolled in the TOUCH® Prescribing Program, the next step is to determine the patient’s drug and medical coverage. Payers have different requirements for coverage, and it is important to know the key clinical and coverage criteria. This information is acquired through a Benefit Investigation.

If requested on the TOUCH Prescribing Program Prescriber/Patient Enrollment form, a Benefit Investigation can be conducted by Above MS™ support coordinators. A Benefit Investigation helps clarify patient coverage including any Prior Authorization or Pre-Certification, step therapy, or Pre-Determination requirements set forth by a patient’s payer. Most patients will have either a copay or coinsurance responsibility for the drug and the administration of TYSABRI® (natalizumab).

To discuss a patient’s Above MS Benefit Investigation, your office can contact a Support Coordinator from Above MS by calling 1-800-456-2255.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
If the patient is going to be infused in the office, your office will be asked to select one of 3 choices on the TOUCH® Prescribing Program Prescriber/Patient Enrollment Form:

1. **“No services required”**
   This means that Above MS™ will provide no further services. Your office would select this if there are no questions regarding patient coverage or if you prefer to do the Benefit Investigation yourself.

2. **“Forward this prescription to a specialty pharmacy provider to investigate pharmacy coverage and coordinate delivery to prescriber’s office”**
   Above MS will forward the prescription to a specialty pharmacy, and will not conduct a Benefit Investigation. The specialty pharmacy will conduct a benefit investigation and will generally communicate benefits directly to the patient.

3. **“Please conduct insurance research and procurement options for TYSABRI”**
   Upon receiving the TOUCH Prescribing Program Prescriber/Patient Enrollment Form, Above MS will conduct a Benefit Investigation and send a completed Summary of Benefits to your office.

When filling out the TOUCH Prescribing Program Prescriber/Patient Enrollment Form, your office will need to indicate where the patient is going to be infused and what services may be required.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
BENEFIT INVESTIGATION FOR TYSABRI® (natalizumab) (CONT’D)

If your office is referring the patient to an infusion site or if it requests the TOUCH® Prescribing Program’s help in locating an infusion site, then your office will not be conducting a Benefit Investigation. Above MS™ will reach out to the infusion site to find out if they would like Above MS to investigate benefits. If the infusion site requests that Biogen conduct a Benefit Investigation, your office will receive a completed Summary of Benefits for your records.

The TYSABRI® Benefit Investigation Worksheet (pictured right) can assist your office with an in-office Benefit Investigation. It goes through the steps of gathering the necessary information from the patient’s payer.

A list of possible health plan restrictions can be found on the next page. Restrictions are requirements that your patient and your office must fulfill before the health plan will agree to cover the cost of TYSABRI.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
**BENEFIT INVESTIGATION FOR TYSABRI (natalizumab) (CONT’D)**

When conducting a Benefit Investigation, suggested specific items to research are:

<table>
<thead>
<tr>
<th>Prior Authorization and required documentation</th>
<th>Step Edit Medical Exception</th>
<th>Acquisition requirements</th>
<th>Coding and claims submission details</th>
<th>Patient financial responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Does the patient need approval from the payer before receiving TYSABRI treatment, in order for it to be covered?</td>
<td>• Does the payer require prior usage of one or more MS therapies before TYSABRI can be used? • It is important to determine how each payer defines “failure” on an MS drug, for example, 6 months on therapy</td>
<td>• If the payer does not cover TYSABRI or if it denies coverage, then your office can seek a Medical Exception • Each payer has a different policy for handling Medical Exceptions</td>
<td>• Does the payer require your office to acquire TYSABRI from a designated specialty pharmacy?</td>
<td>• When submitting a claim to the insurance company, your office will need to use the appropriate billing codes</td>
</tr>
<tr>
<td>• Does the payer require specific documentation—for example, Letter of Medical Necessity, package insert, FDA approval letter, pricing sheet, and clinical reprint—before approving?</td>
<td></td>
<td></td>
<td></td>
<td>• Depending on the patient’s payer, the copay and deductible may vary</td>
</tr>
</tbody>
</table>

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
ABOVE MS™ BENEFIT INVESTIGATION

Above MS™ by Biogen has a service that helps patients gain access to Support Coordinators who can help them understand their insurance coverage and identify the best financial assistance solution for their Biogen relapsing MS medication. In addition to performing the Benefit Investigation, a Support Coordinator from Biogen can follow up with the patient’s payer to ensure that any Prior Authorization or Step Edit requirements have been completed and approved before the patient initiates therapy. Also, Above MS offers personalized assistance to identify the best financial assistance option for your patients, including a copay assistance program for eligible patients. The goal is to ensure that no one forgo Biogen treatment based solely on financial limitations.

If your office requests a Benefit Investigation through the TOUCH® Prescribing Program Prescriber/Patient Enrollment Form, a Support Coordinator from Above MS will conduct the necessary Benefit Investigation, including:

- Researching patient’s insurance coverage for TYSABRI® (natalizumab) and providing a Summary of Benefits to your office
- Working with patient’s insurance company to coordinate coverage through a specialty pharmacy when needed
- Ensuring Prior Authorization and Pre-Certification requirements are met

To successfully complete a Benefit Investigation, Biogen requires the following information from your office to determine if the patient’s benefits will be considered in or out of network:

1. Your payer-specific provider ID #
2. Your Tax ID #
3. Whether you use the CMS-1500 Form for Physician Office Billing or the CMS-1450/UB-04 Form for Hospital Outpatient Billing

If the required information is not on file, a Support Coordinator from Biogen will contact your office to obtain the information. When this information is on file, a Support Coordinator may check in periodically to ensure that the information has not changed.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
Once Above MS™ researches the patient’s insurance benefits, a Support Coordinator from Biogen will send your office and the infusion site of care (if different) a patient-specific Summary of Benefits. This Summary of Benefits can also be viewed at TOUCH® On-Line.

A sample Summary of Benefits can be found on the next page. The Summary of Benefits contains 3 sections:

1. **Patient Information:**
   The patient’s information, including insurance, and infusion administration benefit

2. **Benefit Details:**
   - **Infusion:** The coverage that a patient has for the administration of TYSABRI® (natalizumab)
   - **Buy-and-Bill Option:** The purchasing option that the payer will cover through the medical benefit if a provider purchases TYSABRI and submits a claim to the payer for reimbursement
   - **Specialty Pharmacy Assignment of Benefits Option:**
     The purchasing options that the payer will cover through the medical benefit with the drug shipped to the provider through an authorized TYSABRI Specialty Pharmacy
   - **Specialty Pharmacy Prescription Drug Benefit Option:**
     The purchasing options that the payer will cover through prescription drug benefit with the drug shipped from the specialty pharmacy to the provider

3. **Prior Authorization Requirements:**
   Any Prior Authorization or step-therapy requirements that a provider or administration site must complete to help a patient gain access to therapy

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The Summary of Benefits is NOT a Pre-Certification or guarantee of payment, is not guaranteed by Biogen to be accurate, and should be used as guidance only. It is the responsibility of the infusion site, before each infusion, to confirm that coverage for the patient has not changed.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
SAMPLE SUMMARY
OF BENEFITS

Patient Insurance Overview

1 Patient Information

Patient Information Overview

<table>
<thead>
<tr>
<th>Summary of Benefits for TYSABRI (natalizumab) for John Doe</th>
<th>Date of Birth: XXXX/XXXX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insurance Company Name:</td>
<td>Plan Name:</td>
</tr>
<tr>
<td>Member #: Group #: Plan type:</td>
<td>Phone Number:</td>
</tr>
<tr>
<td>Insurance: Effective date:</td>
<td>Termination date:</td>
</tr>
<tr>
<td>Policy year: Pre-existing condition clause:</td>
<td>Pre-existing condition expires:</td>
</tr>
<tr>
<td>Lifetime maximum: Is there a secondary policy:</td>
<td>Call Facility:</td>
</tr>
<tr>
<td>Drug Code: J2323 - Electronic File</td>
<td>NDC#: 64606-0088-01</td>
</tr>
<tr>
<td>Site of Care: Procedure Code: Billing Preference:</td>
<td></td>
</tr>
</tbody>
</table>

Determine Prior Authorization and Documentation Requirements

3 Prior Authorization Requirements

<table>
<thead>
<tr>
<th>Prior Authorization/PRE-DETERMINATION</th>
<th>Required</th>
<th>Documentation</th>
<th>Required Criteria</th>
<th>Attention To</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Authorization</td>
<td></td>
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<tr>
<td>Pre-Determination</td>
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<tr>
<td>PA Expiration Date:</td>
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<tr>
<td>PA Instructions:</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Sample Summary of Benefits

The Summary of Benefits is NOT a Pre-Certification or guarantee of payment, is not guaranteed by Biogen to be accurate, and should be used as guidance only. It is the responsibility of the infusion site before each infusion to confirm that coverage for the patient has not changed.
PRIOR AUTHORIZATIONS AND PRE-CERTIFICATIONS

Depending on the type of insurance and on a patient’s specific plan or benefits, your office may need to obtain Prior Authorization, Pre-Certification, or a referral from the patient’s primary care physician before the payer agrees to cover the cost of TYSABRI® (natalizumab) and TYSABRI administration.

The physician is required to obtain approval from a payer before prescribing a specific medication or before performing a medical service. Without this prior approval, a payer may not provide coverage or pay for the patient’s medication or service.

Some payers require pre-approval, also known as Pre-Certification, for certain types of healthcare services, such as surgery or hospital visits. This means that your office or patient must contact the insurer to obtain approval before receiving care; otherwise, the insurer may not cover it.

Not all payers and/or services will require pre-approval, but when in doubt, it is best to contact the payer before providing any type of drug or medical service. Payers may change coverage guidelines, which could impact a patient’s ability to access therapy through their insurance. This is most common at the start of each new year. It is a best practice to check with the payer to ensure that nothing has changed. If your office does have questions about payer changes, your Biogen Access and Reimbursement Manager is also available to help.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
PRIOR AUTHORIZATIONS AND PRE-CERTIFICATIONS (CONT’D)

Quick Tips for Prior Authorization and Pre-Certification

- Review a patient’s Summary of Benefits to understand payer-specific guidelines and requirements
- Identify if a Prior Authorization for TYSABRI® (natalizumab) or a Pre-Certification for the entire service is needed
- Submit Prior Authorization and other required documentation directly to the payer, as required
- Ask for processing time frame, monitor progress, and confirm that authorization is approved before infusing patient

Resources to Complete Prior Authorization and Pre-Certification

- Summary of Benefits
- TYSABRI Benefit Investigation Worksheet
- Payer-specific Prior Authorization form, found on the insurance company website
- If a payer requires a separate Letter of Medical Necessity, but does not mandate a specific format, click below for sample letters

Sample Letters of Medical Necessity

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
Above MS™ Prior Authorization Services

First, research the patient’s insurance benefits to determine if a Prior Authorization is required. (This is also available in the Summary of Benefits that can be provided by Above MS™). Be specific in what your office is requesting to be authorized. In most cases, you are asking for authorization of the infusion and TYSABRI® (natalizumab) coverage.

When requesting a Prior Authorization, it is important to understand that each payer has different requirements and that your office will need to be familiar with these specific requirements. When obtaining details on the Prior Authorization process, your office will want to:

- Determine if the information can be phoned in, faxed, emailed, or submitted through the payer website
- Keep—with the authorization—a copy of everything that your office submits
- Find out how long it will take for a decision to be made
- Log any calls your office makes about the request
- Make sure that your office identifies the site of care for the infusion; it may make a difference
- Follow up with the payer if your office does not receive notification of the decision in a timely manner

Remember that your Biogen Access and Reimbursement Manager is also available to assist your office with access- and reimbursement-related inquiries.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
Identify specific documentation that must be submitted with the request. (This is also available in the Summary of Benefits). Some types of documentation that the payer may request are:

- **Letter of Medical Necessity**
- **Chart notes**
- **Specific payer Prior Authorization form**
- **Relevant literature**
- **MRI and other clinical data related to disease**
- **Documented failure of another product**

Your office will also need to determine the Prior Authorization coverage parameters. These can include:

- **Number of visits or infusions**
- **Time limits of authorization**
- **Diagnosis limitations**
- **Required use of specific specialty pharmacy**
- **Submission requirements**
- **Definition of failure on previous therapies**

Please see [Important Safety Information](#) on pages 65-70, and full [Prescribing Information](#) including [Boxed Warning](#).
Above MS™ Prior Authorization Services

As a follow-up to the Benefit Investigation, the Above MS™ team provides a Prior Authorization service that can help manage the requirements of a Prior Authorization to help patients access TYSABRI® (natalizumab). Simply inform the Above MS team of how that patient will obtain TYSABRI. If a Prior Authorization is required, the service will automatically be activated for your office and your patient.

Prior Authorizations often need to be renewed after a certain restriction, such as a time limit or a number of infusions, no longer applies. It’s important to keep track of these parameters and to seek renewal of a Prior Authorization in advance of when it is due. The Above MS team also provides a Prior Authorization Renewal service to help keep track of Prior Authorization expiration dates to ensure that patients don’t have an interruption in therapy because of a Prior Authorization renewal requirement.

To effectively manage Prior Authorization requests, maintain a summary sheet of each payer’s requirements for your most common payers.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
REQUESTING A MEDICAL EXCEPTION

A Medical Exception is a request by your office to the payer to bypass Step Edits or other coverage restrictions so that the patient can immediately begin treatment with a nonpreferred drug. An effective Letter of Medical Necessity is tailored to your patient’s needs. Be clear about your patient’s individual circumstance—your letter should state whether you are initiating or changing treatment, or whether you want to continue your patient’s therapy but their health insurance benefits have changed. The response time from payers on Medical Exceptions is usually no more than 5 days, with some responding in less time. Some payers will do an expedited review if your office believes that the patient needs to begin treatment without delay.

Key Considerations When Writing a Letter of Medical Necessity

Provide background on your patient’s condition

• Summarize their clinical status citing diagnostic disease measures, such as magnetic resonance imaging (MRI) data and Expanded Disability Status Scale (EDSS) score
• If appropriate, list any failed medications, and provide clinical evidence of their inadequate response

Explain why the treatment you recommend is the appropriate choice for your patient

• Provide a clinical justification supporting the treatment you have chosen for your patient
• Review previous treatments you have tried and what results they produced
• State any patient-specific reasons for the treatment choice, such as efficacy, tolerability issues, or route of administration, if applicable
• Cite relevant literature

Explain why the insurer’s suggested treatment is not appropriate for your patient

• List side effects or adverse events that the patient experienced on an insurer’s suggested treatment, if applicable
• Cite experience on similar therapies and why they are not suitable for your patient, if applicable
• List any compliance concerns, if applicable
• Describe individual patient considerations that impact the choice of treatment, as appropriate
• If your office is associated with an MS specialist, many health plans value indicating this information in the Letter of Medical Necessity

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
REQUESTING A MEDICAL EXCEPTION (CONT’D)

Additional documentation that supports your decision will strengthen your request. Be sure to include clinical and other appropriate documentation to help the health plan understand your patient’s needs.

**Examples of Supporting Documentation**

**Details from the patient’s medical record**
- EDSS scores, MRI data, and relapse history
- If appropriate, general medical history listing comorbidities and any medication history, including contraindications
- Provide documentation of clinical evidence for treatment failure such as inadequate response, adverse events, or side effects, as appropriate
- Other relevant patient information may also be included, as appropriate

**Other documentation**
- Letters from consultants or other medical professionals that support your treatment choice
- Clinical information regarding your treatment choice, such as the product’s US Prescribing Information

Not all payers and/or services will require a Letter of Medical Necessity, but when in doubt, it is best to contact the payer before providing any type of drug or medical service. Payers may change coverage guidelines, which could impact a patient’s ability to access therapy through their insurance. This is most common at the start of each new year. It is a best practice to check with the payer to ensure that nothing has changed. If your office does have questions about payer changes or about the Medical Exceptions process, your Biogen Access and Reimbursement Manager is also available to help.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
REQUESTING A MEDICAL EXCEPTION (CONT’D)

There are various scenarios in which a patient may need your office to prepare and submit a Letter of Medical Necessity to obtain coverage for TYSABRI® (natalizumab). The types of letters your office may need are:

- **Step Requirement Not Met for a Treatment-Naive Patient:** Although the patient has not met the step-therapy requirement, the healthcare provider wants to start the patient on TYSABRI based on their clinical presentation.

- **Step Requirement Not Met for a Patient Converting Treatment:** The patient is not having an adequate response to their current therapy, but has not fulfilled the TYSABRI step-therapy requirement; however, the healthcare provider believes that TYSABRI is the appropriate clinical option for that patient.

- **Step Requirement Not Met for a Patient Change of Coverage:** The patient is currently being treated with TYSABRI but either the patient switches health plans or their current health plan undergoes a policy change that requires the patient to go on another therapy to fulfill the step requirement; however, the physician believes that TYSABRI continues to be an appropriate choice and does not want the patient to change therapies.

To download Letters of Medical Necessity templates for treatment-naïve patients, patients wishing to convert therapy, and patients wishing to remain on their current therapy who have experienced a coverage change, click below.

![Letter of Medical Necessity - Treatment-Naive Patient](image_url)

![Letter of Medical Necessity - Patient Converting Treatment](image_url)

![Letter of Medical Necessity - Patient Currently on Therapy](image_url)

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
Acquisition Options

Ordering Requirements by Type of Coverage

Specialty Pharmacy Network for TYSABRI®

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
THREE ACQUISITION OPTIONS FOR ORDERING TYSABRI (natalizumab)

Biogen has provided several options for acquiring TYSABRI®. These options are designed to provide flexibility based on the services your office provides and on your patients’ needs. Some payers may require a specific acquisition method. When researching the patient’s insurance benefits, look into all of the options that are available, to identify the one that is best for your office and your patient.

Option 1
Purchase from your current wholesaler

Option 2
Purchase direct

Option 3
Purchase TYSABRI through a Specialty Pharmacy that is authorized to distribute TYSABRI and is covered by the patient’s insurance company

Note: If a Benefit Investigation is requested, your office will be informed of the particular specialty pharmacy that is required by the payer. Above MS™ support coordinators can also help identify this information through the TOUCH® Prescribing Program and get the TYSABRI prescription to the right specialty pharmacy.

If your office has questions when choosing an option regarding the services you provide, please contact your Biogen Access and Reimbursement Manager.

Only those orders from infusion sites and central pharmacies that are enrolled in, and are authorized by, the TOUCH Prescribing Program will be processed. If your office is using a specialty pharmacy, the order must be placed through the TOUCH Prescribing Program.

The way in which TYSABRI is obtained may influence the financial responsibility of the patient. Your office may want to discuss these options with the patient before determining how TYSABRI will be ordered.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
# ORDERING REQUIREMENTS
## BY TYPE OF COVERAGE

Ordering requirements may differ based on the patient’s payer coverage. These options can be researched during the Benefit Investigation.

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Private Payers</strong></td>
<td>Many private payers (including some Medicare Advantage and Managed Medicaid plans) use a specialty pharmacy to purchase TYSABRI® (natalizumab). It is important to determine procurement options before treatment with TYSABRI.</td>
</tr>
<tr>
<td><strong>Medicaid</strong></td>
<td>Some Medicaid plans use a specialty pharmacy; some require buy-and-bill.</td>
</tr>
<tr>
<td><strong>Medicare</strong></td>
<td>Traditional Medicare is currently buy-and-bill only.</td>
</tr>
</tbody>
</table>

The way in which TYSABRI is purchased may influence the financial responsibility for the patient. Your office may want to discuss these options and requirements with the patient before determining how TYSABRI will be ordered.

Please see [Important Safety Information](#) on pages 65-70, and full [Prescribing Information](#) including [Boxed Warning](#).
SPECIALTY PHARMACY NETWORK FOR TYSABRI (natalizumab)

If you need to check on the status of your TYSABRI® shipments or to follow up on TYSABRI reorders, you can either call the specialty pharmacy directly or check the status on www.TOUCHprogram.com.

The following specialty pharmacy providers have been authorized by Biogen to supply TYSABRI under the restricted distribution requirements of the TOUCH® Prescribing Program. When calling a specialty pharmacy, ask to speak with a member of the TYSABRI team.

<table>
<thead>
<tr>
<th>Specialty Pharmacy Name</th>
<th>Phone</th>
<th>Fax</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcariaHealth</td>
<td>1-877-928-5120</td>
<td>1-877-928-5121</td>
</tr>
<tr>
<td>Accredo</td>
<td>1-866-898-0034</td>
<td>1-800-302-1028</td>
</tr>
<tr>
<td>Aetna Specialty Pharmacy</td>
<td>1-866-782-2779</td>
<td>1-866-329-2779</td>
</tr>
<tr>
<td>AllianceRx Walgreens Prime</td>
<td>1-888-884-8714</td>
<td>1-877-231-8302</td>
</tr>
<tr>
<td>BioScrip Specialty Pharmacy</td>
<td>1-877-517-9299</td>
<td>1-855-265-2342</td>
</tr>
<tr>
<td>BriovaRx</td>
<td>1-855-242-2241</td>
<td>1-877-342-4596</td>
</tr>
<tr>
<td>CVS Caremark Specialty Pharmacy</td>
<td>1-800-498-5601</td>
<td>1-877-287-7226</td>
</tr>
<tr>
<td>Cigna Specialty Pharmacy Services</td>
<td>1-800-351-3606</td>
<td>1-800-351-3616</td>
</tr>
<tr>
<td>CVS Specialty Customer Care</td>
<td>1-800-237-2767</td>
<td>1-800-323-2445</td>
</tr>
</tbody>
</table>

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
CLAIMS INFORMATION FOR TYSABRI® (natalizumab)

Claims Information for TYSABRI®

Physician Office Billing

Hospital Outpatient Billing

Payer Coverage and Payment for Drugs and Services

Appealing Denied Claims

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
CLAIMS INFORMATION FOR TYSABRI (natalizumab)

Once your patient has received each TYSABRI® infusion, your office may submit a claim to the patient’s insurance plan. Depending on the patient’s benefits, your office may submit a claim for the drug, for the administration services, or for both. The information within this section reviews some of the codes commonly associated with the administration of TYSABRI. However, your office should check directly with the patient’s insurance plan to verify coding recommendations.

Quick Tips for Coding

- **ICD-10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification) Diagnosis Code:** G35 (Multiple Sclerosis)\(^1\)
  - As of October 1, 2015, Centers for Medicare & Medicaid Services (CMS) requires the use of the *International Classification of Diseases, TenthRevision, Clinical Modification (ICD-10-CM)* as the medical code set for medical diagnoses and inpatient hospital procedures.\(^2,3\) The transition to ICD-10-CM is also required for all individuals covered by the Health Insurance Portability and Accountability Act (HIPAA).\(^4\) These codes replace the ICD-9-CM codes that were previously used.

- **HCPCS (Healthcare Common Procedure Coding System):** J2323 (Injection, natalizumab, 1 mg)\(^5\)

- **Drug Units:** 300 (Dose of TYSABRI is 300 mg)

- **National Drug Code:** 64406-008-01 (10-digit format)\(^6\)

- **CPT (Current Procedural Terminology) Administration Code:** 96413 (Chemotherapy administration, intravenous infusion technique up to 1 hour, single or initial substance/drug). Some payers may require the use of CPT code 96365 (Intravenous infusion, for therapy, prophylaxis, or diagnosis [specify substance or drug]; initial, up to 1 hour)\(^7\)

The National Drug Code (NDC) for TYSABRI is 64406-008-01.\(^8\) Although FDA uses a 10-digit format when registering NDCs, payers often require an 11-digit NDC format on claim forms for billing purposes. It is important to confirm with your payer which NDC format they require. Guidelines for reporting the NDC in the appropriate format, quantity, and unit of measure vary by state and by payer and should be reviewed prior to submitting a claim.

Providers accessing TYSABRI through the specialty pharmacy will not need to submit a claim for reimbursement for TYSABRI, because it is being ordered by the specialty pharmacy, but will have to submit a claim for reimbursement for administration services associated with TYSABRI. Patients are invoiced directly for any applicable copayments or coinsurances that they are responsible for.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
PHYSICIAN OFFICE BILLING

Physician offices that administer TYSABRI® (natalizumab) to patients submit claims on the CMS-1500 claim form or its electronic equivalent. The following codes may be appropriate for TYSABRI and related services when provided in a physician office.

<table>
<thead>
<tr>
<th>Diagnosis Code</th>
<th>Code and Description</th>
<th>Location on CMS-1500 Payer Form (Electronic Equivalent)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active Code as of October 1, 2015</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>G35 (Multiple Sclerosis)</td>
<td>Field 21 (Loop: 2300; Segment: HI01-2)</td>
</tr>
<tr>
<td><strong>Inactive Code as of October 1, 2015</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD-9-CM</td>
<td>340 (Multiple Sclerosis)</td>
<td></td>
</tr>
</tbody>
</table>

It is important to know that as of October 1, 2015, CMS will NOT accept ICD-9-CM codes on any claims submissions (electronic or paper) that have a date of service or a date of discharge on or after October 1, 2015. Failure to use ICD-10-CM codes will result in the return or rejection of reimbursement claims.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
<th>Location on CMS-1500 Form</th>
<th>Units</th>
<th>Location on CMS-1500 Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2323</td>
<td>Injection, natalizumab, 1 mg</td>
<td>Field 24D</td>
<td>300</td>
<td>Field 24G</td>
</tr>
</tbody>
</table>

When filling in the HCPCS Code, remember that, because J2323 is per 1 mg, it does not represent the entire vial of drug. To report the use of an entire vial of TYSABRI, you must report 300 units in Field 24G.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
### PHYSICIAN OFFICE BILLING (CONT’D)

<table>
<thead>
<tr>
<th>CPT Code*</th>
<th>Description</th>
<th>Location on CMS-1500 Form</th>
<th>Units</th>
<th>Location on CMS-1500 Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>96413</td>
<td>Chemotherapy administration intravenous infusion technique; up to 1 hour, single or initial substance/drug</td>
<td>Field 24D</td>
<td>1</td>
<td>Field 24G</td>
</tr>
</tbody>
</table>

Typically, administration of TYSABRI® (natalizumab) requires approximately 1 hour of infusion. The total number of hours (from when the medication starts dripping until it stops) is reported in the “Days or Units” column (Field 24G) of the CMS-1500 claim form. One (1) unit of code 96413 may be used to report the time from the start of the infusion until 60 minutes into the infusion. In instances where the infusion requires from 61 to 150 minutes, 1 unit of 96415 (chemotherapy administration, intravenous infusion technique; each additional hour, 1 to 8 hours) may also be billed.7

*Some payers may require the use of CPT code 96365 (intravenous infusion, for therapy, prophylaxis, or diagnosis [specify substance or drug]; initial, up to 1 hour). If the payer requires CPT code 96365 for the initial hour of the infusion, use CPT code 96366 (intravenous infusion, for therapy, prophylaxis, or diagnosis [specify substance or drug]; each additional hour) to report each additional hour.7
Physician Office Coding Summary for Electronic Claim Submission for TYSABRI (natalizumab)

The table below provides examples of relevant codes when billing for TYSABRI® when administered in the physician office setting, and where these codes are reported within your electronic claims software. Requirements and location of information will vary by payer.

<table>
<thead>
<tr>
<th>Information</th>
<th>Code</th>
<th>CMS-1500 Location</th>
<th>Electronic Loop</th>
<th>Equivalent Segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS Code⁵</td>
<td>J2323</td>
<td>Field 24D</td>
<td>2400</td>
<td>SV101</td>
</tr>
<tr>
<td>HCPCS Units</td>
<td>300</td>
<td>Field 24G</td>
<td>2400</td>
<td>SV104</td>
</tr>
<tr>
<td>CPT Code⁷</td>
<td>96413</td>
<td>Field 24D</td>
<td>2400</td>
<td>SV101</td>
</tr>
<tr>
<td>CPT Code Units</td>
<td>1</td>
<td>Field 24G</td>
<td>2400</td>
<td>SV104</td>
</tr>
<tr>
<td>ICD-10-CM Code¹ (primary)</td>
<td>G35 (multiple sclerosis)</td>
<td>Field 21</td>
<td>2300</td>
<td>HI01-2 through HI12-2</td>
</tr>
<tr>
<td>National Provider Identification (NPI) Number</td>
<td>Provider specific</td>
<td>Field 17B</td>
<td>2310A</td>
<td>NM109</td>
</tr>
<tr>
<td>Prior Authorization Number</td>
<td>Payer specific</td>
<td>Field 23</td>
<td>2300</td>
<td>REF02</td>
</tr>
</tbody>
</table>

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
SAMPLE CMS-1500 CLAIM FORM

Field 17B: Indicate the National Provider Identification (NPI) number here.

Field 21: Indicate the most medically appropriate diagnosis code. ICD-10-CM code G35 may be appropriate to report MS.


Field 24D: For TYSABRI® (natalizumab), use the HCPCS code required by the payer. Also include appropriate codes to report drug administration procedures. NOTE: For TYSABRI obtained through a specialty pharmacy, report the drug administration codes here. Check with the payer to identify how to report the drug that was infused if needed.

Field 24G: Indicate the appropriate HCPCS and/or CPT code units.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
HOSPITAL OUTPATIENT BILLING

Hospital outpatient departments (eg, hospital-based infusion sites) that administer TYSABRI® (natalizumab) to patients submit claims on the CMS-1450/UB-04 claim form or its electronic equivalent. The following codes may be appropriate for TYSABRI and related services when provided in a hospital outpatient department.

<table>
<thead>
<tr>
<th>Diagnosis Code</th>
<th>Code and Description</th>
<th>Location on CMS-1450/UB40 Form (Electronic Equivalent)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active Code as of October 1, 2015</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ ICD-10-CM&lt;sup&gt;1&lt;/sup&gt;</td>
<td>G35 (Multiple Sclerosis)</td>
<td>Field 67</td>
</tr>
<tr>
<td><strong>Inactive Code as of October 1, 2015</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X ICD-9-CM&lt;sup&gt;3&lt;/sup&gt;</td>
<td>340 (Multiple Sclerosis)</td>
<td></td>
</tr>
</tbody>
</table>

It is important to know that as of October 1, 2015, CMS will NOT accept ICD-9-CM codes on any claims submissions (electronic or paper) that have a date of service or a date of discharge on or after October 1, 2015. Failure to use ICD-10-CM codes will result in the return or rejection of reimbursement claims.<sup>9</sup>

<table>
<thead>
<tr>
<th>HCPCS Code&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Description</th>
<th>Location on CMS-1450/UB-04 Form</th>
<th>Units</th>
<th>Location on CMS-1450/UB-04 Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2323</td>
<td>Injection, natalizumab, 1 mg</td>
<td>Field 44</td>
<td>300</td>
<td>Field 46</td>
</tr>
</tbody>
</table>

Because J2323 is per 1 mg, it does not represent the entire vial of drug. To report the use of an entire vial of TYSABRI, you must report 300 units in Field 46.<sup>5</sup> Some payers prefer that the units of service in Field 46 be equal to the number of vials used. We recommend verifying which method of reporting units of service each payer prefers.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
HOSPITAL OUTPATIENT BILLING (CONT’D)

Revenue codes are required for hospital outpatient billing and will vary depending on the revenue center to which your hospital maps TYSABRI® (natalizumab). Typically, TYSABRI will be reported using revenue codes such as:

<table>
<thead>
<tr>
<th>Revenue Code</th>
<th>Description</th>
<th>Location on CMS-1450/UB-04 Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>0250</td>
<td>Pharmacy general classification</td>
<td></td>
</tr>
<tr>
<td>0636*</td>
<td>Drug requiring detailed coding</td>
<td>Field 42†</td>
</tr>
<tr>
<td>0510</td>
<td>Clinic visit</td>
<td></td>
</tr>
<tr>
<td>0260</td>
<td>IV infusion</td>
<td></td>
</tr>
</tbody>
</table>

*For Medicare, revenue code 0636 must be used in conjunction with HCPCS code 96413. Private payers may also require revenue code 0636 for TYSABRI.
†The appropriate revenue code should be entered into Field 42 of the CMS-1450/UB-04 claim form.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
HOSPITAL OUTPATIENT BILLING (CONT’D)

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Location on CMS-1450/UB-04 Form</th>
<th>Units</th>
<th>Location on CMS-1450/UB-04 Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>96413*</td>
<td>Chemotherapy administration intravenous infusion technique; up to 1 hour, single or initial substance/drug</td>
<td>Field 44</td>
<td>1</td>
<td>Field 46</td>
</tr>
</tbody>
</table>

Typically, administration of TYSABRI® (natalizumab) requires approximately 1 hour of infusion. The total number of hours (from when the medication starts dripping until it stops) is reported in the “Days or Units” column (Field 46) of the CMS-1450/UB-04 claim form. One (1) unit of code 96413 may be used to report the time from the start of the infusion until 60 minutes into the infusion. In instances where the infusion requires from 61 to 150 minutes, 1 unit of 96415 (chemotherapy administration, intravenous infusion technique; each additional hour, 1 to 8 hours) may also be billed.7

*Some payers may require the use of CPT code 96365 (intravenous infusion, for therapy, prophylaxis, or diagnosis [specify substance or drug]; initial, up to 1 hour). If the payer requires CPT code 96365 for the initial hour of the infusion, use CPT code 96366 (intravenous infusion, for therapy, prophylaxis, or diagnosis [specify substance or drug]; each additional hour) to report each additional hour.7

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
Hospital Outpatient Department Coding Summary for Electronic Claim Submission for TYSABRI (natalizumab)

The table below provides examples of relevant codes when billing for TYSABRI® when administered in the hospital outpatient setting and where these codes are reported within your electronic claims software. Requirements and location of information will vary by payer.

<table>
<thead>
<tr>
<th>Information</th>
<th>Code</th>
<th>CMS-1450/UB-04 Location</th>
<th>Electronic Loop</th>
<th>Equivalent Segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS Code⁵</td>
<td>J2323</td>
<td>Field 44</td>
<td>2400</td>
<td>SV202-2</td>
</tr>
<tr>
<td>HCPCS Units</td>
<td>300</td>
<td>Field 46</td>
<td>2400</td>
<td>SV205</td>
</tr>
<tr>
<td>CPT Code⁷</td>
<td>96413</td>
<td>Field 44</td>
<td>2400</td>
<td>SV202-2</td>
</tr>
<tr>
<td>CPT Code Units</td>
<td>1</td>
<td>Field 46</td>
<td>2400</td>
<td>SV205</td>
</tr>
<tr>
<td>ICD-10-CM Code² (primary)</td>
<td>G35 (multiple sclerosis)</td>
<td>Field 67</td>
<td>2300</td>
<td>HI01-2</td>
</tr>
<tr>
<td>National Provider Identification (NPI) Number</td>
<td>Provider specific</td>
<td>Field 56</td>
<td>2010AA</td>
<td>NM1/85/09</td>
</tr>
<tr>
<td>Revenue Code¹¹</td>
<td>0250</td>
<td>Field 42</td>
<td>2400</td>
<td>SV201</td>
</tr>
</tbody>
</table>

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
SAMPLE CMS-1450/UB-04 CLAIM FORM

Field 42: Include appropriate revenue codes.
Field 44: Use appropriate HCPCS/CPT codes to report TYSABRI® (natalizumab) and infusion.
Field 46: Indicate the appropriate HCPCS and/or CPT code units.
Field 67: Indicate the most medically appropriate diagnosis code. In this example, ICD-10-CM G35 is used to report MS.
Field 56: Indicate the National Provider Identification (NPI) number here.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
PAYER COVERAGE AND PAYMENT FOR DRUGS AND SERVICES

Medicare, private payers, and Medicaid have different reimbursement policies. Being familiar with these differences will enable your office to avoid potential challenges with payers.

Medicare (and Sequestration)

Medicare reimburses physician services, including drug administration services, based on the Medicare Physician Fee Schedule (MPFS) at the Average Sales Price (ASP) plus 6%, as published quarterly by the Centers for Medicare & Medicaid Services (CMS). Medicare pays 80% of the allowed charges for TYSABRI® (natalizumab) and its administration, with the beneficiary (or supplemental insurance) responsible for the remaining 20% coinsurance.14

Costs for physician-administered drugs

A 2% across-the-board cut in Medicare provider payments took effect. The sequestration is required by the Budget Control Act that was signed into law in August 2011. All Medicare physician claims with a date of service on or after April 1, 2013, will be subject to a 2% payment cut.15

This link will take you to a website that is outside the control of Biogen. We provide links as a public service and for informational purposes only.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
PAYER COVERAGE AND PAYMENT FOR DRUGS AND SERVICES (CONT’D)

Medicaid and Private Payers

Some payers may require prior authorization for TYSABRI® (natalizumab), or they may have other requirements. Medicaid reimbursement for TYSABRI and its administration service varies by state.

For private payers, reimbursement for TYSABRI and its administration services will vary, depending on the specific provisions outlined in your contract with the payer.

Medicaid rates are updated quarterly and can be found at the link below:

State Medicaid & Children’s Health Insurance Program (CHIP) Policies

This link will take you to a website that is outside the control of Biogen. We provide links as a public service and for informational purposes only.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
APPEALING DENIED CLAIMS

If a claim for TYSABRI® (natalizumab) is denied or is improperly reimbursed, your office may consider submitting an appeal. The appeals process varies by payer, but your office may find the following steps beneficial in your approach. Above MS™ Support Coordinators are available to assist you during the appeals process. Resources that may be helpful as your office goes through the process are:

- TYSABRI Benefit Investigation Worksheet
- Summary of Benefits
- The insurance company website for processes and/or forms
- A sample Letter of Appeal, if the payer does not have a specific appeals format (sample Letter of Appeal can be found on following page)

1. **Understand the Denial Reason**

   Review the Explanation of Benefits for the denial reason(s). See [Physician Office Billing](#) and [Hospital Outpatient Billing](#) for appropriate codes. The most common reasons for denials include:

   - Use of incorrect CPT/HCPCS code(s)
   - Incorrect number of units billed
   - Transposed, missing, or truncated policy numbers
   - No Prior Authorization on file
   - Missing Prior Authorization number on claim
   - Patient’s insurance mandates the use of a specialty pharmacy

2. **Appeal the Claim**

   Contact the payer to obtain their appeals process. Elements to consider in your inquiry include:

   - Your ability to submit the appeal via fax or electronically (online)
   - Address and phone number for their appeals department
   - Payer-specific timeline and process for responding to appeal requests
   - Payer-specific appeals form that must be completed
   - Name and phone number of your provider representative
   - Name and address of their medical director

3. **Monitor the Claim**

   Check with the payer to confirm that they have received your request and to check the status of its decision. Notify the patient of instances where your office may need his or her involvement. Often, the patient, too, can submit an appeal to the payer.

Please see [Important Safety Information](#) on pages 65-70, and full [Prescribing Information](#) including [Boxed Warning](#).
Sample Letter of Appeal

To: [Name of Insurance Company]
   [Address]
   [City], [State] [ZIP Code]

Re: [Patient name]

Diagnosis: [Patient’s diagnosis and ICD-9-CM Code]
Policy Number:
Group Number:
Subscriber Name:

To Whom It May Concern:

I am writing on behalf of my patient [insert name], policy number [insert number], to request reconsideration of a claim. [Insert drug name] was administered to [insert patient name] on [insert date of service]. [Insert drug name] has been approved by the FDA for [insert disease]. You have indicated that [insert drug name] is not covered by [insert insurance company] because [insert reason for denial from Explanation of Benefits].

[Provide a brief description of the patient’s medical history, treatments, and response to drug treatment.]

[Insert patient name] has had a diagnosis of [insert diagnosis] since [insert date] at the age of [insert age]. I have administered [insert drug name] to [insert patient name] as a medically necessary part of [his/her] treatment. I would appreciate a reconsideration of the claim from [insert date of service] for [insert patient name]. To further support the medical necessity of this patient’s treatment with [insert drug name], I am including the following information:

[Bullet out a list of the documentation provided with the request such as product information, clinical literature, and information from the patient’s medical record]

Based on this patient’s diagnosis, disease severity, and medical history, I believe that [insert drug name] is appropriate and medically necessary for this patient, and would appreciate a reconsideration of this service.

If you have any further questions, please contact me at [insert phone number] to discuss. Thank you in advance for your immediate attention to this request for treatment.

Sincerely,

[Insert physician name, practice name, and address]

[Attach supporting documentation such as MRI results, chart notes, etc]
REFERENCES


Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
PATIENT SUPPORT: ABOVE MS™

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
UNDERSTANDING PATIENT FINANCIAL RESPONSIBILITY

Above MS™ provides many resources to help your patients gain access to Support Coordinators who can help them understand their insurance coverage and identify the best financial assistance solution for TYSABRI® (natalizumab). In addition to providing assistance with Benefit Investigations and Prior Authorizations, Above MS can help with patients’ concerns related to cost or insurance. Most patients will have either a copay or coinsurance responsibility for the drug and the administration of TYSABRI.

Above MS offers personalized assistance to identify the best financial assistance option for your patients. The goal of Above MS is to ensure that no patient has to forgo Biogen treatment due solely to financial limitations.

Your office can contact a Support Coordinator from Above MS by calling 1-800-456-2255.

**Copay**
Typically, copay is a flat fee that patients pay each time they receive medical care. The copay may be in addition to other out-of-pocket costs, such as deductibles and coinsurance, and it varies by benefit structure.

**Coinsurance**
A beneficiary cost-sharing amount that begins after the deductible is paid, coinsurance is typically based on a percentage of the cost of services, and it varies by payer.

**Deductible**
A predetermined amount of money that the patient must spend before their payer benefits take effect.

**Maximum Out-of-Pocket (OOP) Costs**
An annual limitation on all cost-sharing for which patients are responsible under a health insurance plan. This limit does not apply to premiums, balance-billed charges from out-of-network healthcare providers, or services that are not covered by the plan.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
Biogen is committed to providing your patients with quality support services for their relapsing MS treatment. Biogen provides comprehensive support through:

<table>
<thead>
<tr>
<th>FINANCIAL ASSISTANCE</th>
<th>INSURANCE ASSISTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$0 Copay Program from Biogen:</strong></td>
<td>Benefit Investigation:</td>
</tr>
<tr>
<td>Offering treatment for just $0 a month for eligible patients, regardless of income</td>
<td>Review insurance coverage and provide assistance with prior authorizations and denied claims</td>
</tr>
<tr>
<td><strong>Infusion Copay Assistance Program:</strong></td>
<td>Insurance Counseling:</td>
</tr>
<tr>
<td>Assistance with the cost of infusion administration for eligible patients</td>
<td>Support identifying coverage options such as Medigap, COBRA, Medicaid, or options through the Health Insurance Marketplaces (HIMs)</td>
</tr>
<tr>
<td><strong>Free Drug Program:</strong></td>
<td></td>
</tr>
<tr>
<td>Providing therapy to eligible patients free of charge, with no time limit to those truly in need</td>
<td></td>
</tr>
<tr>
<td><strong>Charitable Funding:</strong></td>
<td></td>
</tr>
<tr>
<td>Finding your patients assistance with premiums, copays, and other needs</td>
<td></td>
</tr>
</tbody>
</table>

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
ABOVE MS™ FINANCIAL ASSISTANCE PROCESS

Benefit Investigation
- Review insurance coverage
- Assistance with Prior Authorizations and Denied Claims

Copay Assistance
- $0 Copay Program from Biogen for privately insured eligible patients
- Infusion Copay Assistance for eligible patients

Assistance Finding Charitable Funding
- Support finding premium, copay, and transportation assistance

Insurance Counseling
- Support identifying coverage options such as Medigap, COBRA, Medicaid, or options through the Health Insurance Marketplaces (HIMs)

Free Drug
- Free drug to those truly in need
  – Medicare
  – Uninsured

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
INITIATING THE $0 COPAY PROGRAM FROM BIOGEN

This program covers the cost of the drug only and does not cover infusion-related costs.

How It Works and What Your Patients Need to Do*

Have your patients contact Above MS™ to learn about enrolling in the $0 Copay Program from Biogen

For TYSABRI® (natalizumab) obtained through a specialty pharmacy: No action is necessary on the part of the infusion site.

For TYSABRI obtained through Buy-and-Bill: If the patient qualifies for copay assistance, your office will receive a fax from the TOUCH® Prescribing Program notifying you of the patient’s eligibility. Keep the fax, because it has information that your office will need each month for administering the copay assistance.†

*Eligibility: Depending on income or, in some cases, if medication is obtained from an out-of-network provider, there may be an annual cap that limits the amount of assistance that your patient can receive over 1 year. Federal and state laws and other factors may prevent or otherwise restrict eligibility. People covered by Medicare, Medicaid, the VA/DoD, or any other federal plans are not eligible to enroll.

†Your office can check the specific programs that patients may be using to receive their TYSABRI using TOUCH On-Line. TOUCH On-Line lists all of the Above MS programs that a TYSABRI patient is currently enrolled in.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
INITIATING THE $0 COPAY PROGRAM FROM BIOGEN (CONT’D)

For TYSABRI® (natalizumab) Obtained Through Buy-and-Bill:

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Confirm that patient is enrolled in the $0 Copay Program from Biogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Fax an Explanation of Benefits (EOB) to Biogen</td>
</tr>
<tr>
<td>Step 3</td>
<td>Charge appropriate account</td>
</tr>
</tbody>
</table>

Confirm that patient is enrolled in the $0 Copay Program from Biogen at every infusion. This information is available in TOUCH® On-Line.

Fax an EOB to Above MS™ at 1-866-291-6114 after each infusion.*

Upon receipt of the Copay AUTHORIZATION FAX from Biogen, charge the copay to the authorized credit card account.

*Eligibility: Depending on income or, in some cases, if medication is obtained from an out-of-network provider, there may be an annual cap that limits the amount of assistance that your patient can receive over 1 year. Federal and state laws and other factors may prevent or otherwise restrict eligibility. People covered by Medicare, Medicaid, the VA/DoD, or any other federal plans are not eligible to enroll.

For more information on financial assistance for TYSABRI, please call 1-800-456-2255 to speak with a Support Coordinator from Above MS.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
INITIATING INFUSION COPAY ASSISTANCE

This program covers the cost of the infusion only and does not cover the cost of the drug.

Your office can check the specific programs that patients may be using to receive their TYSABRI® (natalizumab) using TOUCH® On-Line. TOUCH On-Line lists all of the Above MS™ programs that a TYSABRI patient is currently enrolled in.

<table>
<thead>
<tr>
<th>INSURED PATIENTS*</th>
<th>UNINSURED PATIENTS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Site of Care (SOC) infuses patient and files insurance claim.</td>
<td>1. SOC infuses patient and generates detailed statement of infusion administration charges.</td>
</tr>
<tr>
<td>2. After receiving Explanation of Benefits (EOB), fax to Above MS at 1-866-291-6114 after each infusion.</td>
<td>2. Fax detailed statement of infusion administration charges to Above MS at 1-866-291-6114 after each infusion.</td>
</tr>
<tr>
<td>3. Upon receipt of Program AUTHORIZATION FAX from Biogen, charge out-of-pocket (OOP) cost up to $250 to VISA account provided. Up to $250 per infusion.†</td>
<td>3. Upon receipt of Program AUTHORIZATION FAX from Biogen, charge cost of infusion administration up to $250 to VISA account provided. Up to $250 per infusion.†</td>
</tr>
</tbody>
</table>

*People covered by any federal healthcare program—including, but not limited to, Medicare, Medicaid, the VA/DoD, TRICARE, and/or state medical or pharmaceutical assistance programs—are not eligible.

†Up to $1300 per year.

For more information on financial assistance for TYSABRI, please call 1-800-456-2255 to speak with a Support Coordinator from Above MS.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
HEALTHCARE REFORM

Refer to HealthCare.gov for more information. This link will take you to a website that is outside the control of Biogen. We provide links as a public service and for informational purposes only.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
HEALTHCARE REFORM

On March 23, 2010, the Affordable Care Act (ACA) was signed into law to improve the insurance options available for individuals and small employers, and to reduce the number of uninsured in the United States. Included below are some key parts of the ACA that were implemented beginning January 1, 2014.1,2

**Principles of Healthcare Reform and the Key Goals of the ACA**

Healthcare reform was founded on 4 principles¹:

- Reduce the number of uninsured
- Improve quality of care
- Improve health insurance markets
- Control costs

Refer to HealthCare.gov for more information. This link will take you to a website that is outside the control of Biogen. We provide links as a public service and for informational purposes only.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
HEALTHCARE REFORM (CONT’D)

The following table illustrates the primary objectives of the ACA:

**Key Goals of the Affordable Care Act**

<table>
<thead>
<tr>
<th>INSURANCE FOR INDIVIDUALS AND SMALL GROUPS</th>
<th>REDUCE THE NUMBER OF UNINSURED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Insurance Marketplaces (HIMs) enable comparison shopping³</td>
<td>• Subsidies for buying insurance⁶</td>
</tr>
<tr>
<td>Insurance sold in HIMs must meet certain standards³</td>
<td>• Penalty for not having insurance⁷</td>
</tr>
<tr>
<td>• No excluding patients based on pre-existing conditions²</td>
<td>• States have the option to expand Medicaid⁸</td>
</tr>
<tr>
<td>• No dropping patients without cause if they become sick⁴</td>
<td></td>
</tr>
<tr>
<td>• No lifetime or annual limits⁴</td>
<td></td>
</tr>
<tr>
<td>• Must offer:</td>
<td></td>
</tr>
<tr>
<td>– Minimum required essential health benefits (EHBs)³</td>
<td></td>
</tr>
<tr>
<td>– Annual out-of-pocket maximums⁵</td>
<td></td>
</tr>
</tbody>
</table>

For more information about the Health Insurance Marketplace, please visit HealthCare.gov. This link will take you to a website that is outside the control of Biogen. We provide links as a public service and for informational purposes only.
ESSENTIAL HEALTH BENEFITS

Plans offered in the Health Insurance Marketplace must provide essential health benefits (EHBs) to their customers. These include but are not limited to:

- Ambulatory services
- Emergency services
- Hospitalization
- Prescription drugs
- Chronic-disease management
- Laboratory services

Plans may provide benefits in excess of the EHBs if they choose. However, it is important to note that MRIs are NOT included in the list of EHBs. Patients who are covered through an HIM may not be covered for MRIs. Patients should confirm that an MRI is a covered benefit under their plan.

Refer to HealthCare.gov for more information. This link will take you to a website that is outside the control of Biogen. We provide links as a public service and for informational purposes only.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
HELPFUL INFORMATION FOR PROVIDERS

Coverage among plans in the Health Insurance Marketplace differs from traditional payer models. We have compiled some of those differences and the information that your office may need to acquire to try to ensure that your patients’ treatment and care continue.

<table>
<thead>
<tr>
<th>IMPORTANT INFORMATION THAT YOUR OFFICE MAY NEED RELATING TO THE AFFORDABLE CARE ACT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marketplace plans tend to have smaller provider networks</strong>&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Am I in my existing patients’ new networks?</td>
</tr>
<tr>
<td>• Which hospitals are in my patients’ networks?</td>
</tr>
<tr>
<td>• Which infusion sites are in my patients’ networks?</td>
</tr>
<tr>
<td><strong>Many patients will have plans with high out-of-pocket costs</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>• What will my patients’ out-of-pocket costs be? Can they afford to pay?</td>
</tr>
<tr>
<td>• Are my patients’ MRIs, which are not an EHB, covered?</td>
</tr>
<tr>
<td>• Is drug copay assistance available for patients?</td>
</tr>
</tbody>
</table>

Refer to [HealthCare.gov](http://HealthCare.gov) for more information. This link will take you to a website that is outside the control of Biogen. We provide links as a public service and for informational purposes only.

Please see [Important Safety Information](#) on pages 65-70, and full [Prescribing Information](#) including [Boxed Warning](#).
QUESTIONS THAT YOUR PATIENTS MAY ASK ABOUT THE HEALTH INSURANCE MARKETPLACE

Patients who receive their coverage from a plan in the Health Insurance Marketplace may have many questions regarding their access and coverage. Below are some frequently asked questions that patients have about the Health Insurance Marketplace.

<table>
<thead>
<tr>
<th>ACCESS TO PROVIDERS</th>
<th>COVERED BENEFITS AND COSTS</th>
<th>COVERAGE FOR PRESCRIPTION MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Are the patient’s providers in network?</td>
<td>• What is the copay for doctor visits?</td>
<td>• What are the options if the provider prescribes an off-formulary drug?</td>
</tr>
<tr>
<td>– Patient should call their providers to confirm</td>
<td>• What is the copay for infusions?</td>
<td>• Are the patient’s medications covered on formulary? On what tier? What are the copay/coinsurance amounts?</td>
</tr>
<tr>
<td>• Which hospitals are in the network?</td>
<td>• Patient should call their providers to inquire</td>
<td>• Is drug copay assistance available for the patient’s therapies?</td>
</tr>
<tr>
<td>• Will the plan require a referral to see a specialist?</td>
<td>• Are there limits on the number of services the patient may receive per year?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Are the services that the patient expects to need covered by the plan?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Patients should calculate their expected medical costs for the year and select the plan that best meets their costs and needs</td>
<td></td>
</tr>
</tbody>
</table>

Biogen has a team prepared to help patients and providers become familiar with insurance options available as a result of the Affordable Care Act. Each patient’s situation differs based on the state where they reside, the plans offered in that state, and other health conditions facing the patient and/or family. It is important that patients are educated on the options and that they make the right decision for themselves and their families.

Refer to HealthCare.gov for more information. This link will take you to a website that is outside the control of Biogen. We provide links as a public service and for informational purposes only.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
HEALTHCARE REFORM RESOURCES

Below are healthcare-related websites that may assist you and your patients with questions about Healthcare Reform, such as choosing insurance from the Health Insurance Marketplace, determining whether their treatment is covered by their plan, and finding answers and resources to assist with costs related to their treatment. If a patient is already enrolled, a good place to start is with the health plan website.

HealthCare.gov
National Multiple Sclerosis Society
Understanding the Affordable Care Act

These links will take you to websites that are outside the control of Biogen. We provide links as a public service and for informational purposes only.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
REFERENCES


Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
FREQUENTLY ASKED QUESTIONS AND GLOSSARY

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
**FREQUENTLY ASKED QUESTIONS (FAQs)**

**Can I report evaluation and management (E/M) services in addition to an infusion?**

In some instances, you may provide an E/M service in addition to the infusion within the physician office (office visit) or hospital outpatient (clinic visit). A separate and identifiable procedure must be performed in order to bill for an E/M service in addition to the drug infusion. To bill for both services, the additional service must be clearly documented in the patient’s medical record. Some payers will also require the use of the -25 modifier, which tells the payer that the additional services were performed within the same visit.

If the payer allows you to bill for an E/M code in addition to the drug infusion, there are many factors that you should consider in determining which E/M code to use:

- Patient status (new or established)
- Level of decision-making required
- Complexity of the case
- Time spent with the patient

The level of clinic visit billed is based on the level of service documented in the patient’s medical record and on the 1995 or 1997 E/M guidelines used by your facility to select the appropriate E/M code for clinic visits. Medicare does not pay for 99211 separately when reported on the same day as a drug-infusion service. The table to the right provides a summary of some of the E/M codes that providers may use.

**E/M of an established patient requires 2 of these 3 key components**

- A comprehensive history
- A comprehensive examination
- Medical decision-making of high complexity

**99215**

**E/M of an established patient requires 2 of these 3 key components**

- A comprehensive history
- A comprehensive examination
- Medical decision-making of moderate complexity

**99214**

**E/M of an established patient requires 2 of these 3 key components**

- A detailed history
- A detailed examination
- Medical decision-making of low complexity

**99213**

**E/M of an established patient that may not require the presence of a physician. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.**

**99212**

Please see [Important Safety Information](#) on pages 65-70, and full [Prescribing Information](#) including [Boxed Warning](#).
FREQUENTLY ASKED QUESTIONS (FAQs) (CONT’D)

How do I submit a claim for an infusion of TYSABRI® (natalizumab) when I did not purchase the drug?
If you have received TYSABRI at no cost (for example, either through a specialty pharmacy or through the Above MS™ program), you may not bill third-party payers for it. Although you may not bill for the drug, you may be able to bill for the administration service. Some payers may require you to enter the J-code on the claim form with a zero charge to identify which drug was administered. To verify if there are special billing guidelines for a drug obtained at no charge, it is important to check with the specific payer.

Does the patient authorization from the TOUCH® Prescribing Program have anything to do with the patient’s insurance coverage?
No. It means that the patient has been authorized to receive TYSABRI. It is NOT an authorization from the insurance company; nor does it address any reimbursement-related issue.

How frequently will payers allow an infusion of TYSABRI to be given?
This varies according to the guidance published by specific payers. It is important to check with the payer regarding their policy. The recommended dose of TYSABRI is 300 mg administered intravenously once every 4 weeks.

What should I do if I drop a vial?
Contact your specialty pharmacy or distributor and Above MS or your Access and Reimbursement Manager to get more information on replacement vials.

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
FREQUENTLY ASKED QUESTIONS (FAQs) (CONT’D)

I received a denial because we infused the drug when the Prior Authorization was “pending.” Now what do we do?
For more information on appealing claims and options for patient assistance, contact Above MS™ or your Access and Reimbursement Manager.

What can I do if the Prior Authorization is denied?
For help in determining the reason(s) for denial and to explore possible options for patient assistance, contact Above MS.
### GLOSSARY

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambulatory Payment</strong></td>
<td>Medicare-reimbursement methodology for hospital outpatient facilities. Medicare assigns a fixed payment to group procedures that are comparable clinically and in terms of resource costs.¹</td>
</tr>
<tr>
<td><strong>Classification</strong></td>
<td>Medicare-reimbursement methodology for Part B–covered drugs. ASP is the sum of gross sales less certain discounts, drawbacks, and rebates divided by the total number of units sold in the United States. Manufacturers submit ASP data to CMS by specific deadlines after the end of each quarterly period.²</td>
</tr>
<tr>
<td><strong>Average Sales Price</strong></td>
<td>A beneficiary cost-sharing amount that begins after the deductible is paid, coinsurance is typically based on a percentage of the cost of services, and it varies by payer.³</td>
</tr>
<tr>
<td><strong>Coinsurance</strong></td>
<td>A copay is a flat fee that patients pay each time they receive medical care. The copay may be in addition to other out-of-pocket costs, such as deductibles and coinsurance, and it varies by benefit structure.⁴</td>
</tr>
<tr>
<td><strong>Copay</strong></td>
<td>The cost for medical care that the patient pays (eg, copay, coinsurance, or deductible).³</td>
</tr>
<tr>
<td><strong>Cost Sharing</strong></td>
<td>A predetermined amount of money that the patient must spend before their payer benefits take effect.³</td>
</tr>
<tr>
<td><strong>Deductible</strong></td>
<td>Document received from the payer detailing specific reimbursement amounts for services rendered.⁵</td>
</tr>
<tr>
<td><strong>Explanation of Benefits</strong></td>
<td></td>
</tr>
</tbody>
</table>

¹ Medicare assigns a fixed payment to group procedures that are comparable clinically and in terms of resource costs.
² Medicare-reimbursement methodology for Part B–covered drugs. ASP is the sum of gross sales less certain discounts, drawbacks, and rebates divided by the total number of units sold in the United States. Manufacturers submit ASP data to CMS by specific deadlines after the end of each quarterly period.
³ A beneficiary cost-sharing amount that begins after the deductible is paid, coinsurance is typically based on a percentage of the cost of services, and it varies by payer.
⁴ A copay is a flat fee that patients pay each time they receive medical care. The copay may be in addition to other out-of-pocket costs, such as deductibles and coinsurance, and it varies by benefit structure.
⁵ The cost for medical care that the patient pays (eg, copay, coinsurance, or deductible).

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
### Glossary (Cont’d)

<table>
<thead>
<tr>
<th><strong>Maximum Out-of-Pocket Costs:</strong></th>
<th>An annual limitation on all cost sharing for which patients are responsible under a health insurance plan. This limit does not apply to premiums, balance-billed charges from out-of-network healthcare providers, or services that are not covered by the plan.³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modifier:</strong></td>
<td>2-digit numeric or alpha code used with another code to indicate that a service or procedure has been altered but is not changed in its definition or code.⁶</td>
</tr>
<tr>
<td><strong>Pre-Certification:</strong></td>
<td>Some health insurers require pre-approval, also known as Pre-Certification, for certain types of healthcare services such as surgery or hospital visits. This means that the physician or patient must contact the insurer to obtain their approval before receiving care; otherwise, the insurer may not cover it. Not all services will require pre-approval, but when in doubt, it is best to contact the insurance company before providing any type of healthcare.⁷</td>
</tr>
<tr>
<td><strong>Prior Authorization:</strong></td>
<td>A requirement that the physician obtain approval from a payer to prescribe a specific medication. Without this prior approval, a payer may not provide coverage or may not pay for a medication for a patient.⁸</td>
</tr>
<tr>
<td><strong>Specialty Pharmacy:</strong></td>
<td>Distribution channel equipped to dispense specialty pharmaceuticals, which carry a unique set of needs relative to care management, reimbursement, shipping, and storage.⁹</td>
</tr>
<tr>
<td><strong>Summary of Benefits:</strong></td>
<td>Document received from Biogen’s Above MS™ detailing Benefit Investigation information.</td>
</tr>
</tbody>
</table>

Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
REFERENCES


Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.
IMPORTANT SAFETY INFORMATION

Please see full Prescribing Information, including Boxed Warning, for additional Important Safety Information.
IMPORTANT SAFETY INFORMATION

Indication
TYSABRI® (natalizumab) is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. 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. See Important Safety Information regarding the risk of PML with TYSABRI.

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 duration of therapy, prior use of immunosuppressants, and presence of anti-JCV antibodies. 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.

Please see full Prescribing Information, including Boxed Warning, for additional Important Safety Information.
• 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 approximately 6 months after discontinuation of TYSABRI.

• Adverse events that may occur during plasma exchange include clearance of other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema. Although plasma exchange has not been 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.

• 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 plasma exchange 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 plasma exchange. 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-Prescriber Enrollment Form.

Please see full Prescribing Information, including Boxed Warning, for additional Important Safety Information.
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.
- 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.

Please see full Prescribing Information, including Boxed Warning, for additional Important Safety Information.
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 intracellulare, 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.

Please see full Prescribing Information, including Boxed Warning, for additional Important Safety Information.
IMPORTANT SAFETY INFORMATION (CONT’D)

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, including Boxed Warning, for additional Important Safety Information.
Please see Important Safety Information on pages 65-70, and full Prescribing Information including Boxed Warning.