Medicines & Healthcare products Regulatory Agency

Public Assessment Report

National Procedure

Tyruko 300 mg concentrate for solution for infusion

natalizumab

PLGB 04416/1706

Sandoz Limited

LAY SUMMARY
Tyruko 300 mg concentrate for solution for infusion
natalizumab

This is a summary of the Public Assessment Report (PAR) for Tyruko 300 mg concentrate for solution for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Tyruko in this lay summary for ease of reading.

This product has been authorised by the Medicines and Healthcare products Regulatory Agency (MHRA) for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 22 September 2023 (EMEA/H/C/005752/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

This application was approved under Regulation 53A of the Human Medicines Regulation 2012, as amended (previously Article 10.4 of Directive 2001/83/EC, as amended).

For practical information about using Tyruko, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Tyruko and what is it used for?
Tyruko is a 'similar biological' medicine (biosimilar). This means that Tyruko is similar to a biological 'reference' medicine already authorised called Tysabri 300 mg concentrate for solution for infusion.

Tyruko is used to treat multiple sclerosis (MS) in adults.
The symptoms of MS vary from patient to patient, and each individual may experience some or none of them. They may include: walking problems, numbness in the face, arms or legs; problems with vision; tiredness; feeling off-balance or light headed; bladder and bowel problems; difficulty in thinking and concentrating; depression; acute or chronic pain; sexual problems; stiffness and muscle spasms. When the symptoms flare up, it is called a relapse (also known as an exacerbation or an attack). When a relapse occurs, the patient may notice the symptoms suddenly, within a few hours, or slowly progressing over several days. Symptoms will then usually improve gradually (this is called a remission).

How does Tyruko work?
Tyruko contains the active substance natalizumab. This is called a monoclonal antibody.
Multiple sclerosis causes inflammation in the brain that damages the nerve cells. This inflammation happens when white blood cells get into the brain and spinal cord. Natalizumab stops the white blood cells getting through to the brain. This reduces nerve damage caused by MS.

How is Tyruko used?
The pharmaceutical form of this medicine is a solution for infusion and the route of administration is infusion (drip) into a vein.

For adults the recommended dose is 300 mg, given as a 1-hour infusion (drip) into a vein once every 4 weeks.

The patient's doctor may switch the patient directly from another medicine for MS to Tyruko if there are no problems caused by the patient's previous treatment.

- the patient's doctor will order blood tests for antibodies to the JC virus and other possible problems.
- the patient's doctor will arrange an MRI scan, which will be repeated during treatment.
- To switch from some MS medicines, the patient's doctor may advise the patient to wait for a certain time to ensure that most of the previous medicine has left the body.

Because the infusion can trigger an allergic reaction, the patient must be monitored during the infusion and for 1 hour afterwards.
After the first 12 intravenous Tyruko doses, patients should continue to be observed during infusion. If the patients have not experienced any infusion reactions, the post dose observation time may be reduced or removed according to clinical judgement.

If there is no clear benefit for the patient after 6 months, the doctor should re-assess the treatment with Tyruko.

For further information on how Tyruko is used, refer to the PIL and Summary Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering doctor/healthcare practitioner if they have any questions concerning their medicine.

What benefits of Tyruko have been shown in studies?
As Tyruko is a similar biological medicine to Tysabri 300 mg concentrate for solution for infusion, studies have been limited to tests to determine that it is similar to the reference medicine.

Laboratory studies comparing Tyruko with Tysabri have shown that the active substance in Tyruko is highly similar to that in Tysabri in terms of structure, purity and biological activity. Studies have also shown that giving Tyruko produces similar levels of the active substance in the body to giving Tysabri.

In addition, a study in 265 patients with relapsing-remitting MS showed that Tyruko produced comparable improvements to those seen with Tysabri. In this study, the average number of new lesions (abnormality) in the brain, as measured by MRI after 24 weeks of treatment, was 1.4 with Tyruko and 1.9 with Tysabri.

Because Tyruko is a biosimilar medicine, the studies on effectiveness and safety of natalizumab carried out with Tysabri do not all need to be repeated for Tyruko. The data submitted were considered sufficient to conclude that Tyruko will behave in the same way as Tysabri in terms of effectiveness and safety in its authorised uses.

What are the possible side effects of Tyruko?
For the full list of all side effects reported with this medicine see Section 4 of the PIL or Section 4.8 of the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Tyruko approved?
MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Tyruko has been authorised with the condition to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Tyruko.

What measures are being taken to ensure the safe and effective use of Tyruko?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Tyruko. The RMP details the important risks of Tyruko, how these risks can be minimised, any uncertainties about Tyruko (missing information), and how more information will be obtained about the important risks and uncertainties.
The following safety concerns have been recognised for Tyruko:

Summary of safety concerns	
Important identified risks	- Progressive multifocal leukoencephalopathy (PML) - Serious herpes infections
Important potential risks	- Malignancies
Missing information	- PML risk following switch from disease modifying therapies with immunosuppressant effect

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Tyruko are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

In addition to routine pharmacovigilance and risk minimisation measures, the following additional, risk minimisation measures have been proposed:

Physician educational materials:
- The Summary of Product Characteristics
- Physician information and management guidelines

Patient information pack:
- Package leaflet

- Patient alert card
- Treatment initiation and treatment continuation forms
- Treatment discontinuation form.

The company will ensure that all physicians who are expected to prescribe Tyruko are provided with physician educational materials. They will also provide a patient information pack to educate patients on the risk of PML.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Tyruko
A marketing authorisation was granted in Great Britain on 09 October 2023.

The full PAR for Tyruko follows this summary.

This summary was last updated in March 2024.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Tyruko 300 mg concentrate for solution for infusion (PLGB 04416/1706) could be approved.

The product indicated as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) (for exceptions and information about washout periods see sections 4.4 and 5.1 of the Summary of Product Characteristics)

or

- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Tyruko contains the active substance natalizumab a monoclonal antibody, classified as immunosuppressants, selective immunosuppressants.
Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils.

Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site and inhibit further recruitment of immune cells into inflamed tissues.

This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 22 September 2023 (EMEA/H/C/005752/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).
For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

This application was approved under Regulation 53A of the Human Medicines Regulation 2012, as amended (previously Article 10.4 of Directive 2001/83/EC, as amended).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted on 09 October 2023.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

V. CLINICAL ASPECTS

MHRA considered that the clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended.
The applicant proposes routine pharmacovigilance and routine risk minimisation measures for all safety concerns.
In addition to routine pharmacovigilance and risk minimisation measures, additional risk minimisation measures have been proposed, see table 12-2 - additional risk minimisation measures apply to progressive multifocal leukoencephalopathy (PML) only:

Table 12-2 Important identified risk: Progressive multifocal leukoencephalopathy (PML)

Evidence for linking the risk to the medicine	Use of natalizumab has been associated with the uncommon event of PML, which may be fatal or result in severe disability (Section 4.4, [Tyruko® SmPC]). PML has been classified as an important identified risk for Tyruko®, consistent with the reference product, Tysabri®.
Risk factors and risk groups	The following risk factors are associated with an increased risk of PML: • The presence of anti-JCV antibodies. • Treatment duration, especially beyond 2 years. After 2 years all patients should be re-informed about the risk of PML with the medicinal product. • Immunosuppressant use prior to receiving the medicinal product. Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive and have received more than 2 years of therapy with this medicinal product and have received prior immunosuppressant therapy) have a significantly higher risk of PML. In anti-JCV antibody positive natalizumab treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response is associated with the level of risk for PML (Section 4.4, [Tyruko® SmPC]). 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 (Section 4.4, [Tyruko® SmPC]). Patients who test as positive for anti-JCV antibodies at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results (Tysabri® RMP summary, 2021).
Risk minimization measures	Routine risk minimization measures: Information in SmPC Sections 4.2, 4.3, 4.4, 4.8, and 5.1; and PL Sections 2 and 4 Legal status: Restricted medical prescription Additional risk minimization measures: Educational tools for HCPs (Physician Information and Management Guideline) Educational tools for patients/carers (patient alert card, treatment initiation form, treatment continuation form, and treatment discontinuation form)

Table 12-3 Important identified risk: Serious herpes infections

Evidence for linking the risk to the medicine	Serious herpes infections has been classified as an important identified risk for Tyruko®, consistent with the reference product, Tysabri®.
Risk factors and risk groups	None identified for natalizumab.
Risk minimization measures	Routine risk minimization measures: Information in SmPC Sections 4.3, 4.4, 4.8; and PL Sections 2 and 4 Legal status: Restricted medical prescription

Table 12-4 Important potential risk: Malignancies

Evidence for linking the risk to the medicine	Malignancies have been classified as an important potential risk for Tyruko®, consistent with the reference product, Tysabri®. Malignancies were included as an important potential risk for Tysabri® based on the class of product and on the scientific literature (Tysabri® RMP summary, 2021). There is currently no evidence to suggest an increased risk for malignancy associated with long-term natalizumab therapy, however, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded (Tysabri® RMP summary, 2021).
Risk factors and risk groups	No risk groups or risk factors have been identified.
Risk minimization measures	Routine risk minimization measures: Information in SmPC Sections 4.3 and 4.8; and PL Section 2 Legal status: Restricted medical prescription

Table 12-5 Missing information: PML risk following switch from disease modifying therapies with immunosuppressant effect

Risk minimization measures	Routine risk minimization measures: Information in SmPC Section 4.4 and PL Section 2. Legal status: Restricted medical prescription

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements, including user consultation.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

Tyruko 300 mg concentrate for solution for infusion has been authorised with the condition to provide additional measures to minimise the risk, The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	Due date
Additional risk minimisation measures: Prior to launch in the UK, the MAH shall agree an educational programme with the MHRA and ensure that all physicians who are expected to prescribe Tyruko are provided with the following items: Physician educational materials: - The Summary of Product Characteristics - Physician information and management guidelines Patient information pack: - Package leaflet - Patient alert card - Treatment initiation and treatment continuation forms - Treatment discontinuation form.	09/10/2028

The Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product are available on the MHRA website.

IX. TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N