SANDOZ

TYRUKO

(natalizumab)

300 mg
Concentrate for solution for infusion

Physician Information and Management Guidelines

“Important Safety Information”

“It is advised to read carefully before prescribing/ dispensing/administering the product.”

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This educational document is intended to provide additional information and guidance for physicians initiating and monitoring treatment of MS patients with TYRUKO (natalizumab) under conditions of the Marketing Authorization, along with the TYRUKO Summary of Product Characteristics (SmPC) to assure its safe and effective use in frame of additional risk mitigation procedures.

Please see the TYRUKO full prescribing information at
https://sdi.sfda.gov.sa/Home/DrugSearch?textFilter

Please see SmPC and Patient Information Leaflet for primary advice, available at
https://sdi.sfda.gov.sa/Home/DrugSearch?textFilter

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA - Version 1.2

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Contents

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I. Introduction

Treatment with TYRUKO is to be initiated and monitored by specialized physicians experienced in the diagnosis and management of neurological conditions like Multiple Sclerosis (MS) with timely access to magnetic resonance imaging (MRI).

It is additionally supported by the Patient Alert Card (Appendix 1) and three forms (Treatment Initiation Form, Treatment Continuation Form, Treatment Discontinuation Form), available in Appendix 2.

This educational document is mainly focused on the risk of progressive multifocal leukoencephalopathy (PML), which so far is the most important adverse event occurring in patients treated with natalizumab. Therefore, the relevant sections of this document should also be shared with the radiologists involved in the differential diagnosis of PML.

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. To promote early diagnosis of progressive multifocal leukoencephalopathy and timely discontinuation of TYRUKO in the event of suspected progressive multifocal leukoencephalopathy.

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1. Progressive Multifocal Leukoencephalopathy

Natalizumab therapy increases the risk of opportunistic infections, including progressive multifocal leukoencephalopathy (PML), a rare opportunistic viral infection of the brain that usually leads to death or severe disability.
Opportunistic infections are microbial infections that usually do not cause harm but can cause disease in patients with weakened immune system. Examples include mycobacterial infections of the lung, candidiasis and spreading of various viral infections.

PML has been reported in patients on natalizumab treatment and up to 6 months after the last dose of natalizumab was administered. Both patients and their caregivers should be alerted of the symptoms that may indicate early onset of PML and be through the treatment duration and also until 6 months after the treatment with natalizumab has been discontinued (see Appendix 1 and 2, Patient Alert Card and Treatment Forms).

If an opportunistic infection is suspected, treatment with natalizumab must be suspended until it can be excluded through additional medical evaluations.

1.1 General Epidemiology of PML

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PML is an opportunistic infection of the central-nervous system (CNS) caused by the John- Cunningham (JC) virus that attacks the nervous system, and almost only occurs in immunocompromised patients. Principally, the reactivated JC virus attacks cells responsible for making myelin, preventing nerves from properly transmitting signals. As of today, PML cannot be prevented nor are there any existing therapies for it once it occurs. There have been reports of PML cases also in patients with autoimmune diseases and organ transplant patients, who have received treatment with immunosuppressants.

PML is a fatal demyelinating disease caused by reactivation of JC virus (JCV), a human polyomavirus (Wollebo et al. 2015). Initial infection with JCV is thought to occur during childhood, thereafter the virus persists primarily in the kidneys. Infection with the virus itself does not cause the disease. However, two factors are thought to lead to a pathogenic form that can pass the brain barrier and infect the CNS:

- Mutations in the noncoding region and then the capsid protein-coding region of the viral deoxyribonucleic acid (DNA). When coupled with an impaired immune system, reactivation of JCV can occurand result in PML.

A seroprevalence study utilising the serum anti-JCV antibody assay (STRATIFY JCV®), the prevalence of anti-JCV antibodies was demonstrated to be around 55% in over 6000 patients with Multiple Sclerosis (MS). In addition, looking at the prevalence of anti-JCV antibodies in MS patients across the European Union (EU), ranges from 48.8-69.5% were reported, regardless of

treatment (Bozic et al. 2014). Moreover, it was found that the anti-JCV antibody prevalence increased with age and was lower in female than in male MS patients in all tested cohorts (Bozic et al. 2014). These findings are in correlation with the prevalence reported in the literature from studies in healthy adults using similar methodologies (Bozic et al. 2014). These studies have shown that in general the prevalence of anti-JCV antibody did not appear to be affected by known risk factors of natalizumab treatment like prior exposure to natalizumab, duration of natalizumab treatment and prior immunosuppressant use (Bozic et al. 2014).

Furthermore, additional systematic reviews and studies reported anti-JCV antibody prevalence in the MS population varying between 40-70%, depending on the geography (Paz et al. 2018, Correia et al. 2017, Tan et al. 2010).

1.2 Pathology

Replication of JCV in the brain causes a lytic infection of oligodendrocytes resulting in the widespread destruction of myelin. Microscopic lesions develop in the subcortical white matter, which enlarge and may coalesce with a characteristic pattern on magnetic resonance imaging (MRI) examination.

Besides oligodendrocytes, JCV can also infect cerebellar granule cell neurons, resulting in JCV granule cell neuronopathy (GCN). JCV GCN is associated with mutations in the C-terminus of the JCV VP1 gene, coding for the major capsid protein. JCV GCN can occur in isolation or in combination with PML. There have been very rare reports of JCV GCN in patients receiving natalizumab [Agnihotri 2014; Schippling 2013].

1.3 PML and Natalizumab

During extended premarketing authorisation trials, 2 cases of PML were reported in patients with MS and a full safety evaluation revealed 1 additional case in a clinical trial patient with Crohn's disease [Yousry 2006]. Patients with confirmed PML in the postmarketing setting are followed up for up to 24 months following diagnosis. Of the 839 natalizumab-treated patients with confirmed PML through 7th Aug 2020, the survival rate was 76% (634 patients are alive), and the mortality rate was 24% (205 patients died).

1.4 Risk Factors for developing PML

These factors should be considered in the context of expected benefit when initiating and continuing treatment with natalizumab.

- **The presence of anti-JCV antibodies in blood or serum**
  Patients who tested positive for anti-JCV antibody in blood or serum are at a higher risk of developing PML compared to patients who are anti-JCV antibody negative. However, PML only occurs in a minority of patients who are anti-JCV positive because JCV infection is only one of several steps required for the development of PML. Usage of anti-JCV antibody testing-with a validated assay is of major importance for assessment of the PML risk in positive-tested patients in combination with the other two identified risk factors.

- **Natalizumab treatment duration**
  The risk of PML is increased with duration of the treatment with natalizumab, particularly beyond 2 years

- **Previous treatment with immunosuppressants**
  Patients who had received treatment with an immunosuppressant (IS) prior the treatment with natalizumab have a higher risk of PML.

The risk of developing PML is higher in patients with all three risk factors. In patients who have received natalizumab treatment for more than 2 years, have an increased amount of JCV antibodies in their blood but:

1. The risk of developing PML is higher in patients with all three risk factors (anti JCV antibodies positive + Natalizumab therapy >24 months + previous immunosuppression with other IS)

2. In patients who have received natalizumab treatment for more than 2 years, have an increased amount of JCV (but without previous IS use) antibodies in their blood.

3. In the patients who have never taken IS before starting natalizumab, if the baseline anti-JCV antibodies level is higher there is a higher risk of developing PML as compared to those having baseline low antibody levels since patients who **have received** IS previously have a higher risk of PML.

Starting treatment with natalizumab, the risk of developing PML is higher in those with high anti-JCV antibody levels compared to those with lower antibody levels (Ho et al 2017).

High clinical vigilance for PML is important and should be maintained in all natalizumab-treated patients, regardless of if the PML risk factors are present, for the duration of the treatment and for 6 months upon discontinuation.

In the retrospective analysis published by Ho and colleagues, anti-JCV antibody status and values as well as prior immunosuppressant use and duration of natalizumab treatment, were incorporated into PML risk estimates algorithm, which may support prediction of PML risk in patients on natalizumab therapy for multiple sclerosis (Ho et al. 2017).

In summary the following stratification was proposed:

The PML Risk Estimates provided in Figure 1 are based on anti-JCV antibody index data obtained from use of the STRATIFY JCV DxSelect assay.

- **For anti-JCV antibody-negative patients:** PML risk estimates are based on data from approximately 125,000 natalizumab-exposed patients where the estimated incidence of PML for anti-JCV antibody-negative patients is 0.1/1000. Anti-JCV antibody-negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status, or a false negative test result.

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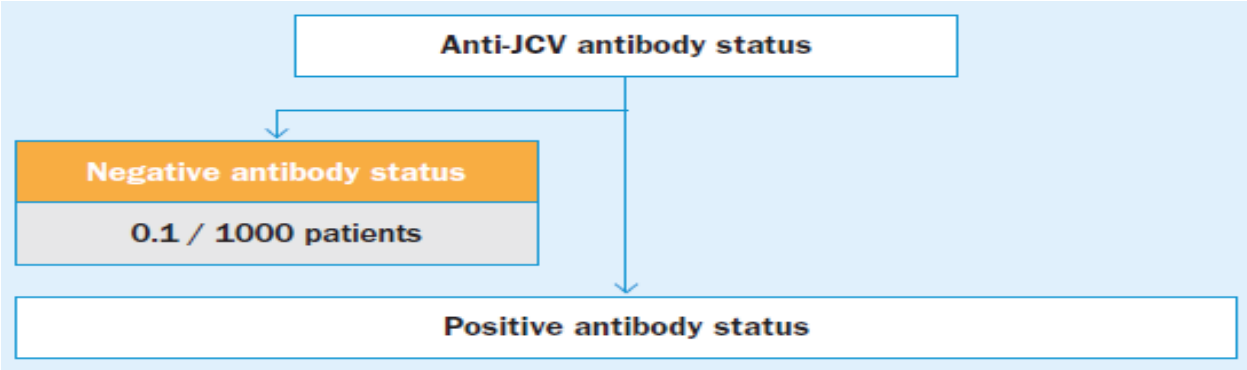
- **For anti-JCV antibody-positive patients:** Risk estimates were derived using the Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical trials. The risk estimates from the Life Table Method are forward-looking in yearly intervals: for example, the risk estimate corresponding to the 25- to 36-month natalizumab exposure period is the PML risk estimated for the following year in patients treated with natalizumab for 24 months. The individual treatment length of each patient takes drop-outs into account (e.g., treatment discontinuation). A higher anti JCV antibody index is associated with an increased risk of PML.

- **For anti-JCV antibody-positive patients who have used IS previously:** These patients are at an increased risk of PML because prior IS use is recognised as an independent risk factor for PML. PML risk estimates for this patient population are based on natalizumab clinical trial data where prior IS use comprised the following 5 IS therapies: mitoxantrone, methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil. The exact mechanism by which prior use of these 5 IS therapies lead to an increased PML risk during natalizumab treatment is unknown. In patients with prior IS, current data do not show an association between higher index and PML risk. The underlying biological explanation for this effect is unknown. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior use of IS was derived from combining the overall yearly risk with the antibody index distribution. The PML Risk Estimates provided in Figure 1 are based on anti-JCV antibody index data obtained from use of the STRATIFY JCV DxSelect assay.



Natalizumab exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use
	No index value	Antibody index ≤ 0.9	Antibody index > 0.9 ≤ 1.5	Antibody index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

Figure 1: PML Risk Estimates Algorithm

IS = immunosuppressant; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy. Exposure is shown up to 72 months only as data beyond 6 years of treatment are scarce.

An additional anti-JCV antibody assay, ImmunoWELL™ JCV IgG test, has been developed. The comparison between STRATIFY JCV®DxSelect® *, and ImmunoWELL JCV IgG tests indicates a potential offset of up to 0.1 in index values (e.g. lower range: ≤ 0.8, higher range: > 1.4 in the table above) when using the ImmunoWELL™ JCV IgG test.

*STRATIFY JCV® is a trademark of Biogen MA Inc. DxSelect® is a trademark of DIASORIN S.p.A.

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- **Extending the Dosing Interval for PML Risk Mitigation**

It should be noted that the only approved dosing interval for natalizumab is 300 mg administered once every 4 weeks (Q4W, standard interval dosing (SID)). Refer to the SmPC Section 4.2 (Posology and method of administration) for the currently approved dosing.

1.5 Monitoring of the patient

Natalizumab patients should be regularly supervised by their specialized physicians. Following monitoring steps are **recommended**:

- **Testing intervals before starting treatment:**
  Every 6 months for antibody-negative patients to monitor for seroconversion.
  Every 6 months for antibody-positive patients during long-term treatment (>24 months).

- **Significance of antibody index values:**
  Low index: Lower PML risk.
  High index: Elevated PML risk, requiring close monitoring.

Anti-JCV antibody testing provides supportive information for risk stratification of treatment with natalizumab. Therefore, it is recommended that anti-JCV antibody status is tested prior initiating natalizumab treatment or in patients with unknown antibody status. It is important to know that anti-JCV antibody negative patients may still be at risk of PML infections due to changing antibody status, a new infection with the JC virus or a false negative test result. It is recommended that anti-JCV antibody negative patients are re-tested every 6 months. Patients with low anti-JCV antibody levels who have not used immunosuppressant treatment previously should be re-tested every 6 months once a time point of 2 years is reached. This also informs about suitable radiological monitoring with MRI.

In an international cohort retrospective study of natalizumab-treated patients it was observed that a positive JCV seroconversion occurred at a rate of 7.3%, which is slightly higher to observations reported in other clinical studies for natalizumab (Dwyer et al. 2021).

In case the anti-JCV antibody test is positive, that patient should be considered to be at a higher risk of PML at any time, regardless of any prior or subsequent antibody test results.

Testing should only be performed using a suitable and validated anti-JCV antibody ELISA assay and it should not be used for PML diagnosis. A commonly used plasmapheresis/plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) in PML-suspected patients, can affect the meaningful interpretation of anti-JCV antibody testing in the serum. Moreover, patients should not be tested for anti-JCV antibodies within the two weeks of PLEX due to removal of the antibodies from the serum, or also within six months of IVIg therapy (i.e. 6 months = 5x half-life of immunoglobulins) as this may lead to false test results.

Current evidence suggests that the risk of PML is low at low index values and increases substantially at high index values for patients who have been on treatment with natalizumab for longer than 2 years.

The anti-JCV antibody index values for the PML risk estimation may depend on the type of assay used for anti-JCV antibody testing. For testing using STRATIFY JCV® DxSelect® *, Ho et al. 2017 published a risk estimate guidance with index values defined for natalizumab-treated patients based on data from > 20.000 MS patients, see Figure 1.

- **MRI surveillance for early detection of PML**

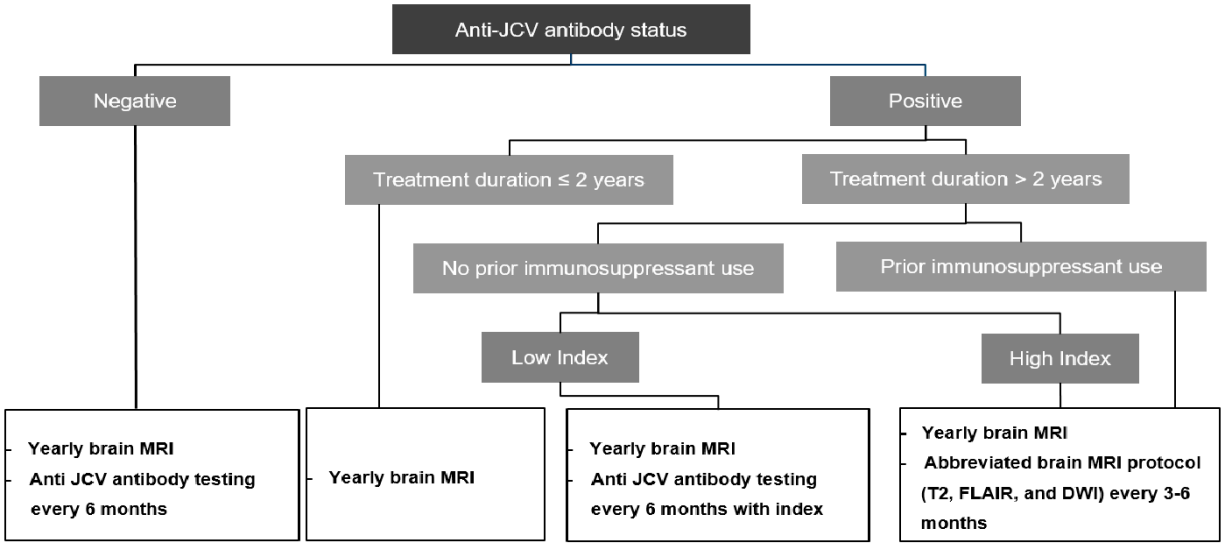
  - **MRI Protocoles,**
    Baseline MRI before starting Natalizumab therapy (no older than 3 months).
    Routine annual MRI for all patients.
    Frequent MRI (every 3-6 months) for high-risk patients (e.g., anti-JCV antibody-positive, treatment >2 years, or prior immunosuppressant use).

  - **Specify imaging techniques, including:**
    T1-weighted, T2-weighted, FLAIR, and diffusion-weighted imaging (DWI).
    Use of gadolinium contrast to identify inflammatory features.

MRI is a useful method for monitoring of patients with MS in clinical practice. It may help in distinguishing actual PML lesions from MS lesions in patients who develop unusual neurological symptoms on natalizumab therapy (Berger et al 2013). MRI findings may be apparent before clinical signs or symptoms suggestive of PML. Therefore, regular MRI screening in patients with increased risk of PML is recommended as it may enable earlier diagnosis of PML and improved clinical outcomes (Prosperini et al. 2016, Wattjes et al. 2015, Scarpazza et al. 2020).
In summary the following MRI monitoring is recommended (Wattjes et al. 2021, Scarpazza et al. 2020):

- Before treatment initiation with natalizumab, a recent MRI, within 3 months, should be available as a baseline reference and be repeated regularly at least on a yearly basis . The yearly full MRI should be evaluated for any signs of PML in all patients on natalizumab treatment.
- Patients with a higher PML risk should: Reinforce the need for continued vigilance for PML signs for 6 months post-treatment, especially in high-risk patients. Recommend scheduled MRIs every 3-6 months during this period for at-risk individuals.
- Patients who have all 3 risk factors for developing PML this includes (anti-JCV antibody positive status, natalizumab treatment for more than 2 years and prior immunosuppressant therapy) and patients with high anti-JCV antibody index who have been on natalizumab therapy for over 2 years without prior immunosuppressant use.
- At first signs of any symptoms indicating PML

Figure 2: Summary of recommended patient monitoring



DWI= diffusion weighted imaging; FLAIR= fluid-attenuated inversion recovery, JCV= John Cunnigham Virus; MRI= magnetic resonance imaging

Table 1: Recommended MRI protocols

Scanner field strength > 1.5 T, slice thickness ≤ 5 mm with no gap and with whole brain coverage. Axial images prescribed from the subcallosal line

Full MRI protocol[1]	Abbreviated MRI protocol[2]
➢ Sagittal and axial 2D FLAIR or 3D FLAIR ➢ Axial FSE proton density/T2 ➢ Axial DWI with ADC ➢ Axial SE T1-weighted pre- and post contrast or 3D T1-weighted pre- and post-contrast ➢ Gd injection 0.1 mmol/kg over 30 seconds ➢ 5 minute delay after contrast injection	➢ Sagittal and axial 2D FLAIR or sagittal 3D FLAIR with axial and coronal reformat ➢ Axial FSE proton density/T2 ➢ Axial DWI with ADC

[1] Baseline and routine annual scans for all patients.
[2] Safety monitoring in high-risk patients.

2D = 2 dimensional; 3D = 3 dimensional; ADC = apparent diffusion coefficient; DWI = diffusion weighted imaging; FLAIR = fluid-attenuated inversion recovery; FSE = fast spin echo; Gd = gadolinium; MRI = magnetic resonance imaging; SE = spin echo

Reference: Wattjes et al 2021.

If MRI lesions suggestive of PML are detected, the full MRI protocol should be extended to include contrast-enhanced T1-weighted imaging to detect inflammatory features and the possible coincidence of PML and PML-immune reconstitution inflammatory syndrome (IRIS), particularly during follow-up. It is also recommended that upon request for follow-up MRI, treating physicians inform radiologists that PML or other opportunistic infections are being considered in the differential diagnosis.

Recommend systematic neurological evaluations at every infusion visit.
Highlight early signs and symptoms of PML or other neurological changes, such as:
Subtle behavioral or cognitive impairments.
New or worsening sensory/motor deficits.
Visual disturbances.

1.6 PML Diagnosis

PML diagnostic criteria were published by the American Academy of Neurology as a consensus statement and requires clinical, radiographic, and virologic findings or typical histopathological findings and the presence of JCV (Berger et al. 2013). These criteria preclude the need for a brain biopsy but require suitable clinical and MRI findings plus detection of JCV DNA in the cerebrospinal fluid (CSF) determined by polymerase chain reaction (PCR) method for an explicit PML diagnosis; however, based on an alternative classification system, physicians are advised that in natalizumab-treated patients with MS, diagnosis of PML can be considered confirmed in the absence of clinical symptoms (Dong-Si et al. 2014)

Necessary considerations

- All natalizumab treated patients should have regular clinical follow-up to allow for early detection of changes in neurological status. **If any new neurological symptoms develop in patients treated with natalizumab, PML should always be considered as a diagnosis.**
- Patients, their partners and caregivers need to be advised of symptoms that may be indicative of early PML (see Patient Alert Card and Treatment Forms) and receive counselling on the need to pay attention for these symptoms while the patient is receiving natalizumab therapy and for approximately 6 months after the last dose of natalizumab (PML has been reported up to 6 months after the last dose of natalizumab in patients who did not have findings suggestive of PML at the time of discontinuation).
- **Natalizumab must be withheld and not restarted until non-MS pathology has been confidently excluded, in all cases where further investigation of change in neurological status or change in brain MRI is determined Dosing with natalizumab should only be restarted when the diagnosis of PML is confidently excluded (if necessary, by repeating clinical, MRI, and laboratory investigations if suspicion of PML remains).**
- The decision to withhold natalizumab may be based on the initial clinical presentation, MRI findings, the evolution of symptoms or signs, and/or the response to corticosteroid treatment.
- **Natalizumab should be permanently discontinued if PML is confirmed.**

Clinical assessment

Risk stratification framework, such as:
Low-risk: Anti-JCV antibody-negative patients.
Intermediate-risk: Antibody-positive with a low index and short treatment duration (<24 months).
High-risk: Antibody-positive with a high index, prolonged treatment, and/or prior immunosuppressant use. Offer clear clinical decision-making pathways based on risk stratification.

Any new or recurrent neurological symptoms should require immediate and careful evaluation in order to ascertain the underlying pathology. In a patient with stable MS disease activity on natalizumab, such changes warrant a clinical suspicion of PML (or other opportunistic infection). It is important to note that the presence of new onset neurologic symptoms is not required to diagnose PML (in the setting of other confirmatory evidence) and cases of asymptomatic PML have been reported. In both high- and low- risk asymptomatic patients, any new suspected lesion on MRI should be carefully evaluated, particularly when an abbreviated protocol has been performed (see Section 'MRI differentiation between PML and MS relapse'). **Table 2** highlights the clinical features that may help differentiate MS lesions from PML. It should be noted that the table is not all inclusive and that symptomatic overlap between symptoms of these conditions exists. **Physicians should be aware that the clinical characteristics of PML or other opportunistic infections can be difficult to distinguish from MS, especially early in the evolution of PML.** The history and pattern of previous and current symptoms and signs are important to note and will facilitate the management of patients.

Table 2: Clinical Symptoms of MS and PML

Onset	Symptoms	
	MS	PML
	Acute	Subacute
Evolution of symptoms	➢ Over hours to days ➢ Typically stabilize ➢ Spontaneously resolved even without treatment	➢ Over weeks ➢ Progressive
Presenting clinical features	➢ Paresthesia ➢ Diplopia ➢ Paraparesis ➢ Myelopathy ➢ Optic neuritis	➢ Aphasia ➢ Ataxia (esp. for GCN) ➢ Behavioural or cognitive changes and neuropsychological alteration ➢ Retrochiasmal visual deficits ➢ Noticeable weaknesses ➢ Hemiparesis ➢ Sensory deficits ➢ Vertigo ➢ Seizures

GCN = granule cell neuronopathy; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Note: PML may present with other clinical features not specified in this table. PML can be detected by MRI prior to the onset of clinical features. Some overlap of clinical features of MS and PML may occur. (Vermersch et al. 2011, Berger et al. 2013, Kappos et al 2011, Clifford et al. 2010)

If PML is considered in a differential diagnosis, further investigations, including MRI evaluation **(Table 3)** and lumbar puncture and CSF evaluation, should be undertaken as soon as possible. Natalizumab dosing should be withheld until PML (or another opportunistic infection) can be ruled out.

JCV GCN symptoms are similar to symptoms of PML (i.e. cerebellar syndrome). In JCV GCN, serial MRI of the brain shows severe progressive cerebellar atrophy over several months and JCV DNA is detected in the CSF (Aginthori et al. 2014). Natalizumab therapy should be withheld if JCV GCN and/or PML is suspected and permanently discontinued if a diagnosis of JCV GCN and/or PML is confirmed.

1.7 Differentiation between PML and MS relapse with MRI

A complete MRI protocol (see **Table 1**), preferably with and without contrast for the follow-up of patients receiving natalizumab, is recommended to achieve the best possible images to assist with clinical decision making (Yousry et al. 2012, Wattjes et al. 2021). The most sensitive sequence or detection of PML is the Fluid-attenuated inversion recovery (FLAIR) (Wattjes et al. 2015). Diffusion-weighted imaging sequences may also be helpful in differentiating new lesions from chronic MS plaques and MRI changes from a previous scan (Wattjes et al. 2021). The MRI sequence parameters for each scanner should be selected for favorable representation of CNS anatomy and visualisation of MS lesions. Using the standard MRI protocol consistently helps recognizing early CNS changes on MRI (**Table 3**).

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Table 3: MRI Characteristics

Shown are features to be considered in the differential diagnosis of MS and PML.

Feature	MS	PML
Atrophy	Diffuse atrophy with progressive MS disease.	Post PML-IRIS –encephalomalacia and diffuse brain atrophy in the affected areas.
Contrast enhancement in acute lesions	Homogenous nodular, ring or open ring enhancement conforms to shape and size of the lesion. Resolution over 1-2 months.	43% of lesions show enhancement at the time of presentation. Patchy or nodular appearance. Enhancement does not conform to size or shape of the lesion. Increased enhancement with IRIS.
DWI	Acute lesions hyperintense. Chronic lesions isointense.	Acute lesions hyperintense. Distinguishes new PML lesions within areas of chronic white matter disease. No restriction on ADC.
FLAIR images	Hyperintense, sharply delineated	Hyperintense. Most sensitive sequence for PML detection.
Lesion location	Focal, periventricular, or deep white matter. Lesions occur in all areas of the brain, optic nerves, and spinal cord.	Asymmetric, focal, or multifocal. Subcortical or diffuse white matter, cortical grey matter, and deep grey matter, brainstem, middle cerebellar peduncles. PML is not seen in spinal cord or optic nerves.
Lesion shape and borders	Ovoid or flame shape, sharp borders, often perilesional edema	Irregular shape, finger-like projections toward the cortex. III-defined border toward the white matter, sharp border toward the grey matter.
Mass effect	Yes (Large acute lesions may have mass effect.)	No.
Mode of extension	Initial enlargement over days or weeks and decrease in size within months.	Progressive increase in size.
T1-weighted images	Acute lesions: hypointense or isointense. Increasing signal intensity over time.	At onset isointense to hypointense with decreasing signal intensity over time.
T2-weighted images	Homogenous hyperintensity with surrounding edema.	Diffuse hyperintensity often with punctate microcystic inclusions. Perilesional nodules in the vicinity of the primary lesion (“Milky Way galaxy”).

ADC = apparent diffusion coefficient; DWI = diffusion -weighted imaging; FLAIR = fluid -attenuated inversion recovery; IRIS = immune reconstitution inflammatory syndrome; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy. References: Vermersch et al. 2011, Kappos 2011, Wattjes and Barkhof 2014, Wattjes et al. 2021, Yousry et al. 2012.

Additional support with regards to MRI analysis for PML diagnostic purposes is available and could be provided by the company.

Laboratory examination

Detecting JCV DNA in the CSF using PCR confirms the diagnosis of PML in patients with relevant and associated MRI findings. Nevertheless, a negative JCV PCR result should not rule out a possible diagnosis of PML, especially because small volume lesions may correspond to lower viral copy numbers (Wijburg et al. 2018). If there is no detection of JCV DNA in CSF and if clinical or MRI-based suspicion of PML persists despite a local or reference laboratory result is negative (i.e. not detected) for JCV DNA by PCR, a repeat lumbar puncture is recommended. Brain biopsyto detect JCV should be considered if JCV DNA is not detected in CSF on repeat testing. The sensitivity of the assay can be critical for determining the diagnosis (Berger et al. 2013).

1.8 PML Management

Immune reconstitution

Early PML recognition is important for an optimal clinical outcome (Clifford 2015, Kappos et al. 2019). Treatment of PML requires reconstitution of the immune system, i.e. removal of natalizumab (Tan et al. 2010). Plasma exchange method PLEX and/or immunoadsorption (IA) has been reported for rapid removal of natalizumab from the body with the intention of accelerated repairing of CNS immunosurveillance. However, a retrospective analysis of natalizumab-treated patients has shown that no difference was observed regarding 2-year survival after PML diagnosis between patients who received PLEX and those who did not (Kappos et al. 2019). Physicians should use medical judgement when considering the use of PLEX to treat PML. And, if PLEX is used, patients should be closely monitored for the development of IRIS (see section 'Treatment of Immune Reconstitution Inflammatory syndrome (IRIS)), a condition that occurs more rapidly in almost all patients treated with PLEX compared to patients who are not (Carruthers and Berger 2014, Clifford et al. 2010).

Use of Antivirals and others

No clinical trial has demonstrated a beneficial effect of antiviral agents when it comes to the management of PML thus far. PML outcomes from real-world reports where antivirals and other therapies such as G-CSF growth factors (i.e., filgrastim) or anti-PD1 checkpoint inhibitors (i.e., pembrolizumab) were used, are mixed and inadequate to recommend any treatment approach (Kappos et al. 2019, Williamson and Berger 2017, Cortese et al. 2019).

Immune Reconstitution Inflammatory syndrome (IRIS)

IRIS occurs in almost all natalizumab-associated PML patients after withdrawal or removal of the medicine (Berger 2011). IRIS is thought to result from the rebound of immune function in patients who developed PML, which can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS and appropriate therapy of the associated inflammation during recovery from PML should be undertaken.

IRIS is generally suspected when patients with PML show signs of clinical worsening mostly, but not necessarily, accompanied by gadolinium enhancement of PML lesions with or without mass effect on brain MRI. The clinical worsening is a result of a local inflammatory reaction, including edema, and manifests as a worsening of neurological symptoms including hemiparesis, ataxia, speech abnormalities, visual disturbance, cognitive/behavioural changes, and seizures (dependent on the site of IRIS). Severe consequences can occur including coma and death. It is also possible that due to the breakdown of the BBB and release of JCV from cells lysed during IRIS, it can be increased, although JCV viral load in the CSF might be expected to decline in the setting of IRIS.

The active immune reaction may become necessary to be treated in order to prevent potential damage caused by IRIS (Elston and Thaker 2009), however it can become life-threatening and may therefore require management in an intensive care unit. Therefore, following PLEX or IA, periodic clinical monitoring of patients, including MRI monitoring, may be useful for the early detection of IRIS. The diagnosis and management of IRIS is a controversial issue and there is no consensus concerning its treatment. However, it has been suggested that corticosteroids may be useful for treatment of IRIS, particularly in patients with severe to life-threatening IRIS (Clifford 2015, Tan et al. 2010).

The following steroid regimens have been reported for the treatment of IRIS in the literature:

- Oral prednisone 1.5 mg/kg/day for 2 weeks with a taper over 2 months.
- Intravenous methylprednisolone (1 g/d for 3 or 5 days) with oral taper over 2 months (Williamson and Berger 2017).

If further deterioration occurs during the steroid taper and this is judged to be due to continuing or new inflammatory reactions, a further course of higher dose steroids may be necessary.

Prophylactic steroid treatment is currently not recommended (Antoniol 2012, Scarpazza 2017).

1.9 PML Prognosis

Following factors have been associated with improved PML survival in patients after natalizumab therapy: a younger age at PML diagnosis, less functional disability before PML diagnosis, a lower JCV load at PML diagnosis, and more localised brain involvement on MRI at diagnosis (Dong-Si et al. 2015). In addition, at PML diagnosis, asymptomatic patients have been reported to have better survival and less functional disability than symptomatic patients (Dong-Si et al. 2014, Prosperini et al. 2016). For information on outcomes associated with PLEX, see section `Management of PML´.

Improved survival from PML after natalizumab therapy has been associated with a younger age at PML diagnosis, less functional disability before PML diagnosis, a lower JCV load at PML diagnosis, and more localised brain involvement on MRI at diagnosis [Dong-Si 2015].
Furthermore, asymptomatic patients at PML diagnosis have been reported to have better survival and less functional disability than symptomatic patients at PML diagnosis [Dong-Si 2014; Prosperini 2016]. For information on outcomes associated with PLEX, see Section 2.8.

1.10 Diagnosis of PML after Discontinuation of Natalizumab

PML has been reported after the discontinuation of natalizumab. Patients and physicians should remain alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months after discontinuation, taking into account the switch to other MS disease-modifying treatments that are associated with a risk of PML.

As of 7th August 2020, a total of 102 confirmed cases of PML have been reported in patients where PML onset occurred more than 4 weeks after the last natalizumab infusion. Of the 102 cases where time from last infusion to onset of PML is known, the majority of cases (80.0%) occurred either prior to or within 3 months of the last infusion, and 101 cases (99%) occurred within 6 months of the last infusion.

II. Educational Guidance

The benefits and risks of natalizumab therapy should be individually reconsidered by the specialist physician and the patient due to this increased risk of developing PML with increasing treatment duration. The patient should be reinformed about the risks of PML with natalizumab after 24 months of treatment and should be instructed together with their partners and caregivers on early signs and symptoms of PML.

Patients who are discontinuing natalizumab therapy should also be informed that cases of PML have occurred in patients up to 6 months after the last dose of natalizumab, hence the same monitoring protocol should be continued for approximately 6 months after discontinuation of natalizumab.

Patients should also be informed of the increased risk of opportunistic infections.

A template Treatment Initiation Form, Treatment Continuation Form, and Treatment Discontinuation Form are provided in Appendix 2.

Clarifying the benefits and risks to the patients

The PL explains both benefits and risks in a patient-friendly language for better understanding.
It is enclosed to every TYRUKO pack and it is also available on

https://sdi.sfda.gov.sa/Home/DrugSearch?textFilter

Treating physicians should advice patients on the importance of undisturbed dosing, particularly in the early months of treatment.

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Pregnant women should be advised on the use of natalizumab during pregnancy taking into account the patient's clinical condition. This benefit- risk conversation should also cover the possible return of disease activity after discontinuing treatment with natalizumab. The newborn should be monitored for potential haematological abnormalities for patients exposed to natalizumab in the third trimester.

Moreover,for a Treatment Initiation Form, a Treatment Continuation Form at 24 months of treatment, and a Treatment Discontinuation Form describing specifically the risk of PML with natalizumab therapy and the importance of monitoring for PML are provided in Appendix 2. These forms should be signed, provided to and discussed with patients before initiation of treatment, after patient counselling at 24 months of treatment, and after discontinuation to ensure that patients are fully informed about the risk of PML. The physician should retain 1 copy of these forms, and 1 copy should be given to the patient.

Patient Alert Card

The Patient Alert Card must be issued to patients to fill out and they need to be instructed to carry the card with them. Their partners and caregivers should also be made aware of the information provided in the Patient Alert Card. The Patient Alert Card has also a recommendation for patients to keep the card for a period of 6 months after the last dose of natalizumabtreatment, because signs and symptoms suggestive of opportunistic infections, including PML (e.g. changes in mood, behaviour, memory, motor weakness, speech, or communication difficulties) may occur up to 6 months after discontinuation. Patients and their partners and caregivers should report any suspect changes in neurological status during this time.

The card contains a space for contact information so that these concerns can be reported.

Treating physician must complete this section when issuing the card for a patient.

Patient Alert Cards (see Appendix 1) are included as part of the Physician Pack.

Additional cards can be ordered from ***patient.safety.sau@sandoz.com***

The card contains a space for contact information so that these concerns can be reported

Treating physician must complete this section when issuing the card for a patient. _

Patient Alert Cards (see Appendix 1) are included as part of the Physician Pack.

Additional cards can be ordered from ***patient.safety.sau@sandoz.com***

Treatment Forms

Treatment forms (see Appendix 2) are included as part of the Physician Pack.

Additional forms can be ordered from ***patient.safety.sau@sandoz.com***

The SmPC and PL are available from ***https://sdi.sfda.gov.sa/Home/DrugSearch?textFilter***

Reporting of side effects:

It is important that you tell your doctor if you have any side effects. This also includes any probable side effects, which are not yet listed in the patient leaflet. You can also report side effects directly via the national reporting system.

Sandoz reporting adverse events:
Email: adverse.event.sau@sandoz.com
Website: https://pvi1j.solutions.iqvia.com/pvi-web/

Saudi Food and Drug Authority National Pharmacovigilance Center
Unified Contact Center: 19999
Email: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

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2. Appendix 1

SANDOZ

Natalizumab 300 mg
Concentrate for solution for infusion

Patient Alert Card

Active substance(s) (INN or common name):	Natalizumab
Product(s) concerned (brand name(s)):	Tyruko®
Document status:	Final
Applicable RMP version number:	1.2
Date of Education material:	9-May-2023

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PATIENT ALERT CARD

This card contains important safety information that you need to be aware of before you are given TYRUKO (natalizumab), during treatment and after stopping treatment with TYRUKO. TYRUKO increases the risk of a rare brain infection called progressive multifocal leukoencephalopathy (PML). Please carry this card with you.

- Present this TYRUKO alert card to all doctors you see, not only to your neurologist at a hospital, but also if you go to the Emergency Room, or to any other healthcare professional that is not your usual treating team (i.e., Neurologist, MS or Infusion Nurse).
- Carefully read the TYRUKO Patient Leaflet before starting your treatment.
- This alert card should be kept with you during your treatment with TYRUKO. It is important that you keep this card for at least 6 months after you have received the last dose of TYRUKO, because side effects may occur even after the treatment with TYRUKO is stopped.

Present this card to your partner or caregivers because they might see PML symptoms that you might not recognize such as changes in your mood or behavior, memory failure and difficulties with speech and communication. Symptoms might occur for up to 6 months after discontinuing treatment with TYRUKO. It is important you and your partner or caregivers remain aware of these symptoms this whole time.

Before starting the treatment with TYRUKO following evaluations need to be considered:

- If you have a severe problem with your immune system, you should not be treated with TYRUKO
- While you are getting the treatment with TYRUKO, you should not take any other multiple sclerosis medicines for a longer term

During treatment with TYRUKO

Risk of Progressive Multifocal Leukoencephalopathy (PML)

Natalizumab is thought to increase the risk of PML, a rare brain infection, which has occurred in patients who have been on natalizumab therapy. PML commonly results in severe disability or death.

The PML risk emerges with the duration of natalizumab treatment, especially after 2 years.

PML symptoms may prevail like a Multiple Sclerosis (MS) relapse. That is why it is very important that you call or see your doctor at the earliest if you feel your MS is worsening or if you notice any new symptoms during and for up to 6 months after stopping your TYRUKO treatment. Symptoms of PML normally develop slower (over days or weeks) than those related to a MS relapse, however they may be comparable to your MS symptoms.
It is important to be aware of the following PML signs

- Changes in behavior
- Changes in concentration and mental capacity
- Problems with your vision
- Muscle weakness on one side of the body
- New neurological symptoms that you have not experienced before

Management of PML

Management of PML requires an immediate stop of TYRUKO treatment.

Be aware of symptoms of other serious infections

Further serious infections may also occur with natalizumab treatment. You should call or see your doctor at the earliest convenience if you think you are experiencing signs of a persistent, severe infection, for example constant fever.

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Contact Details

Patient:

Name:

Date TYRUKO started:

Treating Doctor:

Name:

Phone:

Start date of TYRUKO treatment:

Reporting of side effects:

It is important that you tell your doctor if you have any side effects. This also includes any probable side effects, which are not yet listed in the patient leaflet. You can also report side effects directly via the national reporting system.

Sandoz reporting adverse events:
Email: adverse.event.sau@sandoz.com
Website: https://pvi1j.solutions.iqvia.com/pvi-web/

Saudi Food and Drug Authority National Pharmacovigilance Center
Unified Contact Center: 19999
Email: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

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3. Appendix 2

SANDOZ

Natalizumab 300 mg
Concentrate for solution for infusion

Treatment Initiation Form

Active substance(s) (INN or common name):	Natalizumab
Product(s) concerned (brand name(s)):	Tyruko®
Document status:	Final
Applicable RMP version number:	1.2
Date of Education material:	9-May-2023

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SANDOZ

TYRUKO (natalizumab)

TREATMENT INITIATION FORM

Please read this form carefully before initiating treatment with TYRUKO. This form provides advice and information to ensure that you understand the important adverse effects of natalizumab treatment such as risk of PML (progressive multifocal leukoencephalopathy), IRIS (immune reconstitution inflammatory syndrome) and others.

You should do the following before starting the treatment with TYRUKO:

- **Read the Patient Leaflet**
- **Have a discussion with your doctor about the benefits and risks associated with this treatment.**
- **Read the Patient Alert Card**

PML is a rare brain infection that has occurred in patients receiving natalizumab therapy, which can lead to severe disability or death. Both Patient Leaflet and Patient Alert Card provide important safety information about PML.
John-Cunningham (JC) virus is a common virus, which infects many people but usually does not cause a harmful illness. The reason for the uncontrolled increase of JC virus in the brain resulting in PML in some patients treated with natalizumab is unknown.

The risk of developing PML in natalizumab-treated patients is higher:

- If you have presence of antibodies against JC virus in your blood
- when treatment with natalizumab is longer, especially beyond 2 years
- If you have previously been treated with a medicine that reduces the activity of your immune system (an immunosuppressant medicine) before starting treatment with natalizumab.

The potential PML risk should be discussed between you and your doctor before you start treatment with TYRUKO.

Your blood may be tested to check if you have antibodies against JC virus before you start your treatment with TYRUKO. To check if anything has changed the test may be repeated while you are on TYRUKO treatment. The PML risk is higher if:

- you have all three risk factors listed above, or
- if the levels of JC virus antibodies are higher and you have been on natalizumab treatment for more than 2 years, and
- if you have not taken an immunosuppressant medicine prior to starting TYRUKO.

You will be more closely monitored by your doctor if your risk for PML is higher.

Before you start your treatment with TYRUKO and when you have been on natalizumab therapy for more than 2 years, you should discuss with your doctor if TYRUKO is the most suitable medicine for you.

IRIS (immune reconstitution inflammatory syndrome) is a rare reaction, which is likely to occur in patients after being treated for PML, when natalizumab treatment is removed from your body. IRIS may lead to worsening of your condition, including your brain function getting worse.

Every time before getting the TYRUKO treatment you should read the Patient Leaflet as it may have newer information that is important for your treatment.

The Patient Alert Card contains important safety information about any symptoms you may develop, which could indicate PML. You should keep it with you and if appropriate, show it to your partner or caregiver.

Please ask your doctor to provide you with the Patient Leaflet or the Patient Alert Card if you do not have them before starting the treatment with TYRUKO.

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SANDOZ

Patient´s Name (print) _____

Patient's´ Signature_____**Date:**_____

Doctor´s Name (print)_____

Doctor´s Signature_____**Date:**_____

PML risk estimation:

Patients who are anti-JCV antibody negative

If you do not have antibodies against JC virus your chance of getting PML is low (approximately 1 in 10.000 patients), based on global data.

Patients who are anti-JCV antibody positive

Your risk of developing PML will vary when you have antibodies against JC virus and will depend on the duration of the treatment with natalizumab, the level of anti-JCV antibodies and if you have received previous treatment with an immunosuppressant medicine. The potential risk will be discussed with your doctor before starting your treatment.

Reporting of side effects:

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in the patient leaflet. You can also report side effects directly via the national reporting system. By reporting side effects, you can help provide more information on the safety of this medicine.

Sandoz reporting adverse events:
Email: adverse.event.sau@sandoz.com
Website: https://pvi1j.solutions.iqvia.com/pvi-web/

Saudi Food and Drug Authority National Pharmacovigilance Center
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SANDOZ

Natalizumab 300 mg
Concentrate for solution for infusion

Treatment Continuation Form

Active substance(s) (INN or common name):	Natalizumab
Product(s) concerned (brand name(s)):	Tyruko®
Document status:	Final
Applicable RMP version number:	1.2
Date of Education material:	9-May-2023

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SANDOZ

TYRUKO (natalizumab)

TREATMENT CONTINUATION FORM

Please read this form carefully before continuing treatment with TYRUKO for more than 2 years. This form provides advice and information to ensure that you understand the important adverse effects of natalizumab treatment such as risk of PML (progressive multifocal leukoencephalopathy), IRIS (immune reconstitution inflammatory syndrome) and others. Even though you have been receiving TYRUKO or another natalizumab treatment for two years, it is important to remind you that the risk of PML increases beyond this treatment duration.

You should do the following before continuing the treatment with TYRUKO:

- **Read the Patient Leaflet**
- **Have a discussion with your doctor about the benefits and risks associated with this treatment**
- **Read the Patient Alert Card**

PML is a rare brain infection that has occurred in patients receiving natalizumab therapy, which can lead to severe disability or death. Both Patient Leaflet and Patient Alert Card provide important safety information about PML. John-Cunningham (JC) virus is a common virus, which infects many people but usually does not cause a harmful illness. The reason for the uncontrolled increase of JC virus in the brain resulting in PML in some patients treated with natalizumab is unknown.

The risk of developing PML in natalizumab-treated patients is higher:

- If you have presence of antibodies against JC virus in your blood
- Longer treatment with natalizumab, especially beyond 2 years
- If you have previously been treated with a medicine that reduces the activity of your immune system (an immunosuppressant medicine) before starting treatment with natalizumab

The potential PML risk should be discussed between you and your doctor before you continue treatment with TYRUKO.

Your blood may be tested to check if you have antibodies against JC virus before you start or continue your treatment with TYRUKO. To check if anything has changed the test may be repeated while you are on TYRUKO treatment. The PML risk is higher if:

- you have all three risk factors listed above, or
- if the levels of JC virus antibodies are higher and you have been on natalizumab treatment for more than 2 years, and
- if you have taken an immunosuppressant medicine prior to starting TYRUKO.

You will be more closely monitored by your doctor if your risk for PML is higher.

Your doctor should discuss with you if TYRUKO is the most suitable medicine for you before continuing the treatment with TYRUKO for more than 2 years.

IRIS (immune reconstitution inflammatory syndrome) is a rare reaction, which is likely to occur in patients with PML after the treatment for PML, when natalizumab treatment is removed from your body. IRIS may lead to worsening of your condition, including your brain function getting worse.

The Patient Leaflet may have newer information that is important for your treatment and should be read every time before getting the TYRUKO treatment.

The Patient Alert Card contains important safety information about any symptoms you may develop, which could indicate PML. You should keep it with you and if appropriate, show it to your partner or caregiver.

Please ask your doctor to provide you with the Patient Leaflet or the Patient Alert Card if you do not have them before continuing the treatment with TYRUKO.

Patient´s Name (print) _____

Patient´s Signature_____**Date:**_____

Doctor´s Name (print)_____

Doctor´s Signature_____**Date:**_____

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PML risk estimation:

Patients who are anti-JCV antibody negative

If you do not have antibodies against JC virus your chance of getting PML is low (approximately 1 in 10.000 patients) based on global data.

Patients who are anti-JCV antibody positive

Your risk of developing PML will vary when you have antibodies against JC virus and will depend on the duration of the treatment with natalizumab, the level of anti-JCV antibodies and if you have received previous treatment with an immunosuppressant medicine. The potential risk before continuing your treatment will be discussed with your doctor.

Reporting of side effects:

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in the patient leaflet. You can also report side effects directly via the national reporting system. By reporting side effects, you can help provide more information on the safety of this medicine.

Sandoz reporting adverse events:
Email: adverse.event.sau@sandoz.com
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Saudi Food and Drug Authority National Pharmacovigilance Center
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Website: https://ade.sfda.gov.sa

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Natalizumab 300 mg
Concentrate for solution for
infusion

Treatment Discontinuation Form

Active substance(s) (INN or common name):	Natalizumab
Product(s) concerned (brand name(s)):	Tyruko®
Document status:	Final
Applicable RMP version number:	1.2
Date of Education material:	9-May-2023

EU-RMP1.2May2023

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TYRUKO (natalizumab)

TREATMENT DISCONTINUATION FORM

Please read this form carefully before discontinuing treatment with TYRUKO. This form provides advice and information to ensure that you understand and are fully informed of the continued risk of PML (progressive multifocal leukoencephalopathy) for up to 6 months after discontinuation of natalizumab treatment.

Before starting treatment with TYRUKO a Patient Alert Card, which contains valuable information about PML, should have been given to you by your doctor for your reference. You should keep this Patient Alert Card for 6 months following discontinuation of treatment. The card contains important safety information, especially any symptoms you may develop, which could indicate PML, therefore you should keep the Alert Card with you and if appropriate show it to your partner or caregiver. Please ask your doctor to provide you with a Patient Alert Card that you received when starting TYRUKO if you do not have it anymore.

PML is a rare brain infection that has occurred in patients receiving natalizumab therapy and can lead to severe disability or death. PML has been reported up to 6 months after discontinuation of natalizumab treatment.

PML signs include:

- Changes in behavior
- Changes in concentration and mental ability
- Problems with your vision
- Weakness on one side of the body
- New neurological symptoms that you have not experienced before

PML symptoms may be similar to a Multiple Sclerosis (MS) relapse. It is especially important that you speak with your doctor at the earliest if you feel your MS is worsening or if you notice any new symptoms for up to 6 months after stopping TYRUKO treatment.

During the 6 months period after discontinuation of treatment with TYRUKO, you will be monitored by your doctor who will decide when you should receive MRI imaging. Normally, you will continue to have MRI imaging every 3-6 months if you have one or the other of the two combinations of PML risk factors:

- You have taken natalizumab treatment for more than 2 years, have antibodies against the JC virus and have previously taken an immunosuppressant medicine (a medicine that reduces the activity of your body´s immune response) at any time before starting TYRUKO.
- You have taken natalizumab treatment for more than 2 years, have an increased amount of JC virus antibodies in your blood and have never taken an immunosuppressant medicine before starting treatment with TYRUKO.

If none of the above combinations is applicable to you then you will continue to receive MRI imaging routinely as prescribed by your doctor.

Please ask your doctor if you have any questions about the information above.

Patient´s Name (print) _____

Patient´s Signature_____**Date:**_____

Doctor´s Name (print)_____

Doctor´s Signature_____**Date:**_____

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Reporting of side effects:

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in the patient leaflet. You can also report side effects directly via the national reporting system. By reporting side effects, you can help provide more information on the safety of this medicine.

Sandoz reporting adverse events:
Email: adverse.event.sau@sandoz.com
Website: https://pvi1j.solutions.iqvia.com/pvi-web/

Saudi Food and Drug Authority National Pharmacovigilance Center
Unified Contact Center: 19999
Email: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

This document has been approved by Saudi Food and Drug Authority (SFDA).

Healthcare professionals are asked to continue to report any suspected adverse drug reactions (ADRs).

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