CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761322Orig1s000

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document
TYRUKO (natalizumab-sztn) REMS Program

I. Administrative Information

Risk: progressive multifocal leukoencephalopathy
Application Number: BLA 761322
Application Holder: Sandoz
REMS Approval: 08/2023

II. REMS Goals

The goals of the TYRUKO REMS are:

1. To inform prescribers, infusion site healthcare providers, and patients about the risk of progressive multifocal leukoencephalopathy (PML) associated with TYRUKO including the increased risk of progressive multifocal leukoencephalopathy with the presence of anti-JCV antibodies, longer treatment duration, and prior immunosuppressant use.
2. To warn against concurrent use with antineoplastic, immunosuppressant, or immunomodulating agents, and in patients who are immunocompromised.
3. To promote early diagnosis of progressive multifocal leukoencephalopathy and timely discontinuation of TYRUKO in the event of suspected progressive multifocal leukoencephalopathy.

III. REMS Requirements

Sandoz must ensure that health care providers, patients, pharmacies, infusion sites, and wholesalers-distributors comply with the following requirements:

1. Health Care Providers who prescribe TYRUKO must:

To become certified to prescribe	1. Review the drug's Prescribing Information. 2. Review the following: Educational Slide Set, Overview and Helpful Information for Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO (Multiple Sclerosis) or Understanding PML for Gastroenterologists (Crohn's Disease). 3. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.
Before treatment initiation (first dose)	4. Counsel the patient using the Medication Guide and the Patient Enrollment Form – Multiple Sclerosis or Patient Enrollment Form – Crohn's Disease. Provide a copy of the materials to the patient. 5. Enroll the patient by completing and submitting the Patient Enrollment Form – Multiple Sclerosis or Patient Enrollment Form – Crohn's Disease to the REMS Program. 6. Assess the patient's risk factors that increase the risk of progressive multifocal leukoencephalopathy.
During treatment; 3 months after the first infusion	7. Assess the patient's signs, symptoms and risk factors for progressive multifocal leukoencephalopathy.
During treatment; 6 months after the first infusion and every 6 months thereafter	8. Assess the patient's signs, symptoms and risk factors for progressive multifocal leukoencephalopathy and whether the patient should continue treatment. Document and submit the results to the REMS Program using the Patient Status Report and Reauthorization Questionnaire.

After treatment discontinuation; initially	9. Assess the patient' s signs and symptoms for progressive multifocal leukoencephalopathy. Document and submit to the REMS Program using the Initial Discontinuation Questionnaire.
After treatment discontinuation; 6 months later	10. Assess the patient's signs and symptoms for progressive multifocal leukoencephalopathy. Document and submit to the REMS Program using the 6-Month Discontinuation Questionnaire.
At all times	11. Report cases of progressive multifocal leukoencephalopathy, hospitalizations due to opportunistic infection, or deaths to Sandoz.

2. Patients who are prescribed TYRUKO:

Before treatment initiation	1. Review the Medication Guide and the Patient Enrollment Form – Multiple Sclerosis or Patient Enrollment Form – Crohn's Disease. 2. Receive counseling from the prescriber on the benefits and risks of treatment, and the need to promptly report any new or worsening symptoms that persist over several days, especially nervous system symptoms. 3. Enroll in the REMS Program by completing the Patient Enrollment Form – Multiple Sclerosis or Patient Enrollment Form – Crohn's Disease with the prescriber. Enrollment information will be provided to the REMS Program. 4. Be monitored for risk factors that increase the risk of progressive multifocal leukoencephalopathy.
During treatment, before each infusion	5. Review the Medication Guide. 6. Have a list of medicines and treatments taken during the last month with you. 7. Be monitored for signs, symptoms, and risk factors for progressive multifocal leukoencephalopathy.
During treatment; 3 months and 6 months after the first infusion, and every 6 months thereafter	8. Be monitored for signs, symptoms, and risk factors for progressive multifocal leukoencephalopathy and the appropriateness of continuing TYRUKO.
After treatment discontinuation; initially and 6 months later	9. Be monitored for signs and symptoms of progressive multifocal leukoencephalopathy.
At all times	10. Notify the REMS Program if you switch physicians or infusion sites. 11. Inform the prescriber of new or worsening symptoms that last several days, especially nervous system symptoms including new or sudden change in thinking, eyesight, balance, or strength, and other new or worsening symptoms.

3. Pharmacies that dispense TYRUKO must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy. 2. Have the authorized representative review the Educational Slide Set. 3. Have the authorized representative enroll in the REMS Program by completing the Pharmacy Enrollment Form and submitting it to the REMS Program. 4. Establish processes and procedures to verify that the infusion site is authorized.
Before dispensing	5. Verify that the infusion site is authorized through the processes and procedures established as a requirement of the REMS Program.

At all times	6. Maintain records of the pharmacy's Site Authorization Confirmation. 7. Comply with audits carried out by Sandoz or a third party acting on behalf of Sandoz to ensure that all processes and procedures are in place and are being followed.

4. Infusion sites that dispense TYRUKO must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the infusion site. 2. Have the authorized representative review the Educational Slide Set. 3. Have the authorized representative enroll in the REMS Program by completing the Infusion Site Enrollment Form and submitting it to the REMS Program.
Before administering	4. Obtain authorization to dispense each infusion for administration by contacting the REMS Program or confirm receipt of a Notice of Patient Authorization and no Notice of Patient Discontinuation to verify the patient is authorized to receive the drug. 5. Provide the patient with the Medication Guide. 6. Assess the patients' health status for signs, symptoms and risk factors of progressive multifocal leukoencephalopathy. Document using the Pre-Infusion Patient Checklist.
During treatment; within 1 business day of the patient visit for infusion	7. Submit the Pre-Infusion Patient Checklist to the REMS Program regardless of whether the patient receives the infusion.
At all times	8. Maintain records of the infusion site's Site Authorization Confirmation. 9. Comply with audits carried out by Sandoz or a third party acting on behalf of Sandoz to ensure that all processes and procedures are in place and are being followed.

5. Wholesalers-distributors that distribute TYRUKO must:

To be able to distribute	1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies and infusion sites. 2. Train all relevant staff involved in distributing on the REMS Program requirements.
At all times	3. Distribute only to certified pharmacies and infusion sites. 4. Maintain records to support that all processes and procedures are in place and being followed. 5. Comply with audits carried out by Sandoz or a third party acting on behalf of Sandoz to ensure that all processes and procedures are in place and being followed.

Sandoz must provide training to health care providers who prescribe TYRUKO.
The training includes the following educational materials: Educational Slide Set, Overview, and either Helpful Information for Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO (Multiple Sclerosis) or Understanding PML for Gastroenterologists (Crohn's Disease). The training must be provided online or in hard copy format via fax or mail.

Sandoz must provide training to pharmacies and infusion sites that dispense TYRUKO.
The training includes the following educational materials: Educational Slide Set, Overview, and Pre-Infusion Checklist. The training must be provided online or in hard copy format via fax or mail.

To support REMS Program operations, Sandoz must:

1. Authorize dispensing for each patient based on receipt of the Patient Enrollment Form – Multiple Sclerosis or Patient Enrollment Form – Crohn's Disease, and Patient Status Report and Reauthorization Questionnaire on the following schedule:
   Prior to initiation of treatment, authorize the first dispensing based on the receipt of the Patient Enrollment Form – Multiple Sclerosis or Patient Enrollment Form – Crohn's Disease. If a completed Patient Enrollment Form – Multiple Sclerosis or Patient Enrollment Form – Crohn's Disease is not received, the patient is not authorized to receive the drug.
   For subsequent dispensings, authorize dispensing based on receipt of a valid Patient Status Report and Reauthorization Questionnaire within 183 calendar days of the start of the authorization period indicated on the last Patient Status Report and Reauthorization Questionnaire If a valid Patient Status Report and Reauthorization Questionnaire is not received within 183 calendar days or prior to authorization expiration, the patient is not authorized to receive the drug until the completed form is received.

2. Establish and maintain a REMS Program Website, www.TYRUKO-REMS.com. The REMS Program Website must include the capability to complete prescriber, pharmacy, and infusion site certification or enrollment online, the capability to enroll and manage patients online, and the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program Website. The REMS Program Website must not link back to the promotional product website(s).

3. Ensure infusion sites are able to obtain patient authorization prior to each infusion online and by fax.

   - For www.TYRUKO-REMS.com: obtain the patient authorization status online
   - For paper-based/fax infusion sites: provide the current Notice of Patient Authorization or Notice of Patient Discontinuation

4. Make the REMS Program Website fully operational and all REMS materials available through the website and REMS Program Contact Center within 30 calendar days of REMS approval (08/24/2023).

5. Establish and maintain a REMS Program Contact Center for REMS participants at 1-855-489-7856.

6. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the TYRUKO REMS Program. This database includes a reporting and collection system for all patients to provide information on progressive multifocal leukoencephalopathy.

7. Share duration of natalizumab product exposure, presence of anti-JCV antibodies, prior treatment with immunosuppressants, and prior or current history of Progressive Multifocal Leukoencephalopathy with REMS programs for other natalizumab products for patients switched to or from another natalizumab product.

8. Ensure health care providers, patients, pharmacies, and infusion sites are able to complete prescriber, patient, pharmacy, and infusion site certification or enrollment, complete pre-infusion checklists, report patient status, reauthorize patients, report patient discontinuation, or report a change in prescriber online or via a paper-based process.

9. Ensure that a Medication Guide is made available for dispensing with each TYRUKO prescription.

10. Notify prescribers after they become certified in the REMS Program.

11. Notify pharmacies and infusion sites after they become certified in the REMS Program by providing a Site Authorization Confirmation.

12. Provide certified prescribers access to the database of certified pharmacies, certified infusion sites, and enrolled patients.

13. Provide certified pharmacies access to the database of certified infusion sites and enrolled patients.

14. Provide certified infusion sites access to the database of enrolled patients.

15. Provide authorized wholesaler-distributors access to the database of certified infusion sites and certified pharmacies.

To ensure REMS participants' compliance with the REMS Program, Sandoz must:

16. Ensure the Patient Status Report and Reauthorization Questionnaire is received for each patient. If the form is not received by the date the Patient Status Report and Reauthorization Questionnaire is due, Sandoz must contact the prescriber for the form. The patient is not authorized to receive the drug until the form is received.

17. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: drug distribution and dispensing; certification of prescribers, pharmacies, and infusion sites; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.

18. Establish a plan for addressing non-compliance with REMS Program requirements.

19. Monitor certified prescribers, pharmacies, infusion sites, and wholesalers-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.

20. Audit certified infusion sites, certified pharmacies, specialty pharmacies, and the wholesaler-distributor(s) in accordance with the audit plan each year to ensure compliance with respective REMS requirements.

21. Take reasonable steps to improve implementation of and compliance with the requirements in the TYRUKO REMS Program based on monitoring and evaluation of the TYRUKO REMS Program.

IV. REMS Assessment Timetable

Sandoz must submit REMS Assessments at 6 months and 12 months from the date of the initial approval of the REMS (08/24/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Sandoz must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the TYRUKO REMS:

Enrollment Forms:

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient Enrollment Form (Multiple Sclerosis)
3. Patient Enrollment Form (Crohn's Disease)

Pharmacy:

4. Pharmacy Enrollment Form

Infusion sites:

5. Infusion Site Enrollment Form

Training and Educational Materials:

Prescriber:

6. Educational Slide Set
7. Overview
8. Helpful Information for Evaluation of New Neurologic Symptoms in Patients Receiving TYRUKO (Multiple Sclerosis)
9. Understanding PML for Gastroenterologists (Crohn's Disease)

Patient:

10. Medication Guide

Pharmacy:

11. Educational Slide Set
12. Overview

Infusion sites:

13. Educational Slide Set
14. Overview

Patient Care Form:

15. Pre-Infusion Patient Checklist
16. Patient Status Report and Reauthorization Questionnaire
17. Initial Discontinuation Questionnaire
18. 6-Month Discontinuation Questionnaire

Other Materials:

19. REMS Program Website
20. Change Prescriber Authorization Form

VI. Statutory Elements

This REMS is required under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) and consists of the following elements:

1. Medication Guide
2. Elements to Assure Safe Use (ETASU):
    - Health care providers who prescribe TYRUKO are specially certified under 505-1(f)(3)(A)
    - Pharmacies and health care settings that dispense TYRUKO are specially certified under 505-1(f)(3)(B)
    - TYRUKO is dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D)
    - Each patient using TYRUKO is subject to certain monitoring under 505-1(f)(3)(E)
3. Implementation System
4. Timetable for Submission of Assessments

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
Prescriber Enrollment Form

Complete this form online at www.TYRUKO-REMS.com or complete and fax the form to the TYRUKO (natalizumab-sztn) REMS at 1-833-489-7856.

***indicates required fields**

Prescriber Information

*First Name:	Middle Initial:	*Last Name:
*Address Line 1:		
Address Line 2:		
*City:	*State:	*ZIP Code:
*NPI#:	*Phone Number:	*Fax:	*Email:
Office Contact:		

Prescriber Delegate

First Name:	Last Name:	Email:

Prescriber Acknowledgement

INDICATIONS

MUTLIPLE SCLEROSIS

- I understand that TYRUKO is indicated as monotherapy for relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- I understand that TYRUKO is not ordinarily recommended for patients who are receiving chronic immunosuppressant or immunomodulatory therapy, or who are significantly immunocompromised from any other cause
- I understand that an MRI should be performed prior to initiating therapy with TYRUKO in MS patients

CROHN'S DISEASE

- I understand that TYRUKO is indicated for adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of TNF-α
- I understand that patients receiving TYRUKO should not take concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α
- I understand that TYRUKO should be discontinued if a patient has not experienced a therapeutic benefit by 12 weeks of therapy
- I understand that patients receiving steroid therapy at the time of TYRUKO initiation must undergo a steroid-tapering regimen once a therapeutic response is achieved. If the patient with Crohn's disease cannot be tapered off steroids within 6 months of starting TYRUKO, TYRUKO should be discontinued

All Other Acknowledgments

- I have reviewed the Prescribing Information for TYRUKO (natalizumab-sztn)
- I understand that TYRUKO is only to be used for relapsing forms of MS and moderately to severely active Crohn's disease with evidence of inflammation
- I understand that natalizumab products increase the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. When initiating and continuing treatment with TYRUKO, I should consider whether the expected benefit of TYRUKO is sufficient to offset the risk

- I am aware that cases of PML have been reported in patients taking natalizumab who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving natalizumab monotherapy
- I understand that three risk factors identified thus far that increase the risk of PML in natalizumab-treated patients are:
  - The presence of anti-JCV antibodies
  - Longer treatment duration, especially beyond 2 years
  - Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil)

  These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYRUKO
- I understand that MRI findings may be apparent before clinical signs or symptoms. Periodic monitoring for radiographic signs consistent with PML should be considered to allow for an early diagnosis of PML. Lower PML-related mortality and morbidity have been reported following natalizumab discontinuation in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis
- Before treatment initiation (first dose), I must counsel the patient using the Medication Guide and Patient Enrollment Form – Multiple Sclerosis or Patient Enrollment Form – Crohn's Disease
- I understand that each patient must be seen and evaluated 3 months after the first infusion, 6 months after the first infusion, every 6 months thereafter to determine whether patients should continue on treatment, and for at least 6 months after TYRUKO has been discontinued
- For each patient, I am required to complete reauthorization every 6 months to authorize treatment for another 6 months using the Patient Status Report and Reauthorization Questionnaire. I am required to submit an Initial Discontinuation Questionnaire when TYRUKO is discontinued and a 6-Month Discontinuation Questionnaire following discontinuation of TYRUKO
- I must report, as soon as possible, cases of PML, hospitalizations due to other opportunistic infections, malignancies, and deaths to Sandoz
- I understand that data concerning each patient and me will be entered into the mandatory TYRUKO REMS database. Sandoz requires my cooperation with periodic data collection. Failure to provide the requested information or otherwise comply with the requirements of the TYRUKO REMS may result in discontinuation of TYRUKO for patients and termination of my authorization to prescribe TYRUKO
- I understand that data concerning each patient and me, including duration of natalizumab exposure, presence of anti-JCV antibodies, prior treatment with immunosuppressants, and prior or current history of PML, may be shared with REMS programs for other natalizumab products if a patient switches to or from another natalizumab product
- I have received and reviewed the educational materials regarding the benefits and risks of TYRUKO treatment

***Prescriber Signature:**_____ ***Date (MM/DD/YYYY):**_____

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

If you are a resident of California, California state law creates additional rights associated with how we collect and use your personal information. You have the right to information about the types of personal information that we collect and how that information might be used. More information about these and other rights is available at: https://www.us.sandoz.com/State-Specific

SANDOZ A Novartis Division | TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
Patient Enrollment Form - Multiple Sclerosis

Complete this form online at www.TYRUKO-REMS.com or complete and fax the form to the TYRUKO REMS at 1-833-489-7856.

***indicates required fields**

Patient Information

*First Name:	Middle Initial:	*Last Name:
*Date of Birth (MM/DD/YYYY):		
*Address Line 1:		Address Line 2:
*City:	*State:	*ZIP Code:
Email Address:		*Preferred Phone Number:
Best time:		*Voicemail Allowed: ☐ Yes ☐ No

I allow the sharing of my health information with the designated individual listed below. Sandoz may contact this person to discuss my enrollment in the TYRUKO REMS.

Designated Individual First Name:	Last Name:
Relationship:	

Patient Acknowledgement

Sandoz considers patient safety a priority. Read each section below and **initial in the space provided** if you understand the information. **Do not sign this form if there is anything that you do not understand about all the information you have received. Ask your doctor about anything you do not understand before you initial and sign this form.**

I understand that TYRUKO (natalizumab-sztn) is a medicine approved to treat relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

- I have talked to my doctor and understand the benefits and risks of TYRUKO treatment
- TYRUKO increases the risk of PML. I understand that when starting and continuing treatment with TYRUKO, I should talk to my doctor about whether the expected benefit of TYRUKO is enough to outweigh the risk (see important safety information about PML below)

***Initials: _____**

I understand that TYRUKO increases my chance of getting a rare brain infection that usually leads to death or severe disability.

- This infection is called progressive multifocal leukoencephalopathy (PML). PML usually happens in people with weakened immune systems
- There is no known treatment, prevention, or cure for PML
- My risk for getting PML may be higher if I am also being treated with other medicines that can weaken my immune system, including other MS treatments. Even if I use TYRUKO alone to treat my MS, I can still get PML
- My chance for getting PML increases if I:
  - Have been exposed to John Cunningham Virus (JCV). JCV is a common virus that is harmless in most people but can cause PML in people who have weakened immune systems, such as people taking TYRUKO. Most people who are exposed to JCV do not know it or have any symptoms. This exposure usually happens in childhood. My doctor may do a blood test to check if I have been exposed to JCV before I start receiving TYRUKO or during my treatment
  - Have received TYRUKO from Sandoz or natalizumab from another company for a long time, especially longer than 2 years

- Have received certain medicines that can weaken my immune system before I start receiving TYRUKO

My risk of getting PML is greatest if I have all 3 risk factors listed above. There may be other risk factors for getting PML during TYRUKO treatment that we do not know about yet. My doctor should discuss the risks and benefits of TYRUKO treatment with me before I decide to receive TYRUKO

- I should call my doctor right away if I get any new or worsening symptoms that last several days, especially nervous system symptoms, while I am taking TYRUKO, and for at least 6 months after I stop taking TYRUKO. Some of these symptoms include a new or sudden change in my thinking, eyesight, balance, or strength, but I should also report other new or worsening symptoms

***Initials: _____**

To receive TYRUKO, all patients must be enrolled in a restricted program called the TYRUKO REMS.

- Sandoz, the company that markets TYRUKO, administers the TYRUKO REMS. Under this program, the company is required to collect information about my health at regular time periods. **I cannot receive TYRUKO if I do not agree** to follow the requirements of the TYRUKO REMS
- The company may use and share my information with third parties to meet the regulatory requirements of the TYRUKO REMS, including if I switch to or from another natalizumab product
- I must notify the TYRUKO REMS if I switch physicians or infusion sites
- I have received, read, and understand the Medication Guide
- I will have with me a list of all medicines and treatments that I have taken during the past month prior to each TYRUKO infusion

***Initials: _____**

By signing below, I agree that I have read and understand the statements above pertaining to the use of TYRUKO and the possible risks associated with its use. I understand I must enroll in the TYRUKO REMS in order to be treated with TYRUKO.

*Patient Signature (or personal representative)	*Date (MM/DD/YYYY)	Authority of personal representative (if applicable)

If you are a resident of California, California state law creates additional rights associated with how we collect and use your personal information. You have the right to information about the types of personal information that we collect and how that information might be used. More information about these and other rights is available at: https://www.us.sandoz.com/State-Specific

Patient History

*** indicates required field**

* Date of First MS Symptoms (MM/YYYY):_____

* Please indicate the patient's **MOST RECENT** therapy for MS (if patient was most recently on combination therapy, check all that apply). **Active substance can include FDA-approved generics or biosimilars**.

☐ None	☐ Fingolimod (Gilenya®)	☐ Mycophenolate mofetil (CellCept®)	☐ Rituximab (Rituxan®)
☐ Alemtuzumab (Lemtrada®)	☐ Glatiramer acetate (Copaxone®)	☐ Natalizumab (Tysabri®, TYRUKO®)	☐ Siponimod (Mayzent®)
☐ Azathioprine (Imuran®, Azasan®)	☐ Interferon beta-1a (Rebif®, Avonex®)	☐ Ocrelizumab (Ocrevus®)	☐ Teriflunomide (Aubagio®)
☐ Cyclophosphamide (Cytoxan®, Neosar®)	☐ Interferon beta-1b (Betaseron®, Extavia®)	☐ Ofatumumab (Kesimpta®)	☐ Ublituximab (Briumvi®)
☐ Cladribine (Mavenclad®)	☐ Methotrexate (Methotrex®, Rheumatrex®, Trexall®)	☐ Ozanimod (Zeposia®)	☐ Other _____
☐ Dimethyl fumarate (Tecfidera®)	☐ Mitoxantrone (Novantrone®)	☐ Peginterferon beta-1a (Plegridy®)	
☐ Diroximel fumerate (Vumerity®)	☐ Monomethyl fumarate (Bafiertam®)	☐ Ponesimod (Ponvory™)	

*Please indicate the start and stop dates of most recent therapy: ☐ Not applicable

Start date (MM/YYYY):_____ Stop date (MM/YYYY):_____

*Has the patient **EVER** been treated with natalizumab? (check all that apply)

☐ Yes, Tysabri® ☐ Yes, TYRUKO ☐ No ☐ I don't know

*Has the patient **EVER** been prescribed an immunosuppressant or an antineoplastic therapy for any condition?

☐ Yes ☐ No

If yes, please check all of the following that apply (**active substance can include FDA-approved generics or biosimilars**):

☐ Azathioprine (Imuran®, Azasan®)
☐ Cyclophosphamide (Cytoxan®, Neosar®)
☐ Methotrexate (Methotrex®, Rheumatrex®, Trexall®)
☐ Mitoxantrone (Novantrone®)
☐ Mycophenolate mofetil (CellCept®)
☐ Other, please specify:_____

*Has the patient **EVER** been tested for the presence of anti-JCV antibodies? ☐ Yes ☐ No ☐ Unknown

If yes, has the patient **EVER** tested **POSITIVE** for the presence of anti-JCV antibodies? ☐ Yes ☐ No ☐ Pending

Please provide the most recent anti-JCV antibody index value, if available:_____ -_____-_____

*Patient First Name:	Middle Initial:	*Last Name:
*Date of Birth (MM/DD/YYYY):		

Prescriber Information

*Prescriber First Name:	Middle Initial:	*Last Name:
*Prescriber NPI#:		

Prescriber Acknowledgement

- To my knowledge, this patient had no known contraindications to TYRUKO treatment, including PML
- I have instructed this patient to promptly report to me any continuously worsening symptoms that persist over several days, especially nervous system symptoms
- I have, or another healthcare provider under my direction has, educated this patient on the benefits and risks of treatment with TYRUKO, provided the patient with the Medication Guide and Patient Enrollment Form, instructed the patient to read these materials, and encouraged the patient to ask questions when considering TYRUKO

***Prescriber Signature:**_____ ***Date (MM/DD/YYYY):**_____

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

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TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
Patient Enrollment Form - Crohn's Disease

Complete this form online at www.TYRUKO-REMS.com or complete and fax the form to the TYRUKO REMS at 1-833-489-7856.

***indicates required fields**

Patient Information

*First Name:	Middle Initial:	*Last Name:
*Date of Birth (MM/DD/YYYY):		
*Address Line 1:		Address Line 2:
*City:	*State:	*ZIP Code:
Email Address:		*Preferred Phone Number:
Best time:		*Voicemail Allowed: ☐ Yes ☐ No

I allow the sharing of my health information with the designated individual listed below. Sandoz may contact this person to discuss my enrollment in the TYRUKO REMS.

Designated Individual First Name:	Last Name:
Relationship:	

Patient Acknowledgement

Sandoz considers patient safety a priority. Read each section below and **initial in the space provided** if you understand the information. **Do not sign this form if there is anything that you do not understand about all the information you have received. Ask your doctor about anything you do not understand before you initial and sign this form.**

I understand that TYRUKO (natalizumab-sztn) is a medicine approved to treat patients with moderate to severe Crohn's disease who have not been helped enough by, or cannot tolerate, usual Crohn's disease medicines and medicines called tumor necrosis factor (TNF) inhibitors.

- I have talked to my doctor and understand the benefits and risks of TYRUKO treatment
- I understand that I should not take certain medicines that weaken the immune system while I am taking TYRUKO

***Initials: _____**

I understand that TYRUKO increases my chance of getting a rare brain infection that usually leads to death or severe disability.

- This infection is called progressive multifocal leukoencephalopathy (PML). PML usually happens in people with weakened immune systems
- There is no known treatment, prevention, or cure for PML
- My risk for getting PML may be higher if I am also being treated with other medicines that can weaken my immune system, including other CD treatments. Even if I use TYRUKO alone to treat my CD, I can still get PML
- My chance for getting PML increases if I:
  - Have been exposed to John Cunningham Virus (JCV). JCV is a common virus that is harmless in most people but can cause PML in people who have a weakened immune system, such as people taking TYRUKO. Most people who are exposed to JCV do not know it or have any symptoms. This exposure usually happens in childhood. My doctor may do a blood test to check if I have been exposed to JCV before I start receiving TYRUKO or during my treatment
  - Have received TYRUKO from Sandoz or natalizumab from another company for a long time, especially longer than 2 years
  - Have received certain medicines that can weaken my immune system before I start receiving TYRUKO

My risk of getting PML is greatest if I have all 3 risk factors listed above. There may be other risk factors for getting PML during TYRUKO treatment that we do not know about yet. My doctor should discuss the risks and benefits of TYRUKO treatment with me before I decide to receive TYRUKO

- I should call my doctor right away if I get any new or worsening symptoms that last several days, especially nervous system symptoms, while I am taking TYRUKO, and for at least 6 months after I stop taking TYRUKO. Some of these symptoms include a new or sudden change in my thinking, eyesight, balance, or strength, but I should also report other new or worsening symptoms

***Initials: _____**

To receive TYRUKO, all patients must be enrolled in a restricted program called the TYRUKO REMS.

- Sandoz, the company that markets TYRUKO, administers the TYRUKO REMS. Under this program, the company is required to collect information about my health at regular time periods. **I cannot receive TYRUKO if I do not agree** to follow the requirements of the TYRUKO REMS
- The company may use and share my information with third parties to meet the regulatory requirements of the TYRUKO REMS, including if I switch to or from another natalizumab product
- I must notify the TYRUKO REMS if I switch physicians or infusion sites
- I have received, read, and understand the Medication Guide
- I will have with me a list of all medicines and treatments that I have taken during the past month prior to each TYRUKO infusion

***Initials: _____**

By signing below, I agree that I have read and understand the statements above pertaining to the use of TYRUKO and the possible risks associated with its use. I understand I must enroll in the TYRUKO REMS in order to be treated with TYRUKO.

***Patient Signature (or personal representative)**	***Date (MM/DD/YYYY)**	**Authority of personal representative (if applicable)**

If you are a resident of California, California state law creates additional rights associated with how we collect and use your personal information. You have the right to information about the types of personal information that we collect and how that information might be used. More information about these and other rights is available at: https://www.us.sandoz.com/State-Specific

Patient History

***indicates required field**

*Date of First Crohn's Disease Symptoms (MM/YYYY): _____

*Please indicate the patient's Crohn's disease therapy(ies) within the past one year AND whether the therapy is ongoing or stopped. **Ongoing therapies, except corticosteroids, must be stopped before starting TYRUKO**. (If patient was on multiple therapies, check all that apply). **Active substance can include FDA-approved generics or biosimilars.**

Medication	Ongoing	OR	Stopped	Medication	Ongoing	OR	Stopped
None ☐				Methotrexate (Methotrex®, Rheumatrex®, Trexall®)	☐		☐
Adalimumab (Humira®)	☐		☐	Other immunomodulatory therapy or immunosuppressant therapy (not including aminosalicylates)	☐		☐
Azathioprine (Imuran®, Azasan®) or Mercaptopurine (Purinethol®) or Thioguanine (Tabloid®)	☐		☐	Systemic steroids	☐		☐
Certolizumab Pegol (Cimzia®)	☐		☐	Vedolizumab (Entyvio®)	☐		☐
Infliximab (Remicade®)	☐		☐				
Natalizumab (Tysabri®, TYRUKO®)	☐		☐				

*Has the patient had a surgery for Crohn's disease within the previous year?

☐ Yes ☐ No

*Has the patient ever received natalizumab before? (check all that apply)

☐ Yes, Tysabri® ☐ Yes, TYRUKO ☐ No ☐ I don't know

*Has the patient **EVER** been prescribed an immunosuppressant or an antineoplastic therapy for any condition?

☐ Yes ☐ No

If yes, please check all that apply (**active substance can include FDA-approved generics or biosimilars**):

☐ Adalimumab (Humira®)
☐ Azathioprine (Imuran®, Azasan®) or Mercaptopurine (Purinethol®) or Thioguanine (Tabloid®)
☐ Certolizumab Pegol (Cimzia®)
☐ Infliximab (Remicade®)
☐ Methotrexate (Methotrex®, Rheumatrex®, Trexall®)
☐ Systemic steroids
☐ Vedolizumab (Entyvio®)
☐ Other, please specify:_____

*Has the patient **EVER** been tested for the presence of anti-JCV antibodies? ☐ Yes ☐ No ☐ Unknown

If yes, has the patient **EVER** tested **POSITIVE** for the presence of anti-JCV antibodies? ☐ Yes ☐ No ☐ Pending

Please provide the most recent anti-JCV antibody index value, if available:_____ -_____-_____

*Patient First Name:	Middle Initial:	*Last Name:
*Date of Birth (MM/DD/YYYY):		

Prescriber Information

*Prescriber First Name:	Middle Initial:	*Last Name:
*Prescriber NPI#:		

Prescriber Acknowledgement

- I have discussed other Crohn's disease treatments with this patient
- To my knowledge, this patient had no known contraindications to TYRUKO treatment, including PML
- I have instructed this patient to promptly report to me any continuously worsening symptoms that persist over several days, especially nervous system symptoms
- I have, or another healthcare provider under my direction has, educated this patient on the benefits and risks of treatment with TYRUKO, provided the patient with the Medication Guide and Patient Enrollment Form, instructed the patient to read these materials, and encouraged the patient to ask questions when considering TYRUKO

***Prescriber Signature:**_____ ***Date (MM/DD/YYYY):**_____

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

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TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
Pharmacy Enrollment Form

Only certified pharmacies may dispense to infusion sites certified in the TYRUKO (natalizumab-sztn) REMS. A certified pharmacy is located within a hospital, group practice, or infusion site and is associated with an infusion site.

To become certified in the TYRUKO REMS and dispense TYRUKO, a pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy, review the Educational Slide Set and submit a Pharmacy Enrollment Form to the TYRUKO REMS.

Before dispensing, the pharmacy must verify that the infusion site is authorized through the processes and procedures established as a requirement of the REMS Program.

At all times the pharmacy must:

1) Maintain records of the pharmacy's Site Authorization Confirmation
2) Comply with audits carried out by Sandoz or a third party acting on behalf of Sandoz to ensure that all processes and procedures are in place and are being followed.

This Pharmacy Enrollment Form can be completed online at www.TYRUKO-REMS.com or completed and faxed to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

***indicates required fields**

Certified Pharmacy Information

*Name of Pharmacy:		*NPI# **(on file with your distributor)**:
*Address Line 1:		
Address Line 2:		
*City:	*State:	*ZIP Code:
*Phone Number:	*Fax:	

Ship To Information

This is the ONLY address to which TYRUKO will be shipped.

Ship To Address ☐ Same as Above

*Ship To Contact Name:		
NCPDP:		
*Address Line 1:		
Address Line 2:		
*City:	*State:	*ZIP Code:
*Phone Number:	*Fax:	

Authorized Representative Information

*First Name:	*Last Name:	
*Title:		
*Email:	*Phone Number:	*Fax:

Authorized Infusion Sites

List all potential infusion sites supported by your pharmacy. For **additional space, please attach a separate page.**

Name of Infusion Site:		
*NPI#:		
Contact Name:		
Address:		
City:	State:	ZIP Code:

Name of Infusion Site:		
*NPI#:		
Contact Name:		
Address:		
City:	State:	ZIP Code:

Name of Infusion Site:		
*NPI#:		
Contact Name:		
Address:		
City:	State:	ZIP Code:

Name of Infusion Site:		
*NPI#:		
Contact Name:		
Address:		
City:	State:	ZIP Code:

Certified Pharmacy Acknowledgement

- The pharmacy has received training and educational materials on the TYRUKO REMS.
- Certified pharmacies may dispense TYRUKO only to infusion sites.
- I understand that, per the requirements of the TYRUKO REMS, this certified pharmacy's compliance may be reviewed by the Food and Drug Administration (FDA), and/or audited by Sandoz, and/or a third party designated by Sandoz.
- I understand that continued enrollment in the TYRUKO REMS depends on full compliance of my pharmacy with the REMS requirements.

***Authorized Representative Signature:**_____ ***Date (MM/DD/YYYY):**_____

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

SANDOZ A Novartis Division | TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
Infusion Site Enrollment Form

Only certified infusion sites may receive shipments of and infuse TYRUKO (natalizumab-sztn).

An infusion site may become certified after it has designated an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the infusion site. The authorized representative reviews the Educational Slide Set and completes and submits an Infusion Site Enrollment Form to the TYRUKO REMS.

This Infusion Site Enrollment Form can be completed online at www.TYRUKO-REMS.com or complete and fax to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

***indicates required fields**

Infusion Site Information

*Name of Infusion Site:		*NPI# **(on file with your distributor)**:
*Address Line 1:		
Address Line 2:		
*City:	*State:	*ZIP Code:
*Phone Number:	*Fax:	

☐ Yes ☐ No The infusion site will offer services to provide in-home infusions

Ship To Information

Ship To Address ☐ Same as Above

*Ship To Contact Name:		
*Address Line 1:		
Address Line 2:		
*City:	*State:	*ZIP Code:
*Phone Number:	*Fax:	

Authorized Representative Information

*First Name:	*Last Name:	
*Email:	*Phone Number:	*Fax:

Method of acquiring TYRUKO

***Please select one of the following:**

1. Infusion site will acquire TYRUKO directly.
   If yes, check all that apply: ☐ Buy/Bill ☐ Assignment of Benefits/Specialty Pharmacy

   OR

2. Infusion site will acquire TYRUKO through a certified pharmacy.* ☐

   *A certified pharmacy is located within a hospital, group practice, or infusion site and is associated with an infusion site.

I must contact Sandoz if my infusion site name, administration address, or shipping address changes. By signing below, I understand that I am the TYRUKO REMS Trained Authorized Representative at the infusion site and am responsible for what is outlined in the "Infusion Site Acknowledgment" below.

Infusion Site Acknowledgement

I must contact Sandoz if my infusion site name, administration address, or shipping address changes. By signing below, I understand that I am the TYRUKO REMS Trained Authorized Representative at the infusion site and am responsible for what is outlined in the "Infusion Site Acknowledgment" below.

- The infusion site has received training and educational materials on the TYRUKO REMS
- TYRUKO will be administered only to patients who are currently authorized in the TYRUKO REMS. Patient authorization must be confirmed *prior to each infusion* by:
  - For online infusion sites: Patient status must be "Authorized" or
  - For paper-based infusion sites: Receipt of current Notice of Patient Authorization and verification that no Notice of Patient Discontinuation is on file
- Each patient must receive a copy of the TYRUKO Medication Guide *prior to each infusion*
- The TYRUKO Pre-Infusion Patient Checklist must be completed *prior to each infusion*. The Pre-Infusion Patient Checklist must be submitted to the TYRUKO REMS within 1 business day of the patient visit regardless of whether or not the patient received the infusion by:
  - For paper-based infusion sites: sending a copy of the completed Pre-Infusion Patient Checklist to the TYRUKO REMS. A copy must also be placed in the patient's medical record
  - For online infusion sites: the infusion nurse can read, complete and submit the Pre-Infusion Patient Checklist at www.TYRUKO-REMS.com
- Maintain records of the infusion site's Site Authorization Confirmation
- I understand that, per the requirements of the TYRUKO REMS, this infusion site's compliance may be reviewed by and/or audited by Sandoz and/or a third party designated by Sandoz
- I understand that infusion site contact information may be shared with the REMS programs for other natalizumab products if a patient switches to another natalizumab product
- I understand that noncompliance with the requirements of the TYRUKO REMS will result in de-enrollment of the infusion site and termination of the authorization to infuse TYRUKO

***Authorized Representative Signature:**_____ ***Date (MM/DD/YYYY):**_____

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

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TYRUKO REMS

TYRUKO®
(natalizumab-sztn) 300 mg/15 mL IV

Educational Slide Set

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com

Table of Contents

Objectives:

- Provide an overview of important safety information
- Provide an overview of the TYRUKO REMS
- Review the process steps to complete TYRUKO REMS requirements
- Review of specific TYRUKO REMS materials
- Review the responsibilities of each participant in the TYRUKO REMS

Reference ID: 5232179

Indications and Usage - Multiple Sclerosis (MS)

- TYRUKO (natalizumab-sztn) is indicated as monotherapy for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Indications and Usage - Crohn's Disease (CD)

- TYRUKO is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active CD with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.

- TYRUKO should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α.

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Reference ID: 5232179

BOXED WARNING

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

See full prescribing information for complete boxed warning.

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

For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Contraindications

- TYRUKO is contraindicated in patients who have or have had PML.
- TYRUKO is contraindicated in patients who have had a hypersensitivity reaction to natalizumab products.

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Reference ID: 5232179

Warnings and Precautions - PML

- Three factors that are known to increase the risk of PML in natalizumab-treated patients have been identified:
  - The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.
  - Longer treatment duration, especially beyond 2 years.
  - Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).
- These factors should be considered in the context of expected benefit when initiating and continuing treatment with natalizumab products.
- Retrospective analyses of postmarketing data from various sources, including observational studies and spontaneous reports obtained worldwide, 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).
  - Infection by the JC virus (JCV) is required for the development of PML.
  - Anti-JCV antibody testing should not be used to diagnose PML.

Warnings and Precautions – PML (continued)

- Anti-JCV antibody negative status indicates that antibodies to the JC virus have not been detected.
- Patients who are anti-JCV antibody negative have a lower risk of PML than those who are positive. Patients who are anti-JCV antibody negative are still at risk for the development of PML due to the potential for a new JCV infection, or a false negative test result.

- MRI findings may be apparent before clinical signs or symptoms suggestive of PML.
- Periodic monitoring for radiographic signs consistent with PML should be considered to allow for an early diagnosis of PML.
- Consider monitoring patients at high risk for PML more frequently.
- Patients should continue to be monitored for any new signs or symptoms that may be suggestive of PML for at least six months following discontinuation of TYRUKO.

Warnings and Precautions – PML (continued)

- Lower PML-related mortality and morbidity have been reported following natalizumab discontinuation in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis.
- The reported rate of seroconversion in patients with MS (changing from anti-JCV antibody negative to positive) is 3 to 8 percent annually. In addition, some patients' serostatus may change intermittently. Therefore, patients with a negative anti-JCV antibody test result should be retested periodically.
- For purposes of risk assessment, a patient with a positive anti-JCV antibody test at any time is considered anti-JCV antibody positive regardless of the results of any prior or subsequent anti-JCV antibody testing. When assessed, anti-JCV antibody status should be determined using an analytically and clinically validated immunoassay.
- After plasma exchange (PLEX), wait at least two weeks to test for anti-JCV antibodies to avoid false negative test results caused by the removal of serum antibodies.
- After infusion of intravenous immunoglobulin (IVIg), wait at least 6 months (5 half-lives) for the IVIg to clear in order to avoid false positive anti-JCV antibody test results.

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Reference ID: 5232179

Warnings and Precautions – Herpes Infections

Herpes Encephalitis and Meningitis

- Natalizumab products increase 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 natalizumab products.
- Monitor patients receiving TYRUKO for signs and symptoms of meningitis and encephalitis. If herpes encephalitis or meningitis occurs, TYRUKO should be discontinued, and appropriate treatment for herpes encephalitis/meningitis should be administered.

Acute Retinal Necrosis

- A higher risk of Acute Retinal Necrosis (ARN) has been observed in patients being administered natalizumab products.
- Some ARN cases occurred in patients with central nervous system (CNS) herpes infections (e.g., herpes meningitis or encephalitis).
- Serious cases of ARN led to blindness of one or both eyes in some patients.
- Following clinical diagnosis of ARN, consider discontinuation of TYRUKO. The treatment reported in ARN cases included anti-viral therapy and, in some cases, surgery.

Warnings and Precautions – Hepatotoxicity

- Clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with natalizumab products in a postmarketing setting.
- Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as 6 days after the first dose; and signs of liver injury have also been reported for the first time after multiple doses.
- In some patients, liver injury recurred upon rechallenge, providing evidence that natalizumab caused the injury.
- The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients.
- TYRUKO should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).

Warnings and Precautions – Hypersensitivity/Antibody Formation

- Natalizumab products have been associated with hypersensitivity reactions, including serious systemic reactions (e.g., anaphylaxis), which occurred at an incidence of <1%.
- Patients who receive natalizumab products after an extended period without treatment may be at higher risk of hypersensitivity reactions.
- If a hypersensitivity reaction occurs, discontinue administration of TYRUKO, and initiate appropriate therapy.
- Do not re-treat with TYRUKO.
- Patients who receive natalizumab products 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.

Reference ID: 5232179

Warnings and Precautions – Immunosuppression/Infections

- The immune system effects of natalizumab products may increase the risk for infections.
- Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections, including PML and other opportunistic infections, over the risk observed with use of natalizumab alone.
- The safety and efficacy of natalizumab products in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established.
- For patients with Crohn's disease who start TYRUKO while on chronic corticosteroids, commence steroid withdrawal as soon as a therapeutic benefit has occurred. If the patient cannot discontinue systemic corticosteroids within 6 months, discontinue TYRUKO.

Warnings and Precautions – Thrombocytopenia

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

Adverse Reactions

- The most common adverse reactions in Study MS1, reported at an incidence of ≥10% with natalizumab 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%).
  *Percentage based on female patients only.
- 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%).
- In Study MS2, serious adverse reactions of appendicitis were also more common in patients who received natalizumab (0.8% versus 0.2% in placebo).
- The most common adverse reactions reported at an incidence of ≥10% with natalizumab and ≥2% difference with placebo in induction studies for CD were headache (32% vs 23%), upper respiratory tract infection (22% vs 16%), nausea (17% vs 15%) and fatigue (10% vs 8%).

Adverse Reactions (continued)

- The most common adverse reactions reported at an incidence of ≥10% with natalizumab and ≥2% difference with placebo in the maintenance study for CD were headache (37% vs 31%), influenza (12% vs 5%), back pain (12% vs 8%) and influenza-like illness (11% vs 6%).
- 11% of natalizumab-treated CD patients experienced infusion-related reactions versus 7% in the placebo-treated patients.
- The following serious adverse reactions in the induction Studies CD1 and CD2 were reported more commonly with natalizumab than placebo and occurred at an incidence of at least 0.3%: intestinal obstruction or stenosis (2% vs. 1% in placebo), acute hypersensitivity reactions (0.5% vs. 0%), abdominal adhesions (0.3% vs. 0%), and cholelithiasis (0.3% vs. 0%). Similar serious adverse reactions were seen in the maintenance Study CD3.
- Based on animal data, natalizumab may cause fetal harm. TYRUKO should be used during pregnancy only if the potential benefit justifies the potential risk of the fetus.

What is the TYRUKO REMS?

TYRUKO is only available to prescribers, infusion sites, pharmacies associated with infusion sites, and patients who have enrolled in the TYRUKO REMS.

Note: Some data concerning patients may be shared with the REMS program(s) for other natalizumab product(s) if patients switch to or from another natalizumab product. Enrollment in the TOUCH Prescribing Program is separate from enrollment in other natalizumab REMS programs.

What is the TYRUKO REMS designed to do?

- To inform prescribers, infusion sites, healthcare providers, and patients about the risk of PML associated with TYRUKO, including the increased risk of PML with the presence of anti-JCV antibodies, longer treatment duration, and prior immunosuppressant use.
- To warn against concurrent use with antineoplastic, immunosuppressant, or immunomodulating agents, and in patients who are immunocompromised.
- To promote early diagnosis of PML and timely discontinuation of TYRUKO in the event of suspected PML.

Reference ID: 5232179

REMS Requirement Summary

Enroll	▪ Prescribers and Patients complete the Prescriber Enrollment Form and the Patient Enrollment Form – CD or the Patient Enrollment Form - MS ▪ Pharmacies assign an authorized representative who completes the Pharmacy Enrollment Form ▪ Infusion Sites assign an authorized representative who completes the Infusion Site Enrollment Form
Dispense	▪ Certified pharmacies only dispense to enrolled infusion sites
Infuse	▪ TYRUKO is only administered to enrolled patients who are authorized by their prescriber ▪ Pre-Infusion Patient Checklist is completed and submitted to the TYRUKO REMS for each infusion
Track	▪ Patients are tracked longitudinally to gather important safety information

NOTE: This overview of the TYRUKO REMS does not include a complete list of the REMS requirements.

TYRUKO REMS Materials

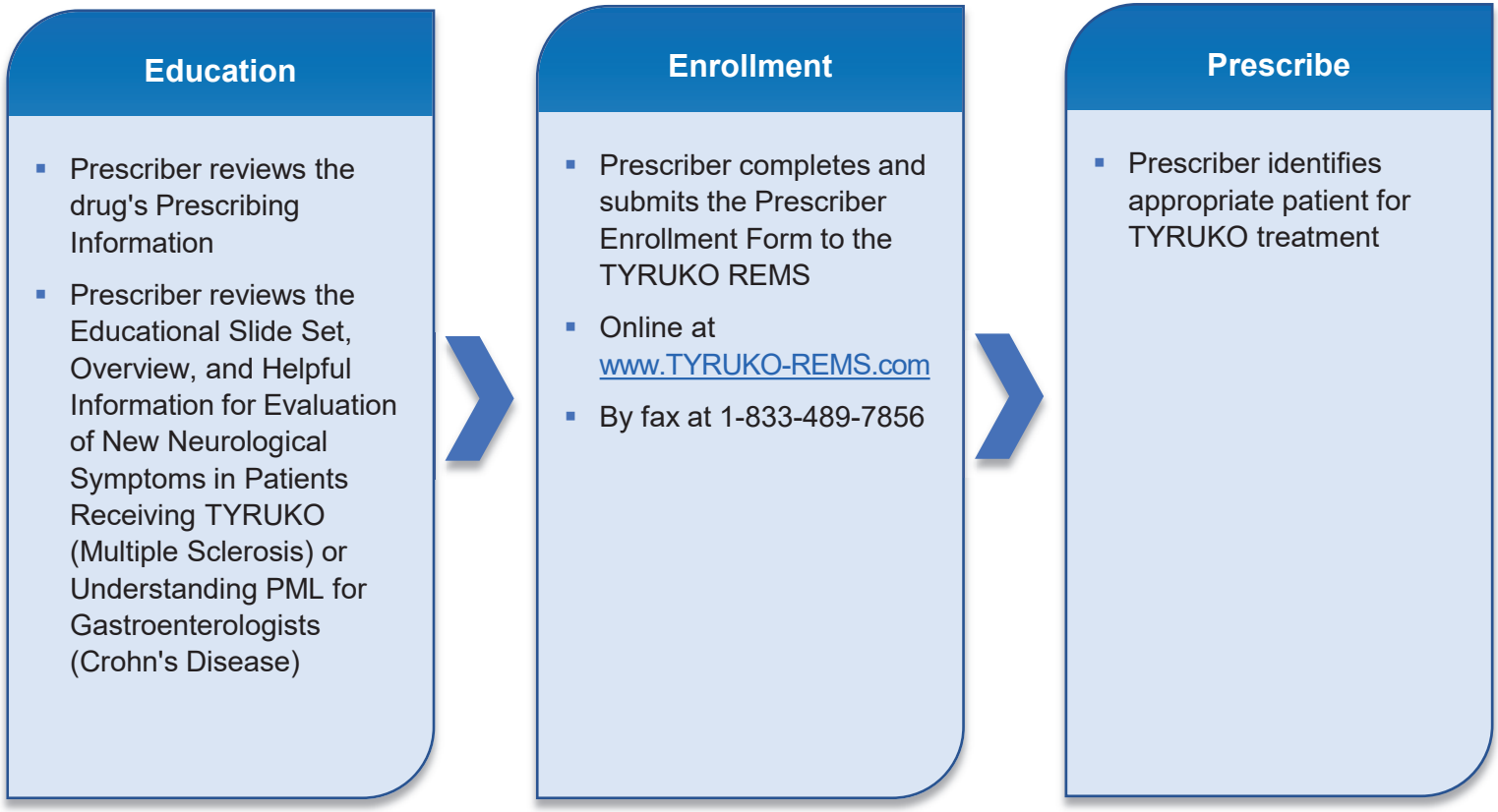
Materials for MS Indication	Materials for CD Indication
Patient Enrollment Form (MS)	Patient Enrollment Form (CD)
Helpful Information for Evaluation of New Neurologic Symptoms in Patients Receiving TYRUKO (MS)	Understanding PML for Gastroenterologists (CD)
Materials for Both Indications	
Prescriber Enrollment Form	
Patient Status Report and Reauthorization Questionnaire	
Initial Discontinuation Questionnaire	
6-Month Discontinuation Questionnaire	
Pharmacy Enrollment Form	
Infusion Site Enrollment Form	
Educational Slide Set	
Overview	
Pre-Infusion Patient Checklist	
REMS Website	
Change in Prescriber Authorization Form	
Medication Guide	

Reference ID: 5232179

Satisfying TYRUKO REMS Requirements

- The TYRUKO REMS has been designed to facilitate appropriate use of TYRUKO.
- In order to assess if the REMS is meeting its goals, registered sites and enrolled participant's compliance may be reviewed by the FDA, and/or audited by Sandoz and/or a third party designated by Sandoz.
- Compliance with the requirements of the TYRUKO REMS is necessary to maintain authorization to prescribe, dispense, infuse, or receive TYRUKO. Failure to comply with these requirements may result in de-enrollment from the TYRUKO REMS and termination of such authorization.

How does the prescriber enroll to become certified in the TYRUKO REMS?



Reference ID: 5232179

Helpful Information for Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO

Resource for:

Neurology specialists

Key topics include:

- Importance of careful evaluation of any new or recurrent symptoms
- Differentiating between the signs, symptoms, and lesion characteristics typical of MS and PML diagnostic algorithm incorporating MRI and CSF assessment
- Action steps when PML is suspected
- Guidance on the treatment of relapse and other neurological symptoms

The information provided in this brochure is an educational resource and is not intended to be a substitute for consultation and review of relevant reference materials and medical literature. Treatment decisions should be made based on the context of the situation and medical judgment.

Understanding PML for Gastroenterologists

Resource for:

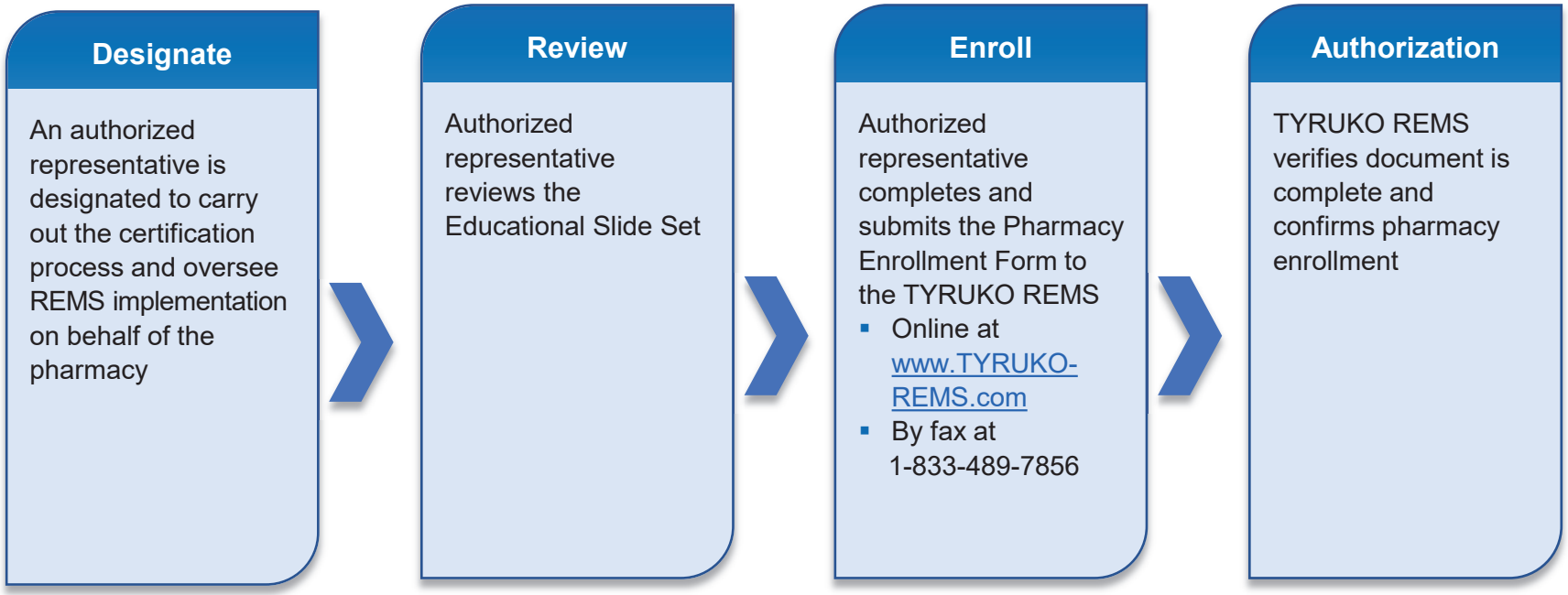
Gastroenterologists, Internists, or other non-Neurology specialists

Key topics include:

- Characteristics of PML
- Guidance on recognizing PML in context of Crohn's disease
- Action steps if PML is suspected

The information provided in this brochure is an educational resource and is not intended to be a substitute for consultation and review of relevant reference materials and medical literature. Treatment decisions should be made based on the context of the situation and medical judgment.

How does a pharmacy* enroll?



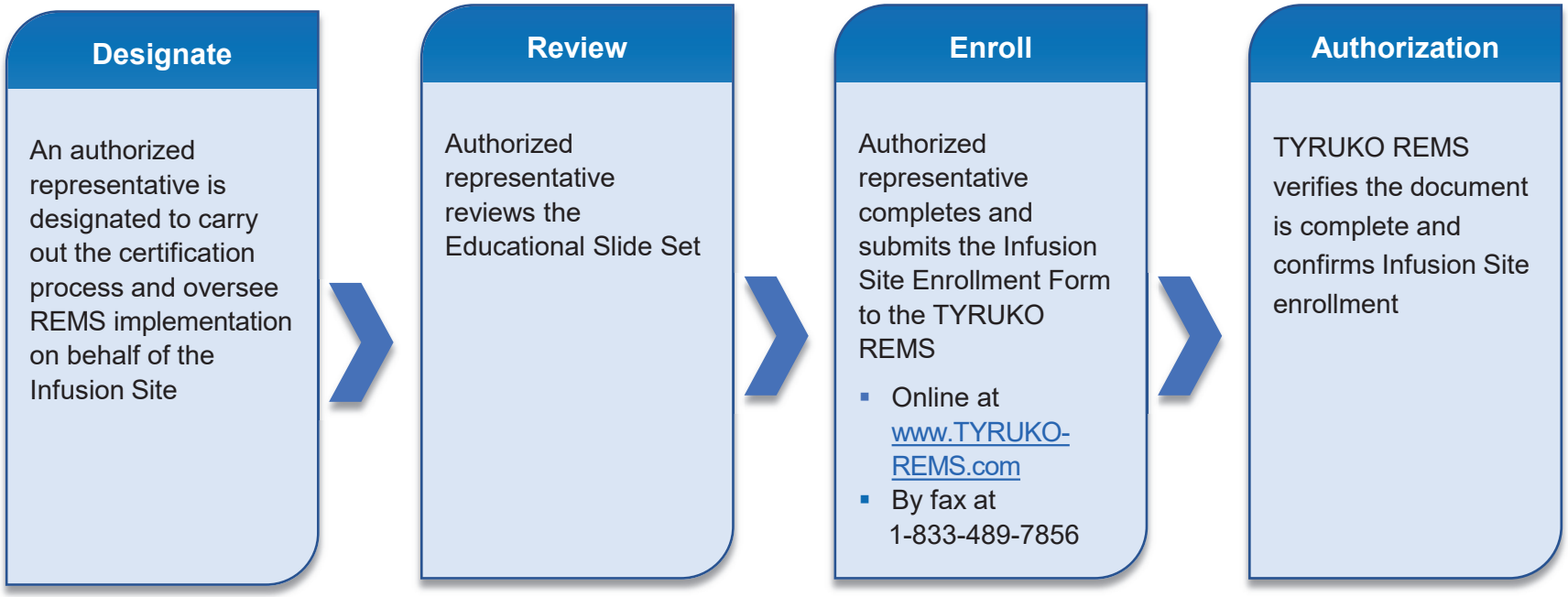
*A pharmacy is defined as a certified pharmacy located within a hospital, group practice, or infusion site and is associated with an infusion site.

Before each dispense a certified pharmacy must:

Confirm that the infusion site is enrolled
Verify online at www.TYRUKO-REMS.com or by calling the REMS at 1-855-489-7856

Reference ID: 5232179

How does an infusion site enroll?



Reference ID: 5232179

What process must be completed in order to infuse TYRUKO?

TYRUKO should NOT be prepared until the Pre-Infusion Patient Checklist has been successfully completed

The Pre-Infusion Patient Checklist MUST be successfully completed before TYRUKO is prepared regardless of whether the patient is infused

Before EVERY infusion of TYRUKO

1. **Refer** to the patient's record prior to every infusion
2. **Confirm** that the patient is currently authorized to receive TYRUKO
    a. verify online at www.TYRUKO-REMS.com,
    b. by checking the patient chart for a current Notice of Patient Authorization and no record of a Notice of Discontinuation, or
    c. by calling the REMS at 1-855-489-7856
3. **Provide** the patient with the Medication Guide
4. **Complete** the Pre-Infusion Patient Checklist online at www.TYRUKO-REMS.com or complete and fax to 1-833-489-7856
5. If the patient answered **YES** to question 1, 2, or 3, in Step 3 of the Pre-Infusion Patient Checklist, **DO NOT INFUSE.** Contact the healthcare provider who prescribed TYRUKO and review the patient's answers. The healthcare provider must authorize the infusion

At every infusion visit, a Pre-Infusion Patient Checklist must be completed, signed, and submitted

Reference ID: 5232179

What process must be completed in order to infuse TYRUKO? (continued)

Administering the Infusion

ONLY upon successful completion of the Pre-Infusion Patient Checklist:

- Start an IV line
- Mix TYRUKO

Infuse TYRUKO over 1 hour and observe patients during all infusions. Post-infusion, for the first 12 infusions, observe patients for 1 hour after the infusion is complete. For patients who have received 12 infusions without evidence of a hypersensitivity reaction, observe patients post-infusion for the 13th and subsequent infusions according to clinical judgment.

Submit completed Pre-Infusion Patient Checklist within 1 business day online at www.TYRUKO-REMS.com or via fax at 1-833-489-7856.

Pre-Infusion Patient Checklist must be completed and submitted regardless of whether the patient infused or not

Reference ID: 5232179

Tracking in the TYRUKO REMS

Infusion Site	Pre-Infusion Patient Checklist (Prior to Each Infusion)	
Prescriber	Patient Status Report and Reauthorization Questionnaire (Every 6 Months)	Initial Discontinuation Questionnaire (At Discontinuation) 6-Month Discontinuation Questionnaire (6 Months After Discontinuation)

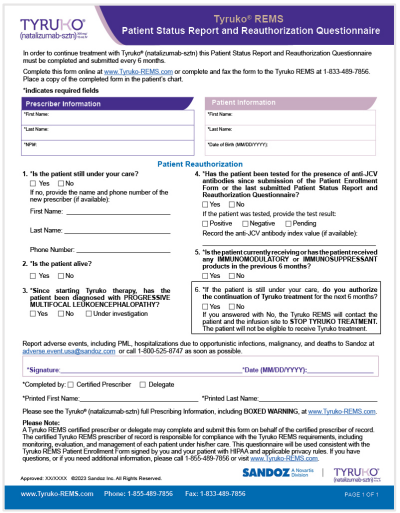
Missing or incomplete TYRUKO REMS forms will prompt follow-up from the TYRUKO REMS Contact Center

Reference ID: 5232179

Requirement to Reauthorize the Use of TYRUKO Every 6 Months

TYRUKO Patient Status Report and Reauthorization Questionnaire

- Prescriber will receive a Patient Status Report and Reauthorization Questionnaire every 6 months
- Completion of this form is required as it determines whether the prescriber authorizes the patient to receive TYRUKO for the next 6 months


Tyruko® REMS
Patient Status Report and Reauthorization Questionnaire

If a patient discontinues TYRUKO, the prescriber is notified

- The prescriber will be sent Discontinuation Questionnaires which must be completed and submitted to the TYRUKO REMS
  - Online at www.TYRUKO-REMS.com or
  - Fax to 1-833-489-7856

  Place original completed form in the patient's file


Tyruko® REMS
Initial Discontinuation Questionnaire

Tyruko® REMS
6-Month Discontinuation Questionnaire

Reference ID: 5232179

Important REMS Responsibilities: Prescribers

Prescriber responsibilities to prescribe TYRUKO include:

- Acknowledging that TYRUKO should only be prescribed in accordance with the Prescribing Information
- Educating patients on the benefits and risks of treatment with TYRUKO using the Medication Guide
- Evaluating the patient at 3 and 6 months after the first infusion, every 6 months thereafter, and for at least 6 months after TYRUKO use has been discontinued
- Evaluating whether the patient should continue treatment every 6 months and, if so, reauthorizing treatment by submitting the Patient Status Report and Reauthorization Questionnaire to the TYRUKO REMS 6 months after starting treatment and every 6 months thereafter
- Reporting any PML, hospitalizations due to opportunistic infections, malignancies, and deaths to Sandoz at adverse.event.usa@sandoz.com or call 1-800-525-8747

Important REMS Responsibilities: Patients

Patient responsibilities in order to receive TYRUKO include:

- Reading and understanding the Medication Guide and asking any questions about treatment before starting TYRUKO and before each TYRUKO infusion
- Bringing a list of all medicines and treatments they have taken during the past month to each infusion appointment
- Immediately reporting any new or worsening symptoms that persist over several days to their prescriber
- Notifying all of their doctors that they are receiving TYRUKO
- Scheduling an appointment with their prescriber at 3 and 6 months after the first infusion and at least every 6 months thereafter and after TYRUKO use has been discontinued

Important REMS Responsibilities: Infusion Sites

Infusion site responsibilities prior to each TYRUKO infusion:

- Verifying that the patient is currently authorized to receive TYRUKO
- Providing the patient with a copy of the TYRUKO Medication Guide for review
- Administering the Pre-Infusion Patient Checklist to every patient
- Submitting the completed Pre-Infusion Checklist to the TYRUKO REMS within 1 business day, regardless of whether the patient was infused

Summary Review

- The TYRUKO REMS makes TYRUKO available only to prescribers, infusion sites, pharmacies associated with infusion sites, and patients who are enrolled in the REMS
- TYRUKO can only be administered to patients who are enrolled and meet all the conditions of the TYRUKO REMS
- Only authorized infusion sites and their associated certified pharmacies may acquire TYRUKO
- TYRUKO REMS activities can be completed online at www.TYRUKO-REMS.com or by contacting the Contact Center by fax (1-833-489-7856) or phone (1-855-489-7856)

How Do I Contact the TYRUKO REMS?

Online at www.TYRUKO-REMS.com

By Phone at 1-855-489-7856

By Fax at 1-833-489-7856

Approved: XX/XXXX

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

Overview of the TYRUKO REMS

Indications & Usage

Multiple Sclerosis

TYRUKO (natalizumab-sztn) is indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

Crohn's Disease

TYRUKO is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. TYRUKO should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine or methotrexate) or inhibitors of TNF-α

TYRUKO REMS

Sandoz is committed to patient safety. The TYRUKO REMS was designed to do the following:

- To inform prescribers, infusion site healthcare providers, and patients about the risk of progressive multifocal leukoencephalopathy (PML) associated with TYRUKO, including the increased risk of PML with the presence of anti-JCV antibodies, longer treatment duration, and prior immunosuppressant use
- To warn against concurrent use with antineoplastic, immunosuppressant, or immunomodulating agents and in patients who are immunocompromised
- To promote early diagnosis of PML and timely discontinuation of TYRUKO in the event of suspected PML

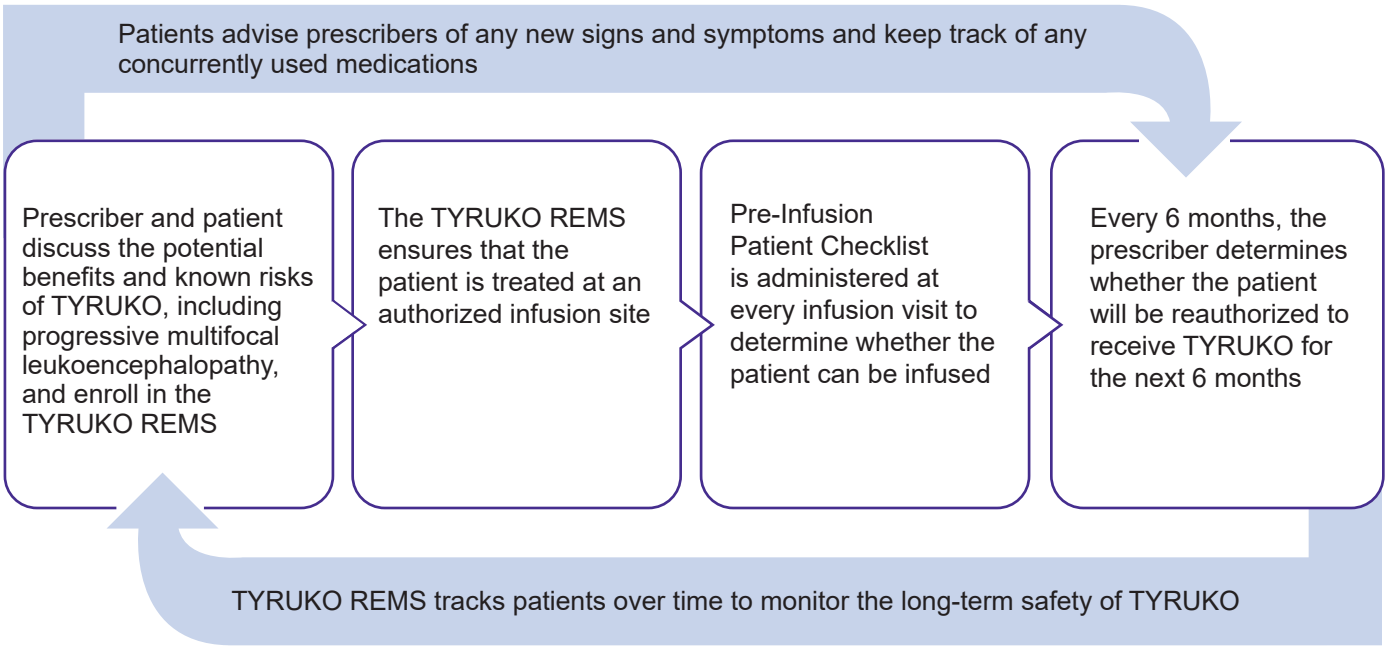
Prescribers, infusion sites, certified pharmacies, and patients must be enrolled in the TYRUKO REMS in order to prescribe, infuse, dispense, or receive TYRUKO. Enrollment forms must be completed online at www.TYRUKO-REMS.com or completed and faxed to the TYRUKO REMS at 1-833-489-7856.

Participation in the TYRUKO REMS

The TYRUKO REMS Website can be accessed by certified prescribers, infusion sites, and pharmacies using a secure username and password to:

- access patient data in real-time
- complete REMS forms online
- maintain compliance with the TYRUKO REMS

How the Program Works



Compliance with the requirements of the TYRUKO REMS is necessary to maintain authorization to prescribe, dispense, infuse, or receive TYRUKO. Failure to comply with these requirements may result in de-enrollment from the TYRUKO REMS and termination of such authorization.

This Overview serves as an introduction to the TYRUKO REMS. More information on the TYRUKO REMS and additional copies of materials can be obtained by contacting the TYRUKO REMS at 1-855-489-7856.
The Medication Guide can also be found online at www.TYRUKO-REMS.com.

Participation in the TYRUKO REMS

Tracking of Patient Data

The TYRUKO REMS will track all patients over time so that Sandoz can inform the FDA, prescribers, and patients in a timely manner of information regarding the safety of TYRUKO.

Prescribers are required to report any case of PML, serious opportunistic infection or death in TYRUKO-treated patients to Sandoz or the FDA. Furthermore, prescribers are also required to cooperate in the investigation of potential adverse events including providing relevant information upon request.

The primary tracking tools include:

- Pre-Infusion Patient Checklist
- Patient Status Report and Reauthorization Questionnaire
- Initial and 6-month Discontinuation Questionnaires

In the event that there are missing or incomplete forms, the TYRUKO REMS will follow up with infusion sites, patients, and/or prescribers to obtain such information to remain compliant with program requirements.

Prescribers, infusion sites, and certified pharmacies may be audited by the FDA, Sandoz, and/or a third party authorized by Sandoz.

Important REMS Responsibilities

Prescriber responsibilities to prescribe TYRUKO include:

- Acknowledging that TYRUKO should only be prescribed in accordance with the Prescribing Information
- Educating patients on the benefits and risks of treatment with TYRUKO using the Medication Guide
- Evaluating the patient at 3 and 6 months after the first infusion, every 6 months thereafter, and for at least 6 months after TYRUKO use has been discontinued
- Evaluating whether the patient should continue treatment every 6 months and, if so, reauthorizing treatment by submitting the Patient Status Report and Reauthorization Questionnaire to the TYRUKO REMS 6 months after starting treatment and every 6 months thereafter
- Reporting any PML, hospitalizations due to opportunistic infections, malignancies, and deaths to Sandoz at adverse.event.usa@sandoz.com or call 1-800-525-8747. You are encouraged to report other adverse reactions to Sandoz or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

Patient responsibilities in order to receive TYRUKO include:

- Reading and understanding the Medication Guide and asking any questions about treatment before starting TYRUKO and before each TYRUKO infusion
- Having a list of all medicines and treatments they have taken during the past month at each infusion appointment
- Immediately reporting any worsening symptoms that persist over several days to their prescriber
- Notifying all of their doctors that they are receiving TYRUKO
- Scheduling an appointment with their prescriber at 3 and 6 months after the first infusion and at least every 6 months thereafter and after TYRUKO use has been discontinued

Infusion site responsibilities prior to each TYRUKO infusion:

- Verifying that the patient is currently authorized to receive TYRUKO
- Providing the patient with a copy of the TYRUKO Medication Guide for review
- Administering the Pre-Infusion Patient Checklist to every patient
- Submitting the completed Pre-Infusion Checklist to the TYRUKO REMS within 1 business day, regardless of whether the patient was infused

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

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SANDOZ A Novartis Division | TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

Reference ID: 5232179

TYRUKO®
(natalizumab-sztn) 300 mg/15 mL IV

Helpful Information for Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO

This information is provided as an education resource for healthcare providers and should be considered current as of the date listed herein. It is not intended to be a substitute for consultation and review of reference materials and medical literature pertaining to individual clinical circumstances. Healthcare providers should make all treatment decisions based on the context of the situation and their own clinical judgment.

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

SANDOZ A Novartis Division

Reference ID: 5232179

Background Information

JCV infections: Progressive multifocal leukoencephalopathy (PML) and JC virus granule cell neuronopathy (JCV GCN)

1. PML

PML is a demyelinating disease that attacks the central nervous system (CNS). It is caused by a polyomavirus called the JC virus (JCV), which is common and widespread in humans. JCV usually remains latent, typically causing PML only in the setting of immunodeficiency.

The clinical picture of PML or other neurological conditions can be difficult to distinguish from multiple sclerosis (MS), especially early in the disease course. Therefore, this information is intended to offer an overview of some of the key issues regarding the definitive diagnosis of PML, especially as they relate to treatment with TYRUKO (natalizumab-sztn). These include:

- Patient monitoring and management
  - Obtaining a pretreatment MRI
  - Performing regular follow-ups
  - Treatment of relapses or other neurological symptoms
- Evaluation of new neurological symptoms in patients receiving TYRUKO
  - Distinguishing PML from MS
  - Suggested diagnostic algorithm
  - Action steps if PML is suspected, including MRI assessment, JCV testing, and plasma exchange (PLEX)
  - Immune Reconstitution Inflammatory Syndrome (IRIS)

2. JCV GCN

JC virus infection of granule cell neurons in the cerebellum (i.e., JCV GCN) has been reported in patients treated with natalizumab. JCV GCN can occur with or without concomitant PML. JCV GCN can cause cerebellar dysfunction (e.g., ataxia, incoordination, apraxia, visual disorders), and neuroimaging can show cerebellar atrophy. For a diagnosis of JCV GCN, an evaluation that includes a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA, is recommended. JCV GCN should be managed similarly to PML.

Adapted from Kappos L et al. Lancet Neurol. 2007;6(5):431-441

Management of Patients Receiving TYRUKO

Pretreatment MRI

Obtaining a pretreatment brain MRI scan is recommended. It may assist in determining whether MRI lesions noted at the time of new neurological signs or symptoms were preexistent. This may assist in the differential diagnosis between PML and MS activity.

Regular Follow-ups

All patients treated with TYRUKO should have regular clinical follow-ups to allow for early detection of changes in neurological status. To that end, Sandoz, in conjunction with the Food and Drug Administration (FDA), developed a risk management program for the United States called the TYRUKO Risk Evaluation and Mitigation Strategy (REMS). As part of the TYRUKO REMS:

- Prescribers must evaluate patients 3 months after the first infusion, 6 months after the first infusion, every 6 months thereafter to determine whether patients should continue on treatment, and for at least 6 months after discontinuing TYRUKO
- Prescribers must submit the Patient Status Report and Reauthorization Questionnaire to the TYRUKO REMS 6 months after initiating treatment and every 6 months thereafter, ensuring additional monitoring and reporting by the TYRUKO REMS
- Infusion sites administer the Pre-Infusion Patient Checklist and report to the prescriber any changes in the patient's status prior to infusing
  - Infusion sites will not infuse TYRUKO if the patient reports a change in symptoms, unless the prescriber authorizes the infusion

Patient History

Knowing the history and pattern of prior and ongoing MS signs and symptoms can help in the management of patients treated with TYRUKO.

Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO

- If new neurological symptoms develop, withhold TYRUKO dosing and evaluate the patient

Distinguishing PML from MS

The following information should be considered when undertaking the assessment and management of new or worsening neurological symptoms in MS patients treated with TYRUKO. There are no pathognomonic signs or symptoms that distinguish an MS relapse from PML, but there are certain clinical features that may help differentiate between the 2 conditions (see Table 1).

Table 1. Clinical signs and symptoms typical of MS relapse and PML

	MS Relapse	PML
ONSET	**Acute**	**Subacute**
EVOLUTION	• Over hours to days • Normally stabilize • Resolve spontaneously or with treatment	• Days to weeks • Progressive
CLINICAL PRESENTATION	• Diplopia • Paresthesia • Paraparesis • Optic neuritis • Myelopathy	• Cortical symptoms/signs • Behavioral and neuropsychological alteration • Retrochiasmal visual deficits • Seizures • Hemiparesis

This list is not intended to be inclusive of all signs and symptoms that are characteristic of MS and PML.

Treatment of MS Relapse

- Relapses should be managed according to usual clinical practice

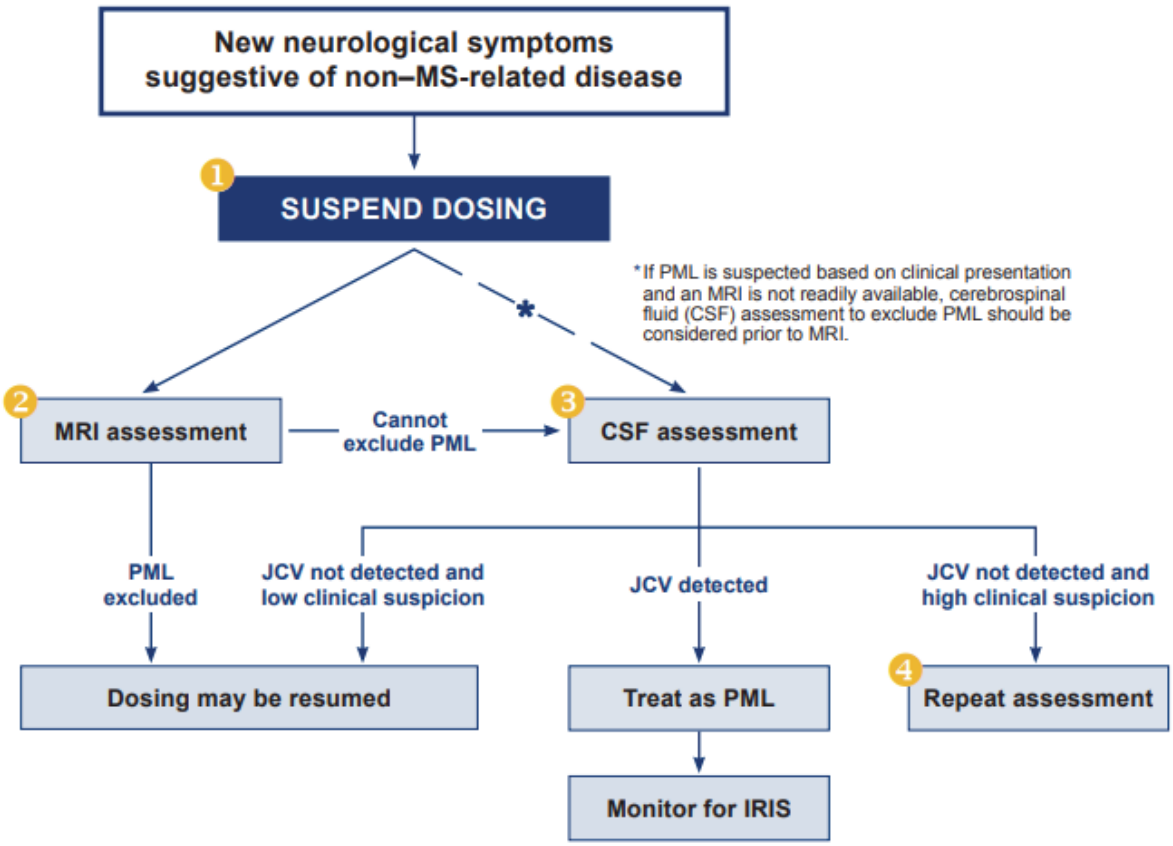
If treating with corticosteroids:
A single, short course of corticosteroids can be considered for cases in which PML is unlikely on clinical grounds

Progression of symptoms, despite treatment with corticosteroids, should trigger further investigation

- In addition to PML and MS, other medical conditions and CNS conditions including other infections should be considered when evaluating a patient with new neurological symptoms.

New or recurrent neurological symptoms should always prompt careful evaluation.

Figure 1. Suggested diagnostic algorithm for natalizumab-treated patients experiencing new neurological symptoms suggestive of non–MS-related disease



Note: TYRUKO dosing should only be restarted when the diagnosis of PML is excluded, if necessary, by repeating clinical, MRI, and cerebrospinal fluid (CSF) assessment if clinical suspicion of PML remains.

CSF assessment for presence of JCV DNA should be performed using a highly sensitive quantitative real-time PCR assay with a limit of quantification (LOQ) of at least 50 copies/mL.

For further information, please contact Sandoz Medical Information at 1-800-525-8747.

Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO

Action Steps if PML is Suspected

1) **SUSPEND DOSING**
   TYRUKO dosing should be suspended **immediately** in all cases in which PML is suspected.

2) **MRI assessment**
   If the clinical presentation is suggestive of PML, further investigation should include brain MRI evaluation as soon as possible.

3) **CSF assessment**
   If MRI evaluation reveals lesions suspicious for PML (see Table 2), a lumbar puncture with evaluation of CSF for the detection of JCV DNA should be undertaken with a highly sensitive quantitative real-time PCR assay.

4) **Repeat Testing**
   If clinical suspicion of PML remains despite a negative evaluation, then MRI and CSF assessments should be repeated to exclude a diagnosis of PML.

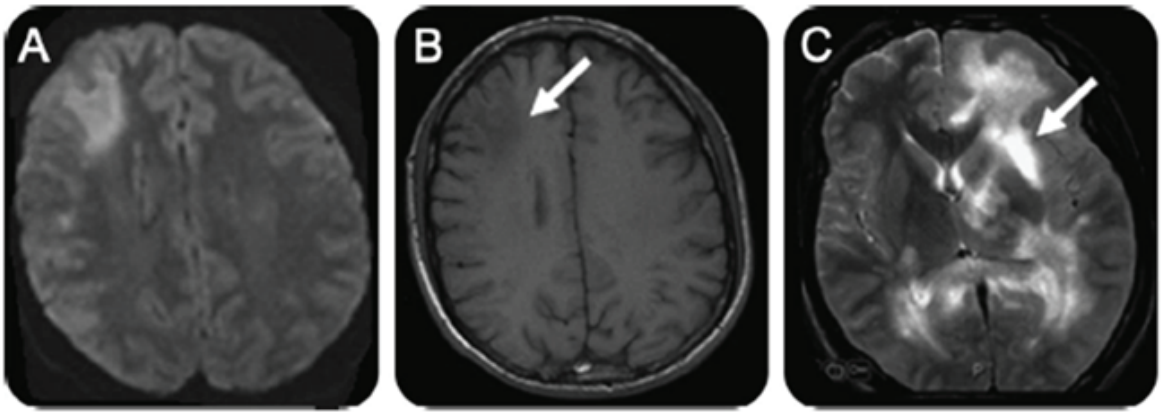
A definitive diagnosis of PML is made by evaluating clinical and MRI findings plus the identification of JCV in the CNS.

- There is no prevention, FDA-approved treatment, or cure for PML. Rapid recognition of PML and early discontinuation of TYRUKO are key interventions
- Plasma Exchange (PLEX) (see page 8) may be considered as a means to accelerate the clearance of TYRUKO
- Healthcare providers should promptly report serious adverse events to Sandoz at adverse.event.usa@sandoz.com or call 1-800-525-8747

MRI Assessment

- There are no pathognomonic findings that differentiate PML from MS. A brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and T1- and T2-weighted sequences, with and without gadolinium (Gd), should be performed to assess patients with neurological changes suggestive of PML (see Table 1)
- Comparison with a baseline scan may assist with interpretation of the finding on the new MRI. Figure 2 and Table 2 show the differences in lesion characteristics that may help differentiate between PML and MS activity

Figure 2. MRI presentation features of PML[1]



(A) Fluid-attenuated inversion recovery image with large subcortical lesion of right frontal lobe. A smaller lesion is observed posterior to this lesion. (B) T1-weighted image shows hypointense lesion (arrow) in the right frontal lobe. (C) T2-weighted image from another patient with extensive high signal intensity lesions in the white matter sparing the cortex. An area of hyperintensity similar to that of CSF suggest an area of cavitation.

Table 2. MRI Lesion Characteristics Typical of PML and MS

Characteristic	MS Lesions	PML Lesions
Location	Periventricular perpendicular to ventricles (Dawson's fingers), deep white matter, isolated U fibers, cerebellum, and spinal cord	• Subcortical WM in parietal, occipital, or frontal lobes • May involve precentral or postcentral gyrus (motor/sensory cortex) or insular region • Follows WM tracks. Can cross the corpus callosum to contralateral hemisphere (butterfly pattern) or extend through internal capsule • Rarely brainstem or cerebellar WM • No spinal cord involvement
Appearance	Well-defined borders	• Infiltrating, ill-defined, confluent WM lesions, which can be multifocal
Mass effect	Large lesions can have a mass effect	• Rare even in large lesions
FLAIR	Flair = T2	• Flair more sensitive for detection of PML lesions in subcortical location
T1W pre-contrast	Isointense or mildly hypointense to grey matter	• Isointense with progressive hypointensity
T1W post contrast	Homogeneous or ring-enhancement – resolves in 1-2 months	• Patchy, punctate, or linear

Adapted from Yousry TA et al. N Eng J Med. 2006;354(9):924-933.

Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO

JCV DNA Testing to Confirm Diagnosis

- Plasma assessment
  - Presence of JCV DNA in plasma has not been correlated with the development of PML
  - Plasma JCV DNA test positivity is highly variable, so the sensitivity and predictive value of this screening method are unclear
  - Plasma JCV DNA testing is not included in the TYRUKO REMS
- CSF assessment
  - The detection of JCV DNA in the CSF of a patient with clinical signs and MRI features suggestive of PML establishes the diagnosis of PML
  - If clinical suspicion of PML remains despite a negative CSF, testing should be repeated
  - It is recommended to test samples using a validated ultrasensitive quantitative PCR test that has a lower limit of quantification of 50 copies per mL or lower
- Brain Biopsy
  - If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis

Note: TYRUKO dosing should only be resumed if the diagnosis of PML is excluded and if deemed appropriate for the ongoing treatment of MS.

Plasma Exchange (PLEX)

- Three sessions of plasma exchange (PLEX) over 5 to 8 days were shown to accelerate natalizumab clearance in a study of 12 patients with MS who did not have PML, although in the majority of patients, α4-integrin receptor binding remained high—a potential sign of continued inhibition of α4-integrin–mediated leukocyte activity
- Additional plasma exchanges (up to a total of 5 over a 10-day period) may more consistently reduce natalizumab plasma concentration and α4-integrin receptor binding to below subtherapeutic levels
- Adverse events that may occur during PLEX include clearance of other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema
- Although PLEX has not been prospectively studied in natalizumab-treated patients with PML, it has been used in such patients in the post marketing setting to remove natalizumab more quickly from the circulation
- There is no evidence that PLEX has any benefit in the treatment of opportunistic infections such as PML
- Physicians should use medical judgment when considering the use of PLEX to treat PML

Adapted from Khatri BO et al. Neurology. 2009;72(5):402-409.

Immune Reconstitution Inflammatory Syndrome (IRIS)

- IRIS has been reported in the majority of patients who developed PML and subsequently discontinued natalizumab
- In almost all cases, IRIS occurred within days to several weeks after plasma exchange was used to accelerate natalizumab clearance
- IRIS usually presents as an unanticipated clinical decline which may be rapid and severe, and may be fatal
- At the time of IRIS, MRI may show additional changes including Gd enhancement
- Monitoring for the development of IRIS and appropriate treatment of the associated inflammation should be undertaken

For up-to-date scientific information concerning products, such as TYRUKO, or to report an adverse event, please contact Sandoz:

Phone: 1-800-525-8747

Fax: 1-720-887-3940

Email: adverse.event.usa@sandoz.com

References:

1. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology. 2013;80(15):1430-1438. doi:10.1212/WNL.0b013e31828c2fa
2. Yousry TA et al. N Eng J Med. 2006;354(9):924-933
3. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. Neurology. 2009;72(5):402-409. doi:10.1212/01.wnl.0000341766.59028.9d
4. Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. Lancet Neurol. 2007;6(5):431-441. doi:10.1016/S1474-4422(07)70078-9

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Approved: XX/XXXX

SANDOZ A Novartis Division | TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS

Understanding Progressive Multifocal Leukoencephalopathy (PML) for Gastroenterologists

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

This information is provided as an educational resource for healthcare providers and should be considered current as of the date listed herein. It is not intended to be a substitute for consultation and review of reference materials and medical literature pertaining to individual clinical circumstances. Healthcare providers should make all treatment decisions based on the context of the situation and their own clinical judgment.

The following information should be considered when undertaking the assessment and management of progressive multifocal leukoencephalopathy (PML) in adult patients treated with TYRUKO (natalizumab-sztn) for moderately to severely active Crohn's disease (CD). During clinical trials for natalizumab, 3 cases of PML were identified (2 in multiple sclerosis and 1 in Crohn's disease). Both multiple sclerosis patients were receiving concomitant immunomodulatory therapy and the Crohn's disease patient had been treated in the past with immunosuppressive therapy. In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis and Crohn's disease patients who were not receiving concomitant immunomodulatory therapy.[1]

About PML

PML is a demyelinating disease that attacks the central nervous system.[2] It is an opportunistic infection caused by the JC virus that typically occurs in patients who are immunocompromised.[1] The virus removes myelin that surrounds the nerves, and without this protection the nerves cannot transmit signals.[3] There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.[1]

How to Recognize PML

Typical symptoms associated with PML are diverse, progress over days to weeks, and include[3,4]:

- Progressive weakness on one side of the body or clumsiness of limbs
- Disturbance of vision
- Changes in thinking, memory, and orientation, leading to confusion and personality changes
- Seizures

PML progression usually leads to death or severe disability over weeks or months.[3] Since these symptoms are very different from those of Crohn's disease, the appearance of any symptom of PML, including those listed above, should be investigated immediately.[4] In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline that could cause diagnostic difficulty while on natalizumab therapy are uncommon.[1]

Action Steps if PML is Suspected

- TYRUKO dosing should be withheld immediately at the first sign or symptom suggestive of PML
- Immediate referral to a neurologist for assessment, potentially including[1]:
  - A brain MRI to determine if lesions that could be due to PML are present
  - Cerebrospinal fluid evaluation for the presence of JCV DNA
- Potential cases of PML should be reported immediately to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747. You are encouraged to report other adverse reactions to Sandoz or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

Note: TYRUKO dosing should be restored only if the diagnosis of PML is excluded and if deemed clinically appropriate for the ongoing treatment of CD in patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α, and who are not taking concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, or methotrexate) or concomitant inhibitors of TNF-α.

Reference ID: 5232179

Indication & Important Safety Information

Indication

TYRUKO (natalizumab-sztn) is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. TYRUKO should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α.

Important Safety Information

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Natalizumab products increase the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Risk factors for the development of PML include the presence of anti-JCV antibodies, duration of therapy, and prior use of immunosuppressants. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYRUKO.

Healthcare professionals should monitor patients on TYRUKO for any new sign or symptom that may be suggestive of PML. TYRUKO 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 is recommended.

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

Progressive Multifocal Leukoencephalopathy (PML)

- Infection by the JC Virus (JCV) is required for the development of PML.
- Anti-JCV antibody testing should not be used to diagnose PML.
- After plasma exchange (PLEX), wait at least two weeks to test for anti-JCV antibodies to avoid false negative test results caused by the removal of serum antibodies. After infusion of intravenous immunoglobulin (IVIg), wait at least 6 months (5 half-lives) for the IVIg to clear in order to avoid false positive anti-JCV antibody test results.
- There are no known interventions that can reliably prevent PML or that can adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYRUKO will mitigate the disease.
- MRI findings may be apparent before clinical signs or symptoms suggestive of PML. Periodic monitoring for radiographic signs consistent with PML should be considered to allow for an early diagnosis of PML. Consider monitoring patients at high risk for PML more frequently. Lower PML-related mortality and morbidity have been reported following natalizumab discontinuation in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis.

Important Safety Information

- PML has been reported after discontinuation of natalizumab products 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 TYRUKO.
- In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline could cause diagnostic difficulty while on natalizumab product therapy.
- Three sessions of PLEX over 5 to 8 days were shown to accelerate natalizumab clearance in a study of 12 patients with MS who did not have PML, although in the majority of patients, alpha-4 integrin receptor binding remained high. Adverse events that may occur during PLEX include clearance of other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema. Although PLEX has not been prospectively studied in natalizumab-treated patients with PML, it has been used in such patients in the postmarketing setting to remove natalizumab more quickly from the circulation. There is no evidence that PLEX has any benefit in the treatment of opportunistic infections such as PML.
- JCV infection of granule cell neurons in the cerebellum, i.e. JCV granule cell neuronopathy (GCN), with symptoms similar to PML, has been reported in patients treated with natalizumab products. 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 natalizumab product-treated patients who developed PML and subsequently discontinued natalizumab products. In almost all cases, IRIS occurred after plasma exchange was used to eliminate circulating natalizumab products. It presents as a clinical decline in the patient's condition after natalizumab product 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. Natalizumab products have not been associated with IRIS in patients discontinuing treatment with natalizumab products for reasons unrelated to PML. In natalizumab product-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

- TYRUKO is contraindicated in patients who have or have had PML.
- TYRUKO is contraindicated in patients who have had a hypersensitivity reaction to natalizumab products.

Important Safety Information

TYRUKO REMS

- TYRUKO is available only through a restricted program under a REMS called the TYRUKO REMS because of the risk of PML.
- Prescribers must be certified and comply with the following:
  - Review the TYRUKO REMS prescriber educational materials including the Prescribing Information.
  - Review, complete, and sign the Prescriber Enrollment Form.
  - Educate patients on the benefits and risks of treatment with TYRUKO, ensure that patients receive the Medication Guide, and encourage them to ask questions.
  - Review, complete, and sign the Patient Enrollment Form for each patient.
  - Evaluate patients 3 months after the first infusion, 6 months after the first infusion, every 6 months thereafter to determine whether patients should continue on treatment, and for at least 6 months after discontinuing TYRUKO.
  - Submit to the TYRUKO REMS the TYRUKO Patient Status Report and Reauthorization Questionnaire 6 months after initiating treatment and every 6 months thereafter.
  - Complete an Initial Discontinuation Questionnaire when TYRUKO is discontinued and a 6-Month Discontinuation Questionnaire following discontinuation of TYRUKO.
  - Report cases of PML, hospitalizations due to opportunistic infections, and deaths to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747. You are encouraged to report other adverse reactions to Sandoz or the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.
- Patients must be enrolled in the TYRUKO REMS, read the Medication Guide, understand the risks associated with TYRUKO, and complete and sign the Patient Enrollment Form.
- Pharmacies and infusion centers must be specially certified to dispense or infuse TYRUKO.

Herpes Infections – Encephalitis, Meningitis and Acute Retinal Necrosis

- Natalizumab products increase 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 natalizumab products.
- The duration of treatment with natalizumab products prior to onset ranged from a few months to several years.
- Monitor patients receiving TYRUKO for signs and symptoms of meningitis and encephalitis. If herpes encephalitis or meningitis occurs, TYRUKO should be discontinued, and appropriate treatment for herpes encephalitis/meningitis should be administered.
- Patients being administered natalizumab products 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 blindless of one or both eyes.
- Following clinical diagnosis of ARN consider discontinuation of TYRUKO.

Hepatotoxicity

- Clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with natalizumab products 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.

Important Safety Information

- In some patients, liver injury recurred upon rechallenge, providing evidence that natalizumab products caused the injury.
- The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients.
- TYRUKO 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 natalizumab products, 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. Generally, these reactions are associated with antibodies to natalizumab products.
- If a hypersensitivity reaction occurs, discontinue administration of TYRUKO, and initiate appropriate therapy. Patients who experience a hypersensitivity reaction should not be re-treated with TYRUKO.
- Hypersensitivity reactions were more frequent in patients with antibodies to natalizumab compared with patients who did not develop antibodies to natalizumab in both MS and CD studies.
- Patients who receive natalizumab products 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 natalizumab products 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 natalizumab-treated patients than in placebo-treated patients. One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received natalizumab 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 natalizumab-treated patients who received steroids was similar to the increase in placebo-treated patients who received steroids.
- Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections over the risk observed with use of natalizumab alone. The safety and efficacy of natalizumab products in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established.
- In Studies MS1 and MS2, the rate of any type of infection was approximately 1.5 per patient-year in both natalizumab-treated patients and placebo-treated patients.
- In Study MS1, the incidence of serious infections was approximately 3% in natalizumab-treated patients and in placebo-treated patients. Most patients did not interrupt treatment with natalizumab during infections.
- In postmarketing experience, serious herpes infections have occurred.
- For patients with Crohn's disease who start TYRUKO while on chronic corticosteroids, commence steroid withdrawal as soon as a therapeutic benefit has occurred. If the patient cannot discontinue systemic corticosteroids within six months, discontinue TYRUKO.

Important Safety Information

Laboratory Test Abnormalities

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

Thrombocytopenia

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

Adverse Reactions

- The most common adverse reactions in Study MS1, reported at an incidence of ≥10% with natalizumab 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%).

  *Percentage based on female patients only.
- 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%).
- In Study MS2, serious adverse reactions of appendicitis were also more common in patients who received natalizumab (0.8% versus 0.2% in placebo).
- The most common adverse reactions reported at an incidence of ≥10% with natalizumab and ≥2% difference with placebo in induction studies for CD were headache (32% vs 23%), upper respiratory tract infection (22% vs 16%), nausea (17% vs 15%) and fatigue (10% vs 8%).
- The most common adverse reactions reported at an incidence of ≥10% with natalizumab and ≥2% difference with placebo in the maintenance study for CD were headache (37% vs 31%), influenza (12% vs 5%), back pain (12% vs 8%) and influenza-like illness (11% vs 6%).
- 11% of natalizumab-treated CD patients experienced infusion-related reactions versus 7% in the placebo-treated patients.
- The following serious adverse reactions in the induction Studies CD1 and CD2 were reported more commonly with natalizumab than placebo and occurred at an incidence of at least 0.3%: intestinal obstruction or stenosis (2% vs. 1% in placebo), acute hypersensitivity reactions (0.5% vs. 0%), abdominal adhesions (0.3% vs. 0%), and cholelithiasis (0.3% vs. 0%). Similar serious adverse reactions were seen in the maintenance Study CD3.
- Based on animal data, natalizumab may cause fetal harm. TYRUKO should be used during pregnancy only if the potential benefit justifies the potential risk of the fetus.

References:

1. TYRUKO Prescribing Information. Princeton, NJ: Sandoz.
2. Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006;354:924-933.
3. Data on file. Cambridge, MA: Biogen.
4. Project Inform. Progressive multifocal leukoencephalopathy (PML). Available at: http://www.projectinform.org/info/pml/index.shtml. Accessed February 14, 2008.
5. What is Crohn's Disease? Crohn's & Colitis Foundation of America. http://www.ccfa.org/what-are-crohns-and-colitis/what-is-crohns-disease/?referrer=https://www.google.com/. Accessed June 24, 2016.

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

SANDOZ A Novartis Division | TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

MEDICATION GUIDE

TYRUKO® (tie-ROO-koh)
(natalizumab-sztn)
injection, for intravenous use

Read this Medication Guide before you start receiving TYRUKO and before you receive each dose. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about TYRUKO?

- **TYRUKO increases your chance (risk) of getting a rare brain infection that usually leads to death or severe disability. This infection is called progressive multifocal leukoencephalopathy (PML). If PML happens, it usually happens in people with weakened immune systems.**
  - **There is no known treatment, prevention, or cure for PML.**
  - **Your chance of getting PML may be higher if you are also being treated with other medicines that can weaken your immune system, including other treatments for Multiple Sclerosis (MS) and Crohn's disease (CD). You should not take certain medicines that weaken your immune system at the same time you are taking TYRUKO. Even if you use TYRUKO alone to treat your MS or CD, you can still get PML.**
  - **Your risk of getting PML is higher if you:**
    - have been infected by the John Cunningham Virus (JCV). JCV is a common virus that is harmless in most people but can cause PML in people who have weakened immune systems, such as people taking TYRUKO. Most people who are infected by JCV do not know it or do not have any symptoms. This infection usually happens in childhood. Before you start receiving TYRUKO or during your treatment, your doctor may do a blood test to check if you have been infected by JCV.
    - have received TYRUKO for a long time, especially longer than 2 years.
    - have received certain medicines that can weaken your immune system before you start receiving TYRUKO.

    Your risk of getting PML is greatest if you have all 3 risk factors listed above. There may be other risk factors for getting PML during TYRUKO treatment that we do not know about yet. Your doctor should discuss the risks and benefits of TYRUKO treatment with you before you decide to receive TYRUKO. See "What are the possible side effects of TYRUKO?"
  - **While you receive TYRUKO, and for 6 months after you stop receiving TYRUKO, it is important that you call your doctor right away if you have any new or worsening medical problems that have lasted several days.**

    These may be new or sudden and include problems with:
    - thinking
    - balance
    - eyesight
    - weakness on 1 side of your body
    - strength
    - using your arms and legs

Tell all your doctors that you are receiving TYRUKO.

- **Because of your risk of getting PML while you receive TYRUKO, TYRUKO is available only through a restricted distribution program called the TYRUKO REMS Program.** To receive TYRUKO, you must talk to your doctor and understand the risks and benefits of TYRUKO and agree to follow all of the instructions in the TYRUKO REMS Program.
  - **TYRUKO is only:**
    - prescribed by doctors who are enrolled in the TYRUKO REMS Program.
    - given by an infusion nurse from an infusion center that is enrolled in the TYRUKO REMS Program.
    - given to people who are enrolled in the TYRUKO REMS Program.
  - **Before you receive TYRUKO, your doctor will:**
    - explain the TYRUKO REMS Program to you.
    - have you sign the TYRUKO REMS Patient Enrollment Form.

What is TYRUKO?

TYRUKO is a prescription medicine used to treat adults with:

- relapsing forms of Multiple Sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease. TYRUKO increases the risk of PML. When starting and continuing treatment with TYRUKO, it is important that you discuss with your doctor whether the expected benefit of TYRUKO is enough to outweigh this risk. See **"What is the most important information I should know about TYRUKO?"**
- moderate to severe Crohn's disease (CD). TYRUKO is used:
  - to reduce signs and symptoms of CD.

- in people who have not been helped enough by, or cannot use the usual CD medicines and medicines called tumor necrosis factor (TNF) inhibitors.

It is not known if TYRUKO is safe and effective in children under 18 years of age.

Who should not receive TYRUKO?

Do not receive TYRUKO if you:

- have PML.
- are allergic to natalizumab products or any of the ingredients in TYRUKO. See the end of this Medication Guide for a complete list of ingredients in TYRUKO.

Talk to your doctor before receiving TYRUKO if you have any of these conditions.

What should I tell my doctor before receiving each dose of TYRUKO?

Before you receive TYRUKO, tell your doctor if you:

- have medical conditions that can weaken your immune system, including:
  - HIV infection or AIDS
  - leukemia or lymphoma
  - an organ transplant
  - other medical conditions that can weaken your immune system
- have any new or worsening medical problems that have lasted several days. These may be new or sudden and include problems with:
  - thinking
  - eyesight
  - strength
  - balance
  - weakness on 1 side of your body
  - using your arms and legs
- have had hives, itching or trouble breathing during or after receiving a dose of TYRUKO.
- have a fever or infection (including shingles or any unusually long lasting infection).
- are pregnant or plan to become pregnant. TYRUKO may cause low platelets, and in some cases also low red blood cells (anemia), in your newborn baby if you take TYRUKO while you are pregnant. It is not known if TYRUKO can cause birth defects.
- are breastfeeding or plan to breastfeed. TYRUKO can pass into your breast milk. It is not known if the TYRUKO that passes into your breast milk can harm your baby. Talk to your doctor about the best way to feed your baby while you receive TYRUKO.

Tell your doctor about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take medicines that can weaken your immune system. Ask your doctor if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I receive TYRUKO?

- TYRUKO is given 1 time every 4 weeks through a needle placed in your vein (IV infusion). Each infusion will last about 1 hour.
- Before each TYRUKO dose you will be asked questions to make sure TYRUKO is still right for you.

What are the possible side effects of TYRUKO?

TYRUKO may cause serious side effects, including:

- **See "What is the most important information I should know about TYRUKO?"**
- **Herpes Infections.** TYRUKO may increase your risk of getting an infection of the brain or the covering of your brain and spinal cord (encephalitis or meningitis) caused by herpes viruses that may lead to death. Call your doctor right away if you have sudden fever, severe headache, or if you feel confused after receiving TYRUKO. Herpes infections of the eye, causing blindness in some patients, have also occurred. Call your doctor right away if you have changes in vision, eye redness, or eye pain.
- **Liver damage.** Symptoms of liver damage can include:
  - yellowing of the skin and eyes (jaundice)
  - nausea
  - vomiting
  - unusual darkening of the urine
  - feeling tired or weak

  Call your doctor right away if you have symptoms of liver damage. Your doctor can do blood tests to check for liver damage.
- **Allergic reactions, including serious allergic reactions.** Symptoms of an allergic reaction can include:
  - hives
  - itching
  - trouble breathing
  - chest pain
  - dizziness
  - wheezing
  - chills
  - rash
  - nausea
  - flushing of skin
  - low blood pressure

  Serious allergic reactions usually happen within 2 hours of the start of your infusion, but they can happen at any time after you receive TYRUKO.

Tell your doctor right away if you have any symptom of an allergic reaction, even if it happens after your infusion. You may need treatment if you are having an allergic reaction.

- **Infections.** TYRUKO may increase your chance of getting an unusual or serious infection because TYRUKO can weaken your immune system. You have a higher risk of getting infections if you also take other medicines that can weaken your immune system.
- **Low platelet counts.** TYRUKO may cause the number of platelets in your blood to be reduced. Call your healthcare provider if you have any of the following symptoms:
  - easy bruising
  - heavier menstrual periods than are normal
  - bleeding from your gums or nose that is new or takes longer than usual to stop
  - bleeding from a cut that is hard to stop
  - small scattered red spots on your skin that are red, pink, or purple

The most common side effects of TYRUKO include:

- headache
- feeling tired
- urinary tract infection
- joint pain
- lung infection
- depression
- pain in your arms and legs
- diarrhea
- vaginitis
- rash
- nose and throat infections
- nausea
- stomach area pain

Tell your doctor about any side effect that bothers you or that does not go away.
These are not all the possible side effects of TYRUKO. Ask your doctor for more information.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TYRUKO.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
This Medication Guide summarizes the most important information about TYRUKO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about TYRUKO that is written for healthcare professionals.

What are the ingredients in TYRUKO?
Active ingredient: natalizumab-sztn.
Inactive ingredients: histidine, L-histidine hydrochloride monohydrate; polysorbate 80, sodium chloride and water for injection.

Manufactured by: Sandoz Inc., Princeton, NJ 08540, US License No. 2003
For more information, go to www.tyruko.com or call 1-800-525-8747.
This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: ##/202#

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
Pre-Infusion Patient Checklist

This Pre-Infusion Patient Checklist must be completed for each patient prior to each infusion. The completed form must be submitted to the TYRUKO (natalizumab-sztn) REMS within 1 business day of the patient's visit regardless of whether the patient is infused or not.

Complete this form online at www.TYRUKO-REMS.com or complete and fax the form to the TYRUKO REMS at 1-833-489-7856.

*indicates required fields

Patient Information

*First Name:	*Last Name:
*Date of Birth (MM/DD/YYYY):	

Infusion Site Information

*Infusion Site Name:	*Infusion Site NPI#:

Step 1: Patient Authorization Confirmation

Access www.TYRUKO-REMS.com to view the patient's previous Pre-Infusion Patient Checklist

- If the prescriber had to be contacted prior to the last infusion and authorization was not provided for the patient to be infused, you must confirm authorization from the prescriber before providing the current infusion

You may also reference the previous Pre-Infusion Patient Checklist by accessing the patient's chart.

Confirm the patient is authorized to receive TYRUKO by:

- Accessing www.TYRUKO-REMS.com
- Contacting the TYRUKO REMS at 1-855-489-7856

You may also reference the patient's chart to verify authorization to receive TYRUKO. To be authorized, the patient must have a current Notice of Patient Authorization on file and no Notice of Patient Discontinuation.

Is the patient currently authorized to receive TYRUKO?

Yes Continue to next step

No **STOP-DO NOT INFUSE.** If authorization cannot be verified at www.TYRUKO-REMS.com **OR** by calling 1-855-489-7856, the patient must be referred back to the healthcare provider who prescribed TYRUKO.

Confirm that the patient has read and understood the Medication Guide including the section "What should I tell my doctor and nurse before each infusion of TYRUKO?"

Step 2: Patient Medical Status Update

Read aloud and mark "Yes" or "No" for the patient's answers to the following questions:

	Yes	No
1. Over the past month, have you had any new or worsening medical problems (such as a new or sudden change in your thinking, eyesight, balance, strength, or other problems) that have persisted over several days?	☐	☐
2. Do you have a medical condition that can weaken your immune system, such as HIV infection or AIDS, leukemia or lymphoma, or an organ transplant, that may suggest that your body is not able to fight infections well?	☐	☐

Crohn's disease ONLY

3. In the past month have you taken, or are you currently on, any medicines other than steroid medicines to treat cancer or **Crohn's disease** or any other medicines that weaken your immune system? (Review the list on the next page with the patient.)

☐ **Yes** ☐ **No**

MS ONLY

3. In the past month, have you taken medicines to treat cancer or **MS** or any other medicines that weaken your immune system? (Review the list on the next page with the patient.)

☐ **Yes** ☐ **No**

Step 3: Record Prescriber Authorization (if required)

If the patient answered YES to question 1, 2 or 3, DO NOT INFUSE. Contact the healthcare provider who prescribed TYRUKO or a prescriber representative and review the patient's answers.

- After discussing the patient's answers, did the prescriber authorize the patient to be infused? ☐ **Yes** ☐ **No**
- Check here if you were unable to contact the prescriber ☐ (See next page for further instructions)

Step 4: Submit Pre-Infusion Patient Checklist

Record infusion information and submit the Pre-Infusion Patient Checklist to Sandoz at www.TYRUKO-REMS.com OR fax to 1-833-489-7856.

☐ **Not infused**

☐ **Date Infused (MM/DD/YYYY):**_____/_____/_____

Infusion Location: ☐ Infusion Site ☐ At Home

Next Scheduled Appointment (MM/DD/YYYY):_____/_____/_____

*Name of Staff Completing the Checklist	*Signature of Staff Completing the Checklist	*Date (MM/DD/YYYY)

Reference ID: 5232179

Please review the following list with the patient when asking question 3 above.

Examples of Immunosuppressants, Antineoplastics, and Immunomodulators

Active substance can include FDA-approved generics or biosimilars.

Multiple Sclerosis

Approved MS Therapies:
Alemtuzumab (Lemtrada®)
Cladribine (Mavenclad®)
Dimethyl fumarate (Tecfidera®)
Diroximel fumarate (Vumerity®)
Fingolimod (Gilenya®)
Glatiramer acetate (Copaxone®)
Interferon beta-1a (Rebif®, Avonex®)
Interferon beta-1b (Betaseron®, Extavia®)
Mitoxantrone
Monomethyl fumarate (Bafiertam®)
Natalizumab (Tysabri®, TYRUKO®)
Ocrelizumab (Ocrevus®)
Ofatumumab (Kesimpta®)
Ozanimod (Zeposia®)
Peginterferon beta-1a (Plegridy®)
Ponesimod (Ponvory™)
Siponimod (Mayzent®)
Teriflunomide (Aubagio®)
Ublituximab (Briumvi®)

Immunosuppressants/Antineoplastics:
Azathioprine (Imuran®, Azasan®)
Cladribine (Leustatin®)
Cyclophosphamide (Cytoxan®, Neosar®)
Cyclosporine (Sandimmune®, Neoral®)
Fludarabine phosphate (Fludara®)
Leflunomide (Arava®)
Mercaptopurine (Purinethol®)
Methotrexate (Methotrex®, Rheumatrex®, Trexall®)
Mycophenolate mofetil (CellCept®)
Pemetrexed (Alimta®)

Additional Immunomodulators and Immunosuppressants:
Other interferons (Actimmune®, Infergen®, Intron® A, Pegasys®, PEG-Intron®, Rebetron®, Roferon®-A)
Adalimumab (Humira®)
Alefacept (Amevive®)
Alemtuzumab (Campath®)
Anakinra (Kineret®)
Daclizumab (Zenapax®)
Efalizumab (Raptiva®)
Etanercept (Enbrel®)
Infliximab (Remicade®)
Intravenous immunoglobulin (IVIG)
Rituximab (Rituxan®)
Trastuzumab (Herceptin®)

Crohn's Disease

Approved TNF-α inhibitors for Crohn's disease:
Infliximab (Remicade®)
Adalimumab (Humira®)

Immunosuppressants/Antineoplastics:
Approved TNF-α inhibitors
Azathioprine (Imuran®, Azasan®)
Chlorambucil (Leukeran®)
Cladribine (Leustatin®)
Cyclophosphamide (Cytoxan®, Neosar®)
Cyclosporine (Sandimmune®, Neoral®)
Fludarabine phosphate (Fludara®)
Leflunomide (Arava®)
Mercaptopurine (Purinethol®)
Methotrexate (Methotrex®, Rheumatrex®, Trexall®)
Mycophenolate mofetil (CellCept®)
Natalizumab (Tysabri®, TYRUKO®)
Pemetrexed (Alimta®)
Thioguanine (Tabloid®)

Additional Immunomodulators and Immunosuppressants:
Interferon beta-1a (Rebif®, Avonex®)
Interferon beta-1b (Betaseron®)
Alefacept (Amevive®)
Abatacept (Orencia®)
Anakinra (Kineret®)
Daclizumab (Zenapax®)
Efalizumab (Raptiva®)
Etanercept (Enbrel®)
Glatiramer acetate (Copaxone®)
Intravenous immunoglobulin (IVIG)
Mitoxantrone (Novantrone®)
Other interferons (Actimmune®, Infergen®, Intron® A, Pegasys®, PEG-Intron®, Rebetron®, Roferon®-A)
Rituximab (Rituxan®)
Trastuzumab (Herceptin®)
Vedolizumab (Entyvio®)

This list does not include all drugs that can suppress the immune system.

- Patients should consult their prescribing physician regarding drugs that may be taken concurrently with TYRUKO
- If there are any questions regarding concurrent therapy, **do not infuse** at this time and consult the healthcare provider who prescribed TYRUKO

If you are unable to contact the prescriber or a prescriber representative:
Instruct the patient to contact their prescriber or prescriber representative to reschedule as soon as possible. Continue efforts to reach the prescriber or prescriber representative to inform them of the reason(s) for not infusing this patient. You will need to confirm authorization from the prescriber or prescriber representative on the subsequent infusion.

A prescriber representative is defined as a prescriber-designated individual who can make decisions regarding patients under their care in their absence. A prescriber representative should be knowledgeable about the Prescribing Information, including Boxed Warning, and should be able to determine whether the patient can receive their infusion.

This Pre-Infusion Patient Checklist does not replace the infusion site's general infusion protocol(s). Nor is this Pre-Infusion Patient Checklist intended to be a substitute for consultation and review of reference materials and medical literature pertaining to individual clinical circumstances. Healthcare providers should make all treatment decisions based on the context of the situation and their clinical judgment.

Please do not make any extraneous marks on the Pre-Infusion Patient Checklist. If there is information that you would like to share with Sandoz and the TYRUKO REMS, please contact us at 1-855-489-7856.

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

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TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
Patient Status Report and Reauthorization Questionnaire

In order to continue treatment with TYRUKO (natalizumab-sztn) this Patient Status Report and Reauthorization Questionnaire must be completed and submitted every 6 months.

Complete this form online at www.TYRUKO-REMS.com or complete and fax the form to the TYRUKO REMS at 1-833-489-7856. Place a copy of the completed form in the patient's chart.

***indicates required fields**

Prescriber Information

*First Name:
*Last Name:
*NPI#:

Patient Information

*First Name:
*Last Name:
*Date of Birth (MM/DD/YYYY):

Patient Reauthorization

1. *Is the patient still under your care?

☐ Yes ☐ No

If no, provide the name and phone number of the new prescriber (if available):

First Name: _____

Last Name: _____

Phone Number: _____

2. *Is the patient alive?

☐ Yes ☐ No

3. *Since starting TYRUKO therapy, has the patient been diagnosed with PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)?

☐ Yes ☐ No ☐ Under investigation

4. *Has the patient been tested for the presence of anti-JCV antibodies since the last submitted Patient Status Report and Reauthorization Questionnaire?

☐ Yes ☐ No

If the patient was tested, provide the test result:

☐ Positive ☐ Negative ☐ Pending

Record the anti-JCV antibody index value (if available):

_____

5. *Is the patient currently receiving or has the patient received any IMMUNOMODULATORY or IMMUNOSUPPRESSANT products in the previous 6 months?

☐ Yes ☐ No

6. *If the patient is still under your care, **do you authorize the continuation of TYRUKO treatment** for the next 6 months?

☐ Yes ☐ No

If you answered with No, the TYRUKO REMS will contact the patient and the infusion site to **STOP TYRUKO TREATMENT.** The patient will not be eligible to receive TYRUKO treatment.

Report adverse events, including PML, hospitalizations due to opportunistic infections, malignancy, and deaths to Sandoz at adverse.event.usa@sandoz.com or call 1-800-525-8747 as soon as possible.

***Signature**:_____ ***Date (MM/DD/YYYY):**_____

*Completed by: ☐ Certified Prescriber ☐ Delegate

*Printed First Name:_____ *Printed Last Name:_____

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Please Note:
A TYRUKO REMS certified prescriber or delegate may complete and submit this form on behalf of the certified prescriber of record. The certified TYRUKO REMS prescriber of record is responsible for compliance with the TYRUKO REMS requirements, including monitoring, evaluation, and management of each patient under his/her care. This questionnaire will be used consistent with the TYRUKO REMS Patient Enrollment Form signed by you and your patient with HIPAA and applicable privacy rules. If you have questions, or if you need additional information, please call 1-855-489-7856 or visit www.TYRUKO-REMS.com.

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Reference ID: 5232179

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
Initial Discontinuation Questionnaire

This TYRUKO (natalizumab-sztn) REMS Discontinuation Questionnaire must be completed for any patient who discontinues treatment with TYRUKO. You may be contacted for additional information in response to answers provided on this discontinuation form.

Complete this form online at www.TYRUKO-REMS.com or complete and fax the form to the TYRUKO REMS at 1-833-489-7856.

***indicates required fields**

Prescriber Information

*First Name:
*Last Name:
*NPI #:

Patient Information

*First Name:
*Last Name:
*Date of Birth (MM/DD/YYYY):

A. ***Is the patient still under your care?**
☐ Yes ☐ No

If no, provide the name and phone number of the new prescriber (if available):

First Name: _____

Last Name: _____

Phone Number: _____

B. ***Is the patient alive?**
☐ Yes ☐ No

C. ***Since starting TYRUKO therapy has the patient been diagnosed with PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)?**

☐ Yes ☐ No ☐ Under investigation

D. ***Has the patient been tested for the presence of anti-JCV antibodies since submitting the Patient Enrollment Form or the last submitted Patient Status Report and Reauthorization Questionnaire?**

☐ Yes ☐ No

If the patient was tested, provide the test result:

☐ Positive ☐ Negative ☐ Pending

Record the anti-JCV antibody index value (if available):

_____

Report adverse events, including PML, hospitalizations due to opportunistic infections, malignancy, and deaths to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747 as soon as possible.

***Signature**:_____ ***Date (MM/DD/YYYY):**_____

Completed by: ☐ Certified Prescriber ☐ Delegate

*Printed First Name: _____ *Printed Last Name:_____

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Please Note:

A TYRUKO REMS certified prescriber or delegate may complete and submit this form on behalf of the certified prescriber of record. The certified TYRUKO REMS prescriber of record is responsible for compliance with the TYRUKO REMS requirements, including monitoring, evaluation, and management of each patient under his/her care. This questionnaire will be used consistent with the TYRUKO REMS Patient Enrollment Form signed by you and your patient with HIPAA and applicable privacy rules. If you have questions, or if you need additional information, please call 1-855-489-7856 or visit www.TYRUKO-REMS.com.

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TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
6-Month Discontinuation Questionnaire

This TYRUKO (natalizumab-sztn) REMS Discontinuation Questionnaire must be completed for each patient 6 months after discontinuing TYRUKO. You may be contacted for additional information in response to answers provided on this discontinuation form.

Complete this form online at www.TYRUKO-REMS.com or complete and fax the form to the TYRUKO REMS at 1-833-489-7856.

***indicates required fields**

Prescriber Information

*First Name:
*Last Name:
*NPI #:

Patient Information

*First Name:
*Last Name:
*Date of Birth (MM/DD/YYYY):

A. ***Is the patient still under your care?**

☐ Yes ☐ No

If no, provide the name and phone number of the new prescriber (if available):

First Name: _____

Last Name: _____

Phone Number: _____

B. ***Is the patient alive?**

☐ Yes ☐ No

C. ***Since starting TYRUKO therapy has the patient been diagnosed with PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)?**

☐ Yes ☐ No ☐ Under investigation

D. ***Has the patient been tested for the presence of anti-JCV antibodies since submitting the Patient Enrollment Form or the last submitted Patient Status Report and Reauthorization Questionnaire?**

☐ Yes ☐ No

If the patient was tested, provide the test result:

☐ Positive ☐ Negative ☐ Pending

Record the anti-JCV antibody index value (if available):

_____

Report adverse events, including PML, hospitalizations due to opportunistic infections, malignancy, and deaths to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747 as soon as possible.

***Signature**:_____ ***Date (MM/DD/YYYY):**_____

*Completed by: ☐ Certified Prescriber ☐ Delegate

*Printed First Name: _____ *Printed Last Name:_____

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Please Note:
A TYRUKO REMS certified prescriber or delegate may complete and submit this form on behalf of the certified prescriber of record. The certified TYRUKO REMS prescriber of record is responsible for compliance with the TYRUKO REMS requirements, including monitoring, evaluation, and management of each patient under his/her care. This questionnaire will be used consistent with the TYRUKO REMS Patient Enrollment Form signed by you and your patient with HIPAA and applicable privacy rules. If you have questions, or if you need additional information, please call 1-855-489-7856 or visit www.TYRUKO-REMS.com.

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What is the TYRUKO REMS (Risk Evaluation and Mitigation Strategy)?

A REMS is a strategy to manage known or potential risks associated with a drug and is required by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

TYRUKO (natalizumab-sztn) is available only through a restricted distribution program called the TYRUKO REMS because of the increased risk of progressive multifocal leukoencephalopathy (PML) associated with natalizumab product use.

The goals of the TYRUKO REMS are:

1. To inform prescribers, infusion site healthcare providers, and patients about the risk of PML associated with TYRUKO, including the increased risk of PML with the presence of anti-JCV antibodies, longer treatment duration, and prior immunosuppressant use.
2. To warn against concurrent use with antineoplastic, immunosuppressant, or immunomodulating agents, and in patients who are immunocompromised.
3. To promote early diagnosis of PML and timely discontinuation of TYRUKO in the event of suspected PML.

Quick Links

Educational Materials

- Educational Slide Set
- Prescribing Information
- Medication Guide
- Helpful Information for Evaluation of New Neurological Symptoms
- Understanding PML for Gastroenterologists

Online Enrollment

- Prescriber
- Infusion Site
- Pharmacy
- Patient

(only prescribers who have enrolled first may enroll patients)

Program Requirements

Prescriber	Infusion Site	Pharmacy	Patient
Prescribers must be certified in the TYRUKO REMS to prescribe TYRUKO	Infusion Sites must be certified in the TYRUKO REMS in order to administer TYRUKO	Pharmacies must be certified in the TYRUKO REMS in order to dispense TYRUKO to Infusion Sites	Patients must be enrolled in the TYRUKO REMS in order to receive TYRUKO
Learn more about Prescriber Certification	Learn more about Infusion Site Certification	Learn more about Pharmacy Certification	Learn more about Patient Enrollment

Indication

- TYRUKO is indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
- TYRUKO is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.
  - TYRUKO should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α.

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

For TYRUKO REMS information contact:
Phone: 1-855-4TYRUKO (1-855-489-7856)
Fax: 1-833-4TYRUKO (1-833-489-7856)

Prescriber

Prescribers of TYRUKO

Prescribers, infusion sites, certified pharmacies and patients must be enrolled in the TYRUKO REMS in order to prescribe, infuse, dispense, or receive TYRUKO.

How does the prescriber enroll to become certified in the TYRUKO REMS?

Education	Enrollment	Prescribe
• Prescriber reviews the drug's Prescribing Information • Prescriber reviews the **Educational Slide Set**, **Overview**, and **Helpful Information for Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO (Multiple Sclerosis)** or **Understanding PML for Gastroenterologists (Crohn's Disease)**	• Prescriber completes and submits the **Prescriber Enrollment Form** to the TYRUKO REMS ◦ **Online** ◦ **By fax at 1-833-489-7856**	• Prescriber identifies appropriate patient for TYRUKO treatment

How does a prescriber enroll a patient in the TYRUKO REMS?

Education	Treatment Decision	Enrollment	Authorization
• Prescriber and Patient discuss TYRUKO as a treatment option	• Patient reads the Medication Guide and discusses the benefits and risks of TYRUKO with his/her prescriber	• Prescriber and patient complete and sign the **Patient Enrollment Form** • The prescriber submits ALL pages of the **Patient Enrollment Form** to the TYRUKO REMS to initiate therapy ◦ **Online** ◦ **By fax at 1-833-489-7856**	• TYRUKO REMS confirms that enrollment is complete and updates patient status to 'Authorized' • Patient is eligible for infusion

Prescriber requirements during treatment include:

- Evaluate patients 3 months after the first infusion, 6 months after the first infusion, every 6 months thereafter to determine whether patients should continue on treatment, and for at least 6 months after discontinuing TYRUKO
- Determine every 6 months whether a patient should continue on TYRUKO and if so, authorize every 6 months

PDFs for Download

Prescriber Resources

Overview
Educational Slide Set
Change in Prescriber Authorization Form
Prescriber Enrollment Form
Patient Status Report and Reauthorization Questionnaire
Initial Discontinuation Questionnaire
6-Month Discontinuation Questionnaire

Crohn's Disease (CD)

Understanding PML for Gastroenterologists (CD)
Patient Enrollment Form - CD

Multiple Sclerosis (MS)

Helpful Information for Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO (MS)
Patient Enrollment Form - MS

Patient Resources

Medication Guide
Patient Enrollment Form - CD
Patient Enrollment Form - MS

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Prescriber Enrollment Form

Complete this form online or complete and fax to the TYRUKO (natalizumab-sztn) REMS at 1-833-489-7856.

(* indicates required fields)

Prescriber Information

***NPI#**

Continue

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Prescriber Enrollment Form

Complete this form online or complete and fax to the TYRUKO (natalizumab-sztn) REMS at 1-833-489-7856.

(** indicates required fields*)

Prescriber Information

*NPI#
1234567890

*First Name | Middle Initial | *Last Name

*Address Line 1 | Address Line 2

*City | *State (-- Please Select --) | *ZIP Code

*Phone Number | *Fax | *Email

Office Contact

Prescriber Delegate

Note: First Name, Last Name and Email are required if Prescriber Delegate is provided.

First Name | Last Name | Email

Prescriber Acknowledgement

INDICATIONS

MULTIPLE SCLEROSIS

- I understand that TYRUKO is indicated as monotherapy for relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- I understand that TYRUKO is not ordinarily recommended for patients who are receiving chronic immunosuppressant or immunomodulatory therapy, or who are significantly immunocompromised from any other cause
- I understand that an MRI should be performed prior to initiating therapy with TYRUKO in MS patients

CROHN'S DISEASE

- I understand that TYRUKO is indicated for adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of TNF-α
- I understand that patients receiving TYRUKO should not take concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α
- I understand that TYRUKO should be discontinued if a patient has not experienced a therapeutic benefit by 12 weeks of therapy
- I understand that patients receiving steroid therapy at the time of TYRUKO initiation must undergo a steroid-tapering regimen once a therapeutic response is achieved. If the patient with Crohn's disease cannot be tapered off steroids within 6 months of starting TYRUKO, TYRUKO should be discontinued

All Other Acknowledgements

- I have reviewed the Prescribing Information for TYRUKO (natalizumab-sztn)
- I understand that TYRUKO is only to be used for relapsing forms of MS and moderately to severely active Crohn's disease with evidence of inflammation
- I understand that natalizumab products increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. When initiating and continuing treatment with TYRUKO, I should consider whether the expected benefit of TYRUKO is sufficient to offset the risk
- I am aware that cases of PML have been reported in patients taking natalizumab who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving natalizumab monotherapy
- I understand that three risk factors identified thus far that increase the risk of PML in natalizumab-treated patients are:
  - The presence of anti-JCV antibodies
  - Longer treatment duration, especially beyond 2 years
  - Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil)

  These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYRUKO
- I understand that MRI findings may be apparent before clinical signs or symptoms. Periodic monitoring for radiographic signs consistent with PML should be considered to allow for an early diagnosis of PML. Lower PML-related mortality and morbidity have been reported following natalizumab discontinuation in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis
- Before treatment initiation (first dose), I must counsel the patient using the Medication Guide and Patient Enrollment Form – Multiple Sclerosis or Patient Enrollment Form – Crohn's Disease
- I understand that each patient must be seen and evaluated 3 months after the first infusion, 6 months after the first infusion, every 6 months thereafter to determine whether patients should continue on treatment, and for at least 6 months after TYRUKO has been discontinued
- For each patient, I am required to complete reauthorization every 6 months to authorize treatment for another 6 months using the Patient Status Report and Reauthorization Questionnaire. I am required to submit an Initial Discontinuation Questionnaire when TYRUKO is discontinued and a 6-Month Discontinuation Questionnaire following discontinuation of TYRUKO
- I must report, as soon as possible, cases of PML, hospitalizations due to other opportunistic infections, malignancies, and deaths to Sandoz
- I understand that data concerning each patient and me will be entered into the mandatory TYRUKO REMS database. Sandoz requires my cooperation with periodic data collection. Failure to provide the requested information or otherwise comply with the requirements of the TYRUKO REMS may result in discontinuation of TYRUKO for patients and termination of my authorization to prescribe TYRUKO
- I understand that data concerning each patient and me, including duration of natalizumab exposure, presence of anti-JCV antibodies, prior treatment with immunosuppressants, and prior or current history of PML, may be shared with REMS programs for other natalizumab products if a patient switches to or from another natalizumab product
- I have received and reviewed the educational materials regarding the benefits and risks of TYRUKO treatment

☐ *Prescriber Signature

Cancel | Submit

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

If you are a resident of California, California state law creates additional rights associated with how we collect and use your personal information. You have the right to information about the types of personal information that we collect and how that information might be used. More information about these and other rights is available at: https://www.us.sandoz.com/State-Specific

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

Prescriber Delegate

Note: First Name, Last Name and Email are required if Prescriber Delegate is provided.

*First Name	*Last Name	*Email
Steve		

Prescriber Acknowledgement

TYRUKO REMS Prescriber Enrollment Successful

You have successfully completed and submitted the Prescriber Enrollment Form.

The TYRUKO REMS will notify you of successful enrollment by sending a confimation to the email address provided, along with a link to create your login credentials.

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

Login →

Infusion Site

Infusion Sites Administering TYRUKO

Prescribers, infusion sites, certified pharmacies and patients must all enroll in the TYRUKO REMS in order to prescribe, infuse, dispense, or receive TYRUKO.

How does my infusion site enroll to become certified in the TYRUKO REMS?

Designate	Review	Enroll	Authorize
An authorized representative is designated to carry out the certification process and oversee REMS implementation on behalf of the Infusion Site	Authorized representative reviews the **Educational Slide Set**	Authorized representative completes and submits the **Infusion Site Enrollment Form** to the TYRUKO REMS • **Online** • **By fax at 1-833-489-7856**	TYRUKO REMS verifies the document is complete and confirms Infusion Site enrollment

Infusion site requirements prior to each TYRUKO infusion:

- Administer TYRUKO only to patients who are currently authorized in the TYRUKO REMS. Patient authorization must be confirmed
- Provide each patient a copy of the TYRUKO Medication Guide
- Complete a **Pre-Infusion Patient Checklist**. The **Pre-Infusion Patient Checklist** must be submitted to the TYRUKO REMS within 1 business day of the patient visit

PDFs for Download

Infusion Site Resources

- Educational Slide Set
- Infusion Site Enrollment Form
- Pre-Infusion Patient Checklist

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

For TYRUKO REMS information contact:
Phone: 1-855-4TYRUKO (1-855-489-7856)
Fax: 1-833-4TYRUKO (1-833-489-7856)

TYRUKO REMS Infusion Site Enrollment Form

Only certified infusion sites may receive shipments of and infuse TYRUKO (natalizumab-sztn).

An infusion site may become certified after it has designated an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the infusion site. The authorized representative reviews the Educational Slide Set and completes and submits an Infusion Site Enrollment Form to the TYRUKO REMS.

This Infusion Site Enrollment Form can be completed online below or complete and fax to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

(** indicates required fields*)

Infusion Site Information

*NPI# (on file with your distributor)

*Authorized Representative Email

Continue

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Infusion Site Enrollment Form

Only certified infusion sites may receive shipments of and infuse TYRUKO (natalizumab-sztn).

An infusion site may become certified after it has designated an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the infusion site. The authorized representative reviews the Educational Slide Set and completes and submits an Infusion Site Enrollment Form to the TYRUKO REMS.

This Infusion Site Enrollment Form can be completed online below or complete and fax to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

(* ***indicates required fields***)

Infusion Site Information

*NPI# (on file with your distributor)
1234567890

*Authorized Representative Email
a@a.com

*Name of Infusion Site
ABC Healthcare Setting

*Address Line 1
123 Main Street

Address Line 2

*City
Philadelphia

*State
PA

*ZIP Code
99999

*Phone Number

*Fax

The infusion site will offer services to provide in-home infusions
○ Yes ○ No

Ship To Information

☐ Ship to Address - Same as Above

*Ship To Contact Name

*Address Line 1

Address Line 2

*City

*State
-- Please Select --

*ZIP Code

*Phone Number

*Fax

Authorized Representative Information

*First Name

*Last Name

*Email

*Phone Number

*Fax

Method of acquiring TYRUKO

*Please select one of the following:
- ○ Infusion site will acquire TYRUKO directly.
- ○ Infusion site will acquire TYRUKO through a certified pharmacy.*

*A certified pharmacy is located within a hospital, group practice, or infusion site and is associated with an infusion site.

I must contact Sandoz if my infusion site name, administration address, or shipping address changes. By signing below, I understand that I am the TYRUKO REMS Trained Authorized Representative at the infusion site and am responsible for what is outlined in the "Infusion Site Acknowledgment" below.

Infusion Site Acknowledgement

- The infusion site has received training and educational materials on the TYRUKO REMS
- TYRUKO will be administered only to patients who are currently authorized in the TYRUKO REMS. Patient authorization must be confirmed *prior to each infusion* by:
  - For online infusion sites: Patient status must be "Authorized" or
  - For paper-based infusion sites: Receipt of current Notice of Patient Authorization and verification that no Notice of Patient Discontinuation is on file
- Each patient must receive a copy of the TYRUKO Medication Guide *prior to each infusion*
- The TYRUKO Pre-Infusion Patient Checklist must be completed *prior to each infusion*. The Pre-Infusion Patient Checklist must be submitted to the TYRUKO REMS within 1 business day of the patient visit regardless of whether or not the patient received the infusion by:
  - For paper-based infusion sites: sending a copy of the completed Pre-Infusion Patient Checklist to the TYRUKO REMS. A copy must also be placed in the patient's medical record
  - For online infusion sites: the infusion nurse can read, complete and submit the Pre-Infusion Patient Checklist at www.TYRUKO-REMS.com
- Maintain records of the infusion site's Site Authorization Confirmation
- I understand that, per the requirements of the TYRUKO REMS, this infusion site's compliance may be reviewed by and/or audited by Sandoz and/or a third party designated by Sandoz
- I understand that infusion site contact information may be shared with the REMS programs for other natalizumab products if a patient switches to another natalizumab product
- I understand that noncompliance with the requirements of the TYRUKO REMS will result in de-enrollment of the infusion site and termination of the authorization to infuse TYRUKO

☐ *Authorized Representative Signature

Cancel Submit

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Infusion Site Enrollment Form

Only certified infusion sites may receive shipments of and infuse TYRUKO (natalizumab-sztn).

An infusion site may become certified after it has designated an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the infusion site. The authorized representative reviews the Educational Slide Set and completes and submits an Infusion Site Enrollment Form to the TYRUKO REMS.

This Infusion Site Enrollment Form can be completed online below or complete and fax to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

(* *indicates required fields*)

Infusion Site Information

*NPI# (on file with your distributor): 1234567890

*Authorized Representative Email: a@a.com

*Name of Infusion Site: ABC Healthcare Setting

*Address Line 1: 123 Main Street

Address Line 2:

*City: Philadelphia

*State: PA

*ZIP Code: 99999

*Phone Number:

*Fax:

The infusion site will offer services to provide in-home infusions

○ Yes ○ No

Ship To Information

☑ Ship to Address - Same as Above

Authorized Representative Information

*First Name:

*Last Name:

*Email:

*Phone Number:

*Fax:

Method of acquiring TYRUKO

*Please select one of the following:

◉ Infusion site will acquire TYRUKO directly.

○ Infusion site will acquire TYRUKO through a certified pharmacy.*

*Check all that apply

☐ Buy/Bill ☐ Assignment of Benefits/Specialty Pharmacy

*A certified pharmacy is located within a hospital, group practice, or infusion site and is associated with an infusion site.

I must contact Sandoz if my infusion site name, administration address, or shipping address changes. By signing below, I understand that I am the TYRUKO REMS Trained Authorized Representative at the infusion site and am responsible for what is outlined in the "Infusion Site Acknowledgment" below.

Infusion Site Acknowledgement

- The infusion site has received training and educational materials on the TYRUKO REMS
- TYRUKO will be administered only to patients who are currently authorized in the TYRUKO REMS. Patient authorization must be confirmed *prior to each infusion* by:
  - For online infusion sites: Patient status must be "Authorized" or
  - For paper-based infusion sites: Receipt of current Notice of Patient Authorization and verification that no Notice of Patient Discontinuation is on file
- Each patient must receive a copy of the TYRUKO Medication Guide *prior to each infusion*
- The TYRUKO Pre-Infusion Patient Checklist must be completed *prior to each infusion*. The Pre-Infusion Patient Checklist must be submitted to the TYRUKO REMS within 1 business day of the patient visit regardless of whether or not the patient received the infusion by:
  - For paper-based infusion sites: sending a copy of the completed Pre-Infusion Patient Checklist to the TYRUKO REMS. A copy must also be placed in the patient's medical record
  - For online infusion sites: the infusion nurse can read, complete and submit the Pre-Infusion Patient Checklist at www.TYRUKO-REMS.com
- Maintain records of the infusion site's Site Authorization Confirmation
- I understand that, per the requirements of the TYRUKO REMS, this infusion site's compliance may be reviewed by and/or audited by Sandoz and/or a third party designated by Sandoz
- I understand that infusion site contact information may be shared with the REMS programs for other natalizumab products if a patient switches to another natalizumab product
- I understand that noncompliance with the requirements of the TYRUKO REMS will result in de-enrollment of the infusion site and termination of the authorization to infuse TYRUKO

☐ *Authorized Representative Signature

Cancel Submit

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Infusion Site Enrollment Successful

You have successfully completed and submitted the Infusion Site Enrollment Form.

The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation to the email address provided, along with a link to create your login credentials.

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

Login →

Pharmacy

Pharmacies Dispensing TYRUKO

Prescribers, infusion sites, certified pharmacies and patients must all enroll in the TYRUKO REMS in order to prescribe, infuse, dispense, or receive TYRUKO.

How does my pharmacy enroll to become certified in the TYRUKO REMS?

Designate	Review	Enroll	Authorization
An authorized representative is designated to carry out the certification process and oversee REMS implementation on behalf of the pharmacy	Authorized representative reviews the Educational Slide Set	Authorized representative completes and submits the **Pharmacy Enrollment Form** to the TYRUKO REMS • Online • By fax at 1-833-489-7856	TYRUKO REMS verifies document is complete and confirms pharmacy enrollment

Pharmacy requirements prior to dispensing TYRUKO:

- Dispense TYRUKO only to authorized infusion sites

PDFs for Download

Pharmacy Resources

- Educational Slide Set
- Pharmacy Enrollment Form

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Pharmacy Enrollment Form

Only certified pharmacies may dispense to infusion sites certified in the TYRUKO (natalizumab-sztn) REMS. A certified pharmacy is located within a hospital, group practice, or infusion site and is associated with an infusion site.

To become certified in the TYRUKO REMS and dispense TYRUKO, a pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy, review the Educational Slide Set and submit a Pharmacy Enrollment Form to the TYRUKO REMS.

Before dispensing, the pharmacy must verify that the infusion site is authorized through the processes and procedures established as a requirement of the REMS Program. At all times the pharmacy must:

1) Maintain records of the pharmacy's Site Authorization Confirmation.
2) Comply with audits carried out by Sandoz or a third party acting on behalf of Sandoz to ensure that all processes and procedures are in place and are being followed.

This Pharmacy Enrollment Form can be completed online below or completed and faxed to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

(** indicates required fields*)

Certified Pharmacy Information

*NPI# (on file with your distributor)

*Authorized Representative Email

Continue

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Pharmacy Enrollment Form

Only certified pharmacies may dispense to infusion sites certified in the TYRUKO (natalizumab-sztn) REMS. A certified pharmacy is located within a hospital, group practice, or infusion site and is associated with an infusion site.

To become certified in the TYRUKO REMS and dispense TYRUKO, a pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy, review the Educational Slide Set and submit a Pharmacy Enrollment Form to the TYRUKO REMS.

Before dispensing, the pharmacy must verify that the infusion site is authorized through the processes and procedures established as a requirement of the REMS Program. At all times the pharmacy must:

1) Maintain records of the pharmacy's Site Authorization Confirmation.
2) Comply with audits carried out by Sandoz or a third party acting on behalf of Sandoz to ensure that all processes and procedures are in place and are being followed.

This Pharmacy Enrollment Form can be completed online below or completed and faxed to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

(* *indicates required fields*)

Certified Pharmacy Information

*NPI# (on file with your distributor) 1234567890

*Authorized Representative Email a@a.com

*Name of Pharmacy ABC Pharmacy

*Address Line 1 123 Main Street

Address Line 2

*City Philadelphia

*State PA

*ZIP Code 99999

*Phone Number

*Fax

Ship To Information

This is the ONLY address to which TYRUKO will be shipped.

Ship To Address - Same as Above

*Ship To Contact Name

NCPDP

*Address Line 1

Address Line 2

*City

*State -- Please Select --

*ZIP Code

*Phone Number

*Fax

Authorized Representative Information

*First Name

*Last Name

*Title

*Email

*Phone Number

*Fax

Authorized Infusion Sites

Enter all potential infusion sites supported by your pharmacy.

*NPI#

Continue

Certified Pharmacy Acknowledgement

- The pharmacy has received training and educational materials on the TYRUKO REMS.
- Certified pharmacies may dispense TYRUKO only to infusion sites.
- I understand that, per the requirements of the TYRUKO REMS, this certified pharmacy's compliance may be reviewed by the Food and Drug Administration (FDA), and/or audited by Sandoz, and/or a third party designated by Sandoz.
- I understand that continued enrollment in the TYRUKO REMS depends on full compliance of my pharmacy with the program requirements.

*Authorized Representative Signature

Cancel Submit

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

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Only certified pharmacies may dispense to infusion sites certified in the TYRUKO (natalizumab-sztn) REMS. A certified pharmacy is located within a hospital, group practice, or infusion site and is associated with an infusion site.

To become certified in the TYRUKO REMS and dispense TYRUKO, a pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy, review the Educational Slide Set and submit a Pharmacy Enrollment Form to the TYRUKO REMS.

Before dispensing, the pharmacy must verify that the infusion site is authorized through the processes and procedures established as a requirement of the REMS Program. At all times the pharmacy must:

1) Maintain records of the pharmacy's Site Authorization Confirmation.
2) Comply with audits carried out by Sandoz or a third party acting on behalf of Sandoz to ensure that all processes and procedures are in place and are being followed.

This Pharmacy Enrollment Form can be completed online below or completed and faxed to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

(* indicates required fields)

Certified Pharmacy Information

*NPI# (on file with your distributor): 1234567890
*Authorized Representative Email: a@a.com
*Name of Pharmacy: ABC Pharmacy
*Address Line 1: 123 Main Street
Address Line 2:
*City: Philadelphia
*State: PA
*ZIP Code: 99999
*Phone Number:
*Fax:

Ship To Information

This is the ONLY address to which TYRUKO will be shipped.

☑ Ship To Address - Same as Above

Authorized Representative Information

*First Name:
*Last Name:
*Title:
*Email:
*Phone Number:
*Fax:

Authorized Infusion Sites

Enter all potential infusion sites supported by your pharmacy.

*NPI#: 1111111111
Name of Infusion Site: ABC Infusion Site
Contact Name:
Address: 123 Main Street
City: Philadelphia
State: PA
ZIP Code: 99999

If you are associating more than one infusion site for which the authorized representative is responsible, click on "Add Infusion Site" below and provide the information for each site below.

+ Add Infusion Site

Certified Pharmacy Acknowledgement

- The pharmacy has received training and educational materials on the TYRUKO REMS.
- Certified pharmacies may dispense TYRUKO only to infusion sites.
- I understand that, per the requirements of the TYRUKO REMS, this certified pharmacy's compliance may be reviewed by the Food and Drug Administration (FDA), and/or audited by Sandoz, and/or a third party designated by Sandoz.
- I understand that continued enrollment in the TYRUKO REMS depends on full compliance of my pharmacy with the program requirements.

☐ *Authorized Representative Signature

Cancel Submit

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Pharmacy Enrollment Form

Only certified pharmacies may dispense to infusion sites certified in the TYRUKO (natalizumab-sztn) REMS. A certified pharmacy is located within a hospital, group practice, or infusion site and is associated with an infusion site.

To become certified in the TYRUKO REMS and dispense TYRUKO, a pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy, review the Educational Slide Set and submit a Pharmacy Enrollment Form to the TYRUKO REMS.

Before dispensing, the pharmacy must verify that the infusion site is authorized through the processes and procedures established as a requirement of the REMS Program. At all times the pharmacy must:

1) Maintain records of the pharmacy's Site Authorization Confirmation.
2) Comply with audits carried out by Sandoz or a third party acting on behalf of Sandoz to ensure that all processes and procedures are in place and are being followed.

This Pharmacy Enrollment Form can be completed online below or completed and faxed to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

(** indicates required fields*)

Certified Pharmacy Information

*NPI# (on file with your distributor): 1234567890
*Authorized Representative Email: a@a.com
*Name of Pharmacy: AEC Pharmacy
*Address Line 1: 123 Main Street
Address Line 2:
*City: Philadelphia
*State: PA
*ZIP Code: 99999
*Phone Number:
*Fax:

Ship To Information

This is the ONLY address to which TYRUKO will be shipped.

☑ Ship To Address - Same as Above

Authorized Representative Information

*First Name:
*Last Name:
*Title:
*Email:
*Phone Number:
*Fax:

Authorized Infusion Sites

Enter all potential infusion sites supported by your pharmacy.

*NPI#: 1111111111
Name of Infusion Site: AEC Infusion Site
Contact Name:
Address: 123 Main Street
City: Philadelphia
State: PA
ZIP Code: 99999
*NPI#:
Continue

If you are associating more than one infusion site for which the authorized representative is responsible, click on "Add Infusion Site" below and provide the information for each site below.

+ Add Infusion Site

Certified Pharmacy Acknowledgement

- The pharmacy has received training and educational materials on the TYRUKO REMS.
- Certified pharmacies may dispense TYRUKO only to infusion sites.
- I understand that, per the requirements of the TYRUKO REMS, this certified pharmacy's compliance may be reviewed by the Food and Drug Administration (FDA), and/or audited by Sandoz, and/or a third party designated by Sandoz.
- I understand that continued enrollment in the TYRUKO REMS depends on full compliance of my pharmacy with the program requirements.

☐ *Authorized Representative Signature

Cancel Submit

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Pharmacy Enrollment Form

Only certified pharmacies may dispense to infusion sites certified in the TYRUKO (natalizumab-sztn) REMS. A certified pharmacy is located within a hospital, group practice, or infusion site and is associated with an infusion site.

To become certified in the TYRUKO REMS and dispense TYRUKO, a pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy, review the Educational Slide Set and submit a Pharmacy Enrollment Form to the TYRUKO REMS.

Before dispensing, the pharmacy must verify that the infusion site is authorized through the processes and procedures established as a requirement of the REMS Program.
At all times the pharmacy must:

1) Maintain records of the pharmacy's Site Authorization Confirmation.
2) Comply with audits carried out by Sandoz or a third party acting on behalf of Sandoz to ensure that all processes and procedures are in place and are being followed.

This Pharmacy Enrollment Form can be completed online below or completed and faxed to the TYRUKO REMS at 1-833-489-7856. The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation.

(* *indicates required fields*)

Certified Pharmacy Information

*NPI# (on file with your distributor): 123456789
*Authorized Representative Email: a@a.com
*Name of Pharmacy: ABC Pharmacy
*Address Line 1: 123 Main Street
Address Line 2:
*City: Philadelphia
*State: PA
*ZIP Code: 99999
*Phone Number:
*Fax:

Ship To Information

This is the ONLY address to which TYRUKO will be shipped.

Ship To Address - Same as Above

Authorized Representative Information

*First Name:
*Last Name:
*Title:
*Email:
*Phone Number:
*Fax:

Authorized Infusion Sites

Enter all potential infusion sites supported by your pharmacy.

*NPI#: 1111111111
Name of Infusion Site: ABC Infusion Site
Contact Name:
Address: 123 Main Street
City: Philadelphia
State: PA
ZIP Code: 99999

*NPI#: 2222222222
Name of Infusion Site: XYZ Medical Center
Address: 999 Broadway
City: Philadelphia
State: PA
ZIP Code: 99999

✕ Remove Infusion Site

If you are associating more than one infusion site for which the authorized representative is responsible, click on "Add Infusion Site" below and provide the information for each site below.

+ Add Infusion Site

Certified Pharmacy Acknowledgement

- The pharmacy has received training and educational materials on the TYRUKO REMS.
- Certified pharmacies may dispense TYRUKO only to infusion sites.
- I understand that, per the requirements of the TYRUKO REMS, this certified pharmacy's compliance may be reviewed by the Food and Drug Administration (FDA), and/or audited by Sandoz, and/or a third party designated by Sandoz.
- I understand that continued enrollment in the TYRUKO REMS depends on full compliance of my pharmacy with the program requirements.

*Authorized Representative Signature

Cancel Submit

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO REMS Pharmacy Enrollment Successful

You have successfully completed and submitted the Pharmacy Enrollment Form.

The TYRUKO REMS will notify the authorized representative with confirmation of successful enrollment by sending a Site Authorization Confirmation to the email address provided, along with a link to create your login credentials.

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

Login →

Resources

Prescriber Resources

- Overview
- Educational Slide Set
- Change in Prescriber Authorization Form
- Prescriber Enrollment Form
- Patient Status Report and Reauthorization Questionnaire
- Initial Discontinuation Questionnaire
- 6-Month Discontinuation Questionnaire

Crohn's Disease (CD)

- Understanding PML for Gastroenterologists (CD)
- Patient Enrollment Form - CD

Multiple Sclerosis (MS)

- Helpful Information for Evaluation of New Neurological Symptoms in Patients Receiving TYRUKO (MS)
- Patient Enrollment Form - MS

Infusion Site Resources

- Educational Slide Set
- Infusion Site Enrollment Form
- Pre-Infusion Patient Checklist

Pharmacy Resources

- Educational Slide Set
- Pharmacy Enrollment Form

Patient Resources

- Medication Guide
- Patient Enrollment Form - CD
- Patient Enrollment Form - MS

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

Login →

Locator

*Please select a certified participant to locate

○ Prescriber/Infusion Site ○ Specialty Pharmacy

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

For TYRUKO REMS information contact:
Phone: 1-855-4TYRUKO (1-855-489-7856)
Fax: 1-833-4TYRUKO (1-833-489-7856)

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

Login →

Locator

*Please select a certified participant to locate

(•) Prescriber/Infusion Site ( ) Specialty Pharmacy

*Zip Code

*Search Radius

-- Please Select --

Search

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

For TYRUKO REMS information contact:
Phone: 1-855-4TYRUKO (1-855-489-7856)
Fax: 1-833-4TYRUKO (1-833-489-7856)

Locator

*Please select a certified participant to locate

(•) Prescriber/Infusion Site ( ) Specialty Pharmacy

Prescribers | Infusion Sites

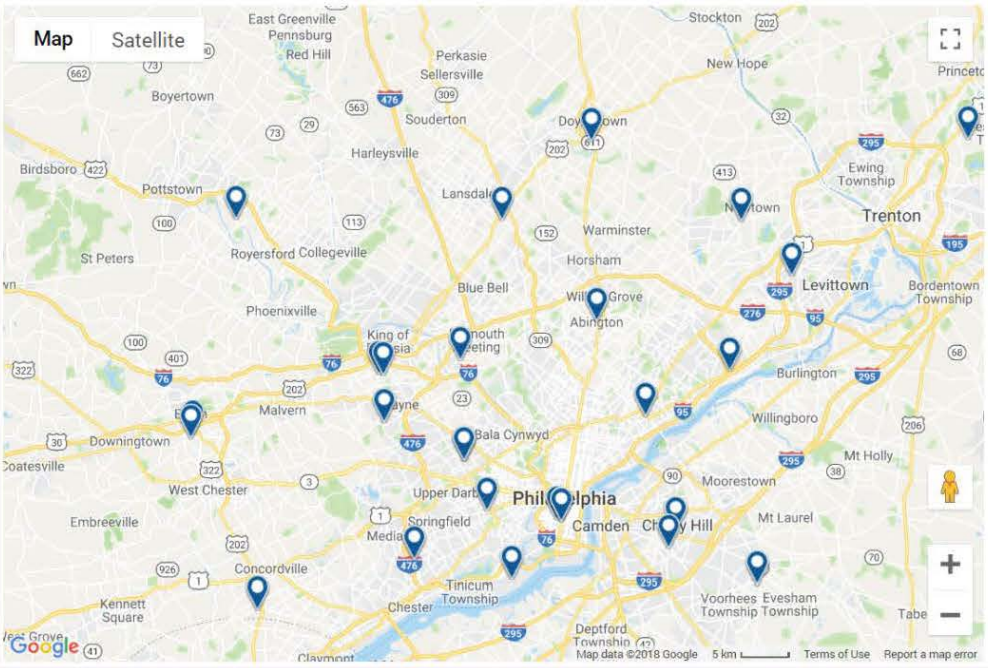
*Zip Code

12345

*Search Radius

Within 25 miles

Search



Prescriber Name 75.1 miles
100 Main St
Blue Bell, PA 19422
555 555-1212
Directions

Prescriber Name 75.6 miles
100 Main St
Blue Bell, PA 19422
555 555-1212
Directions

Prescriber Name 75.6 miles
100 Main St
Blue Bell, PA 19422
555 555-1212
Directions

Prescriber Name 75.6 miles
100 Main St
Blue Bell, PA 19422
555 555-1212
Directions

Prescriber Name 76.2 miles
100 Main St
Blue Bell, PA 19422
Directions

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

Locator

*Please select a certified participant to locate

(•) Prescriber/Infusion Site ( ) Specialty Pharmacy

Prescribers | Infusion Sites

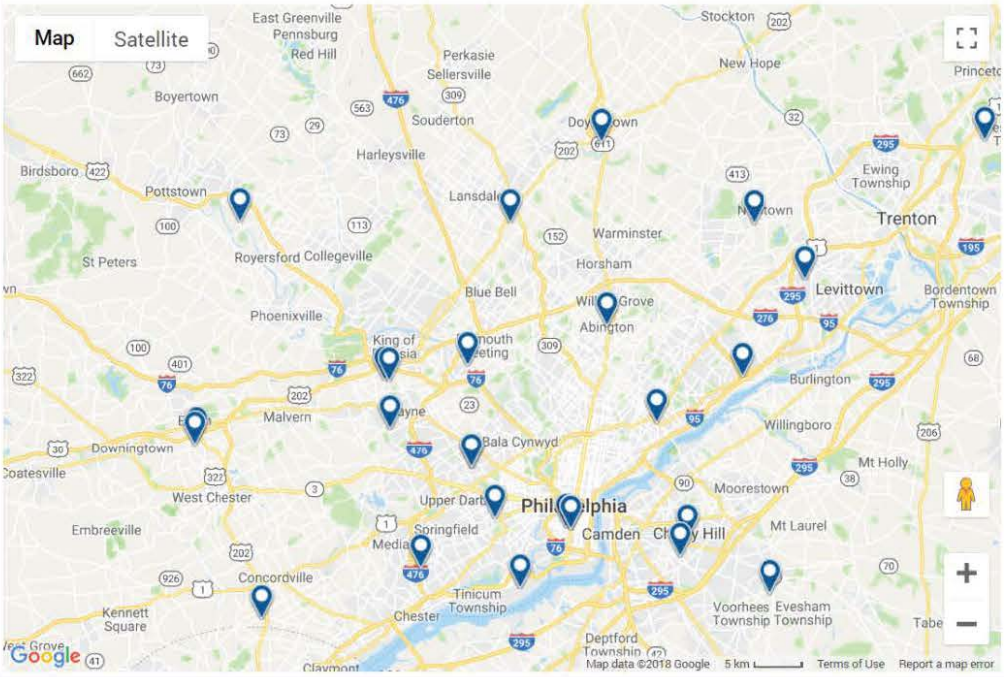
*Zip Code

12345

*Search Radius

Within 25 miles

Search



Infusion Site Name 75.6 miles
920 Harvest Drive
Blue Bell, PA 19422
555 555-1212
Directions

Infusion Site Name 75.6 miles
920 Harvest Drive
STE 200
Blue Bell, PA 19422
555 555-1212
Directions

Infusion Site Name 75.6 miles
920 Harvest Drive
#200
Blue Bell, PA 19422
555 555-1212
Directions

Infusion Site Name 76.6 miles
2703 Aspen Cir
Blue Bell, PA 19422
555 555-1212
Directions

Infusion Site Name 77.1 miles
eolmibni
Directions

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

Login →

Locator

*Please select a certified participant to locate

○ Prescriber/Infusion Site ◉ Specialty Pharmacy

Specialty Pharmacies

Pharmacy Name	Phone Number
ABC Pharmacy	555 555-1212

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

For TYRUKO REMS information contact:
Phone: 1-855-4TYRUKO (1-855-489-7856)
Fax: 1-833-4TYRUKO (1-833-489-7856)

Contact Us

Contact the TYRUKO REMS

Phone	Fax	Hours of Operation
1-855-489-7856	1-833-489-7856	Monday - Friday 8:00 AM - 8:00 PM ET

Healthcare providers should report suspected adverse events or product quality complaints associated with TYRUKO to Sandoz at adverse.event.usa@sandoz.com or at 1-800-525-8747.

TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

TYRUKO REMS
Change in Prescriber Authorization Form

In order to accept care of a patient being treated with TYRUKO (natalizumab-sztn), this Change in Prescriber Authorization Form must be completed and submitted to the TYRUKO REMS. You may be contacted for more information on the transfer of this patient.

- **If you agree to accept this patient**, complete this form online at www.TYRUKO-REMS.com or complete and fax the form to the TYRUKO REMS at 1-833-489-7856. A copy of this completed form must also be placed in the patient's record.
- **If you do not agree to accept this patient or have inquiries about the TYRUKO REMS**, call the TYRUKO REMS at 1-855-489-7856, Monday through Friday 8:00 AM to 8:00 PM ET.

***indicates required fields**

*Date (MM/DD/YYYY):

Prescriber Information
*First Name:
*Last Name:
*NPI #:

Patient Information
*First Name:
*Last Name:
*Date of Birth (MM/DD/YYYY):

By signing below, I accept the above-named patient to be under my care for TYRUKO treatment.

I hereby authorize Sandoz as my delegated agent and on behalf of my patient to (1) process the information on this form to maintain the patient's participation in the TYRUKO REMS and (2) provide the information on this form to the patient's infusion site that is administering TYRUKO, if applicable.

***Signature (stamp not acceptable):**_____ ***Date (DD/MM/YYYY):**_____

Please see the TYRUKO (natalizumab-sztn) Prescribing Information, including **BOXED WARNING**, at www.TYRUKO-REMS.com.

SANDOZ A Novartis Division | TYRUKO® (natalizumab-sztn) 300 mg/15 mL IV

Reference ID: 5232179

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL R LEE
08/24/2023 03:30:47 PM