ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tyruko 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 20 mg of natalizumab.

When diluted (see section 6.6), the solution for infusion contains approximately 2.6 mg per mL of natalizumab.

Natalizumab is a recombinant humanised anti-α4-integrin antibody produced in a Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology.

Excipient with known effect

Each vial contains 2.3 mmol (or 52 mg) sodium (see section 4.4 for further information).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Colourless, clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tyruko is 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)

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.

4.2 Posology and method of administration

Therapy is to be initiated and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI.

Patients treated with this medicinal product must be given the patient alert card and be informed about the risks of the medicinal product (see also package leaflet). After 2 years of treatment, patients should be re-informed about the risks, especially the increased risk of Progressive Multifocal Leukoencephalopathy (PML), and should be instructed together with their caregivers on early signs and symptoms of PML.

Resources for the management of hypersensitivity reactions and access to MRI should be available.

Some patients may have been exposed to immunosuppressive medicinal products (e.g. mitoxantrone, cyclophosphamide, azathioprine). These medicinal products have the potential to cause prolonged immunosuppression, even after dosing is discontinued. Therefore the physician must confirm that such patients are not immunocompromised before starting treatment (see section 4.4).

Posology

Tyruko 300 mg is administered by intravenous infusion once every 4 weeks.

Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months.

Data on the safety and efficacy of natalizumab at 2 years were generated from controlled, double–blind studies. After 2 years continued therapy should be considered only following a reassessment of the potential for benefit and risk. Patients should be re-informed about the risk factors for PML, like duration of treatment, immunosuppressant use prior to receiving the medicinal product and the presence of anti-John Cunningham virus (JCV) antibodies (see section 4.4).

Readministration

The efficacy of re-administration has not been established, (for safety see section 4.4).

Special populations

Elderly

This medicinal product is not recommended for use in patients aged over 65 due to a lack of data in this population.

Renal and hepatic impairment

Studies have not been conducted to examine the effects of renal or hepatic impairment.

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in patients with renal or hepatic impairment.

Paediatric population

The safety and efficacy of natalizumab in children and adolescents up to 18 years have not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Method of administration

This medicinal product is for intravenous use.

For instructions on dilution of the medicinal product before administration (see section 6.6).

After dilution (see section 6.6), the infusion is to be administered over approximately 1 hour and patients are to be observed during the infusion and for 1 hour after the completion of the infusion for signs and symptoms of hypersensitivity reactions.

After the first 12 intravenous 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.

Patients restarting natalizumab treatment after a treatment gap ≥ 6 months are to be observed during the infusion and for 1 hour after the completion of the infusion for signs and symptoms of hypersensitivity reactions for the first 12 intravenous infusions after restarting therapy.

Tyruko 300 mg concentrate for solution for infusion must not be administered as a bolus injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Progressive multifocal leukoencephalopathy (PML).

Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies (see sections 4.4 and 4.8)).

Combination with other DMTs.

Known active malignancies, except for patients with cutaneous basal cell carcinoma.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Progressive Multifocal Leukoencephalopathy (PML)

Use of natalizumab has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of treatment should be individually reconsidered by the specialist physician and the patient; patients must be monitored at regular intervals throughout and should be instructed together with their caregivers on early signs and symptoms of PML. JC virus also causes JCV granule cell neuronopathy (GCN) which has been reported in patients treated with natalizumab. Symptoms of JCV GCN are similar to symptoms of PML (i.e. cerebellar syndrome).

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 natalizumab **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 (index) is associated with the level of risk for PML.

In anti-JCV antibody positive patients, extended interval dosing of natalizumab (average dosing interval of approximately 6 weeks) is suggested to be associated with a lower PML risk compared to approved dosing. If utilising extended interval dosing, caution is required because the efficacy of extended interval dosing has not been established and the associated benefit/risk balance is currently unknown (see section 5.1, *Intravenous administration Q6W*). For further information, refer to the Physician Information and Management Guidelines.

Patients considered at high risk treatment with this treatment should only be continued if the benefits outweigh the risks. For the estimation of PML risk in the different patient subgroups, please refer to the Physician Information and Management Guidelines.

Anti-JCV antibody testing

Anti-JCV antibody testing provides supportive information for risk stratification of treatment with this medicinal product. Testing for serum anti-JCV antibody prior to initiating therapy or in patients receiving the medicinal product with an unknown antibody status is recommended. 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. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. Retesting low index patients who have no history of prior immunosuppressant use every 6 months once they reach the 2 year treatment point is recommended.

The anti-JCV antibody assay (ELISA) should not be used to diagnose PML. Use of plasmapheresis/plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) can affect meaningful interpretation of serum anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies within 2 weeks of PLEX due to removal of antibodies from the serum, or within 6 months of IVIg (i.e. 6 months = 5x half-life for immunoglobulins).

Testing for serum anti-JCV antibody should be performed using a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, testing for serum anti-JCV antibody should be performed using an alternative validated test.

For further information on anti-JCV antibody testing please see Physician Information and Management Guidelines.

MRI screening for PML

Before initiation of treatment with this medicinal product, a recent (usually within 3 months) MRI should be available as a reference, and be repeated at least on a yearly basis. More frequent MRIs (e.g. on a 3 to 6 monthly basis) using an abbreviated protocol should be considered for patients at higher risk of PML. This includes:

- 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),

or

- Patients with a high anti-JCV antibody index who have received more than 2 years of therapy with this medicinal product and without prior history of immunosuppressant therapy.

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. Index threshold values for low/high PML risk depend on the specific anti-JCV antibody test used (see the Physician Information and Management Guidelines for further information).

No studies have been performed to evaluate the efficacy and safety of natalizumab when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to this treatment have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to natalizumab).

PML should be considered as a differential diagnosis in any MS patient taking Tyruko presenting with neurological symptoms and/or new brain lesions in MRI. Cases of asymptomatic PML based on MRI and positive JCV DNA in the cerebrospinal fluid have been reported.

Physicians should refer to the Physician Information and Management Guidelines for further information on managing the risk of PML in natalizumab-treated patients.

If PML or JCV GCN is suspected, further dosing must be suspended until PML has been excluded.

The specialised physician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML or JCV GCN. If any doubt exists, further evaluation, including MRI scan preferably with contrast (compared with pre-treatment baseline MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered as described in the Physician Information and Management Guidelines (see Educational guidance). Once the clinician has excluded PML and/or JCV GCN (if necessary, by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains), dosing may resume.

The physician should be particularly alert to symptoms suggestive of PML or JCV GCN that the patient may not notice (e.g. cognitive, psychiatric symptoms or cerebellar syndrome). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

PML has been reported following discontinuation of natalizumab in patients who did not have findings suggestive of PML at the time of discontinuation. Patients and physicians should continue to follow the same monitoring protocol and be alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of Tyruko.

If a patient develops PML the dosing of natalizumab must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML improved outcome has been seen.

Based on a retrospective analysis of natalizumab-treated patients since its approval, no difference was observed on 2-year survival after PML diagnosis between patients who received PLEX and those who did not. For other considerations on the management of PML, see the Physician Information and Management Guidelines.

PML and IRIS (Immune Reconstitution Inflammatory Syndrome)

IRIS occurs in almost all PML patients treated with natalizumab after withdrawal or removal of the medicinal product. IRIS is thought to result from the restoration of immune function in patients with PML, which can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS and appropriate treatment of the associated inflammation during recovery from PML should be undertaken (see the Physician Information and Management Guidelines for further information).

Infections including other opportunistic infections

Other opportunistic infections have been reported with use of natalizumab, primarily in patients with Crohn's disease who were immunocompromised or where significant co-morbidity existed, however increased risk of other opportunistic infections with use of the medicinal product in patients without these co-morbidities cannot currently be excluded. Opportunistic infections were also detected in MS patients treated with natalizumab as a monotherapy (see section 4.8).

This treatment increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the post-marketing setting in multiple sclerosis patients receiving the treatment (see section 4.8). If herpes encephalitis or meningitis occurs, the medicinal product should be discontinued, and appropriate treatment for herpes encephalitis or meningitis should be administered.

Acute retinal necrosis (ARN) is a rare fulminant viral infection of the retina caused by the family of herpes viruses (e.g. varicella zoster). ARN has been observed in patients being administered natalizumab and can be potentially blinding. Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN. Following clinical diagnosis of ARN, discontinuation of this medicinal product should be considered in these patients.

Prescribers should be aware of the possibility that other opportunistic infections may occur during therapy and should include them in the differential diagnosis of infections that occur in natalizumab-treated patients. If an opportunistic infection is suspected, dosing is to be suspended until such infections can be excluded through further evaluations.

If a patient receiving this medicinal product develops an opportunistic infection, dosing of the medicinal product must be permanently discontinued.

Educational guidance

All physicians who intend to prescribe the medicinal product must ensure they are familiar with the Physician Information and Management Guidelines.

Physicians must discuss the benefits and risks of natalizumab therapy with the patient and provide them with a patient alert card. Patients should be instructed that if they develop any infection then they should inform their physician that they are being treated with this medicinal product.

Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment (see hypersensitivity).

Hypersensitivity

Hypersensitivity reactions have been associated with natalizumab, including serious systemic reactions (see section 4.8). These reactions usually occurred during the infusion or up to 1 hour after completion of the infusion. The risk for hypersensitivity was greatest with early infusions and in patients re-exposed to treatment following an initial short exposure (one or two infusions) and extended period (three months or more) without treatment. However, the risk of hypersensitivity reactions should be considered for every infusion administered.

Patients are to be observed during the infusion and for 1 hour after the completion of the infusion (see section 4.8). Resources for the management of hypersensitivity reactions should be available.

This product should be discontinued and appropriate therapy initiated at the first symptoms or signs of hypersensitivity.

Patients who have experienced a hypersensitivity reaction must be permanently discontinued from treatment with natalizumab.

Concurrent treatment with immunosuppressants

The safety and efficacy of natalizumab in combination with other immunosuppressive and antineoplastic therapies have not been fully established. Concurrent use of these agents with this medicinal product may increase the risk of infections, including opportunistic infections, and is contraindicated (see section 4.3).

In phase 3 MS clinical trials with natalizumab intravenous infusion, concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection. Short courses of corticosteroids can be used in combination with this medicinal product.

Prior treatment with immunosuppressive or immunomodulatory therapies

Patients with a treatment history of immunosuppressant medications are at increased risk for PML. No studies have been performed to evaluate the efficacy and safety of the medicinal product when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to this medicinal product have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to this medicinal product, see MRI screening for PML).

Care should be taken with patients who have previously received immunosuppressants to allow sufficient time for immune function recovery to occur. Physicians must evaluate each individual case to determine whether there is evidence of an immunocompromised state prior to commencing treatment (see section 4.3).

When switching patients from another DMT to this medicinal product, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A Complete Blood Count (CBC, including lymphocytes) is recommended prior to initiating treatment to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

Patients can switch directly from beta interferon or glatiramer acetate to natalizumab providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia and lymphopenia.

When switching from dimethyl fumarate, the washout period should be sufficient for lymphocyte count to recover before treatment is started.

Following discontinuation of fingolimod, lymphocyte count progressively returns to normal range within 1 to 2 months after stopping therapy. The washout period should be sufficient for lymphocyte count to recover before treatment is started.

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide Summary of Product Characteristics is recommended or alternatively washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from teriflunomide to this medicinal product.

Alemtuzumab has profound prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with this medicinal product after alemtuzumab is not recommended unless the benefits clearly outweigh the risks for the individual patient.

Immunogenicity

Disease exacerbations or infusion related events may indicate the development of antibodies against natalizumab. In these cases the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, treatment should be discontinued, as persistent antibodies are associated with a substantial decrease in efficacy of natalizumab and an increased incidence of hypersensitivity reactions (see section 4.8).

Since patients who have received an initial short exposure to natalizumab and then had an extended period without treatment are at a higher risk of developing anti-natalizumab antibodies and/or hypersensitivity upon redosing, the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, the patient should not receive further treatment with natalizumab (see section 5.1).

Hepatic events

Spontaneous serious adverse reactions of liver injury have been reported during the post-marketing phase (see section 4.8). These liver injuries may occur at any time during treatment, even after the first dose. In some instances, the reaction reoccurred when treatment was reintroduced. Some patients with a past medical history of an abnormal liver test have experienced an exacerbation of abnormal liver test while on treatment. Patients should be monitored as appropriate for impaired liver function, and be instructed to contact their physician in case signs and symptoms suggestive of liver injury occur, such as jaundice and vomiting. In cases of significant liver injury this medicinal product should be discontinued.

Thrombocytopenia

Thrombocytopenia, including immune thrombocytopenic purpura (ITP), has been reported with the use of natalizumab. Delay in the diagnosis and treatment of thrombocytopenia may lead to serious and life-threatening sequelae. Patients should be instructed to report to their physician immediately if they experience any signs of unusual or prolonged bleeding, petechiae, or spontaneous bruising. If thrombocytopenia is identified, discontinuation of natalizumab should be considered.

Stopping therapy

If a decision is made to stop treatment with natalizumab, the physician needs to be aware that natalizumab remains in the blood, and has pharmacodynamic effects (e.g increased lymphocyte counts) for approximately 12 weeks following the last dose. Starting other therapies during this interval will result in a concomitant exposure to natalizumab. For medicinal products such as interferon and glatiramer acetate, concomitant exposure of this duration was not associated with safety risks in clinical trials. No data are available in MS patients regarding concomitant exposure with immunosuppressant medication. Use of these medicinal products soon after the discontinuation of natalizumab may lead to an additive immunosuppressive effect. This should be carefully considered on a case-by-case basis, and a wash-out period of natalizumab might be appropriate. Short courses of steroids used to treat relapses were not associated with increased infections in clinical trials.

Sodium content

Before dilution, this medicinal product contains 52 mg sodium per vial of medicinal product, equivalent to 2.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Natalizumab is contraindicated in combination with other DMTs (see section 4.3).

Immunisations

In a randomised, open label study of 60 patients with relapsing MS there was no significant difference in the humoral immune response to a recall antigen (tetanus toxoid) and only slightly slower and reduced humoral immune response to a neoantigen (keyhole limpet haemocyanin) was observed in patients who were treated with natalizumab for 6 months compared to an untreated control group. Live vaccines have not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If a woman becomes pregnant while taking this medicinal product, discontinuation should be considered. A benefit/risk evaluation of the use of this medicinal product during pregnancy should take into account the patient's clinical condition and the possible return of disease activity after stopping the medicinal product.

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3).

Data from clinical trials, a prospective pregnancy registry, post-marketing cases and available literature do not suggest an effect of natalizumab exposure on pregnancy outcomes.

The completed prospective natalizumab pregnancy registry contained 355 pregnancies with available outcomes. There were 316 live births, 29 of which were reported to have birth defects. Sixteen of the 29 were classified as major defects. The rate of defects corresponds to the defect rates reported in other pregnancy registries involving MS patients. There is no evidence of a specific pattern of birth defects with natalizumab.

There are no adequate and well-controlled studies of natalizumab therapy in pregnant women.

Thrombocytopenia and anaemia in infants born to women exposed to natalizumab during pregnancy were reported in the post-marketing setting. Monitoring of platelet counts, haemoglobin, and haematocrit is recommended in neonates born to women exposed to natalizumab during pregnancy.

This medicinal product should be used during pregnancy only if clearly needed. If a woman becomes pregnant while taking natalizumab, discontinuation of natalizumab should be considered.

Breast-feeding

Natalizumab is excreted in human milk. The effect of natalizumab on newborns/infants is unknown. Breast-feeding should be discontinued during treatment with natalizumab.

Fertility

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility. It is considered unlikely that natalizumab will affect fertility performance in humans following the maximum recommended dose.

4.7 Effects on ability to drive and use machines

Tyruko has a minor influence on the ability to drive and use machines. Dizziness may occur following administration of natalizumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In placebo-controlled trials in 1 617 MS patients treated with natalizumab for up to 2 years (placebo: 1 135), adverse events leading to discontinuation of therapy occurred in 5.8% of patients treated with natalizumab (placebo: 4.8%). Over the 2-year duration of the studies, 43.5% of patients treated with natalizumab reported adverse reactions (placebo: 39.6%).

In clinical trials in 6 786 patients treated with natalizumab (intravenous infusion and subcutaneous injection), the most frequently occurring adverse reactions were headache (32%), nasopharyngitis (27%), fatigue (23%), urinary tract infection (16%), nausea (15%), arthralgia (14%), and dizziness (11%) associated with natalizumab administration.

Tabulated list of adverse reactions

Adverse reactions arising from clinical studies, post-authorisation safety studies and spontaneous reports are presented in Table 1, below. Within the system organ classes they are listed under the following headings: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1 000 to <1/100); Rare (≥1/10 000 to <1/1 000); Very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions

MedDRA System Organ Class	Frequency of adverse reactions				
	Very Common	*Common*	*Uncommon*	*Rare*	*Not known*
Infections and infestations	Nasopharyngitis Urinary tract infection	Herpes infection	Progressive multifocal leukoencephalopathy	Herpes ophthalmic	Meningoencephalitis herpetic JC virus granule cell neuropathy

MedDRA System Organ Class	Frequency of adverse reactions				
	Very Common	*Common*	*Uncommon*	*Rare*	*Not known*
					Necrotising herpetic retinopathy
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia, Immune thrombocytopenic purpura (ITP) Eosinophilia	Haemolytic anaemia Nucleated red cells	
Immune system disorders		Hypersensitivity	Anaphylactic reaction Immune reconstitution inflammatory syndrome		
Nervous system disorders	Dizziness Headache				
Vascular disorders		Flushing			
Respiratory, thoracic and mediastinal disorders		Dyspnoea			
Gastrointestinal disorders	Nausea	Vomiting			
Hepatobiliary disorders				Hyperbilirubinaemia	Liver injury
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria		Angioedema	
Musculoskeletal and connective tissue disorders	Arthralgia				
General disorders and administration site conditions	Fatigue	Pyrexia Chills Infusion site reaction Injection site reaction	Face oedema		
Investigations		Hepatic enzyme increased Drug specific antibody present			
Injury, poisoning and procedural complications	Infusion related reaction				

Description of selected adverse reactions

Infusion-related reactions (IRR)

In 2-year controlled clinical trials in MS patients, an infusion-related event was defined as an adverse event occurring during the infusion or within 1 hour of the completion of the infusion. These occurred in 23.1% of MS patients treated with natalizumab (placebo: 18.7%). Events reported more commonly with natalizumab than with placebo included dizziness, nausea, urticaria and rigors.

Hypersensitivity reactions

In 2-year controlled clinical trials in MS patients, hypersensitivity reactions occurred in up to 4% of patients. Anaphylactic/anaphylactoid reactions occurred in less than 1% of patients receiving natalizumab. Hypersensitivity reactions usually occurred during the infusion or within the 1-hour period after the completion of the infusion (see section 4.4). In post-marketing experience, there have been reports of hypersensitivity reactions which have occurred with one or more of the following associated symptoms: hypotension, hypertension, chest pain, chest discomfort, dyspnoea, angioedema, in addition to more usual symptoms such as rash and urticaria.

Immunogenicity

Anti-natalizumab antibodies may develop during natalizumab treatment. Persistent antibodies were associated with a substantial decrease in the effectiveness of natalizumab and an increased incidence of hypersensitivity reactions. Additional infusion-related reactions associated with persistent antibodies included rigors, nausea, vomiting and flushing (see section 4.4).

If, after approximately 6 months of therapy, persistent antibodies are suspected, either due to reduced efficacy or due to occurrence of infusion-related events, they may be detected and confirmed with a subsequent test 6 weeks after the first positive test. Given that efficacy may be reduced or the incidence of hypersensitivity or infusion-related reactions may be increased in a patient with persistent antibodies, treatment should be discontinued in patients who develop persistent antibodies.

Infections, including PML and opportunistic infections

In 2-year controlled clinical trials in MS patients, the rate of infection was approximately 1.5 per patient-year in both natalizumab- and placebo-treated patients. The nature of the infections was generally similar in natalizumab- and placebo-treated patients. A case of *cryptosporidium* diarrhoea was reported in MS clinical trials. In other clinical trials, cases of additional opportunistic infections have been reported, some of which were fatal. The majority of patients did not interrupt natalizumab therapy during infections and recovery occurred with appropriate treatment.

In clinical trials, herpes infections (Varicella-Zoster virus, Herpes-simplex virus) occurred slightly more frequently in natalizumab-treated patients than in placebo-treated patients. In post-marketing experience, serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in multiple sclerosis patients receiving natalizumab. The duration of treatment with natalizumab prior to onset ranged from a few months to several years (see section 4.4).

In post-marketing experience, rare cases of ARN have been observed in patients receiving natalizumab. Some cases have occurred in patients with central nervous system (CNS) herpes infections (e.g. herpes meningitis and encephalitis). Serious cases of ARN, either affecting one or both eyes, led to blindness in some patients. The treatment reported in these cases included anti-viral therapy and in some cases, surgery (see section 4.4).

Cases of PML have been reported from clinical trials, post-marketing observational studies and post-marketing passive surveillance. PML usually leads to severe disability or death (see section 4.4).

Cases of JCV GCN have also been reported during post-marketing use of natalizumab. Symptoms of JCV GCN are similar to PML.

Hepatic events

Spontaneous cases of serious liver injuries, increased liver enzymes, hyperbilirubinaemia have been reported during the post-marketing phase (see section 4.4).

Anaemia and haemolytic anaemia

Rare, serious cases of anaemia and haemolytic anaemia have been reported in patients treated with natalizumab in post-marketing observational studies.

Malignancies

No differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded (see section 4.3).

Effects on laboratory tests

In 2-year controlled clinical trials in MS patients treatment with natalizumab was associated with increases in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells. Elevations in neutrophils were not seen. Increases from baseline for lymphocytes, monocytes, eosinophils and basophils ranged from 35% to 140% for individual cell types but mean cell counts remained within normal ranges with IV administration. During treatment with IV form of natalizumab, small reductions in haemoglobin (mean decrease 0.6 g/dL), haematocrit (mean decrease 2%) and red blood cell counts (mean decrease 0.1 x 10^6/L) were seen. All changes in haematological variables returned to pre-treatment values, usually within 16 weeks of last dose of natalizumab and the changes were not associated with clinical symptoms. In post-marketing experience, there have also been reports of eosinophilia (eosinophil count >1,500/mm^3) without clinical symptoms. In such cases where therapy was discontinued the elevated eosinophil levels resolved.

Thrombocytopenia

In post-marketing experience, thrombocytopenia and immune thrombocytopenic purpura (ITP) have been reported with uncommon frequency.

Paediatric population

Serious adverse events were evaluated in 621 MS paediatric patients included in a meta-analysis (see also section 5.1). Within the limitations of these data, there were no new safety signals identified in this patient population. 1 case of herpes meningitis was reported in the meta-analysis. No cases of PML were identified in the meta-analysis, however, PML has been reported in natalizumab-treated paediatric patients in the post-marketing setting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Safety of doses higher than 300 mg has not been adequately evaluated. The maximum amount of natalizumab that can be safely administered has not been determined.

There is no known antidote for natalizumab overdose. Treatment consists of discontinuation of the medicinal product and supportive therapy as needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, monoclonal antibodies, ATC code: L04AG03

Tyruko is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Pharmacodynamic effects

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.

In MS, lesions are believed to occur when activated T-lymphocytes cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and endothelial cells of the vessel wall. The interaction between α4β1 and its targets is an important component of pathological inflammation in the brain and disruption of these interactions leads to reduced inflammation. Under normal conditions, VCAM-1 is not expressed in the brain parenchyma. However, in the presence of pro-inflammatory cytokines, VCAM-1 is upregulated on endothelial cells and possibly on glial cells near the sites of inflammation. In the setting of central nervous system (CNS) inflammation in MS, it is the interaction of α4β1 with VCAM-1, CS-1 and osteopontin that mediates the firm adhesion and transmigration of leukocytes into the brain parenchyma and may perpetuate the inflammatory cascade in CNS tissue. Blockade of the molecular interactions of α4β1 with its targets reduces inflammatory activity present in the brain in MS and inhibits further recruitment of immune cells into inflamed tissue, thus reducing the formation or enlargement of MS lesions.

Clinical efficacy

AFFIRM clinical study

Efficacy as monotherapy has been evaluated in one randomised, double-blind, placebo-controlled study lasting 2 years (AFFIRM study) in RRMS patients who had experienced at least 1 clinical relapse during the year prior to entry and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5. Median age was 37 years, with a median disease duration of 5 years. The patients were randomised with a 2:1 ratio to receive natalizumab-300 mg (n = 627) or placebo (n = 315) every 4 weeks for up to 30 infusions. Neurological evaluations were performed every 12 weeks and at times of suspected relapse. MRI evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually.

Study features and results are presented in the Table 2.

Table 2. AFFIRM study: Main features and results		
Design	Monotherapy; randomised double-blind placebo-controlled parallel-group trial for 120 weeks	
Subjects	RRMS (McDonald criteria)	
Treatment	Placebo / Natalizumab 300 mg i.v. every 4 weeks	
One year endpoint	Relapse rate	
Two year endpoint	Progression on EDSS	
Secondary endpoints	Relapse rate derived variables / MRI-derived variables	
Subjects	Placebo	Natalizumab
Randomised	315	627
Completing 1 years	296	609
Completing 2 years	285	589
Age yrs, median (range)	37 (19-50)	36 (18-50)
MS-history yrs, median (range)	6.0 (0-33)	5.0 (0-34)
Time since diagnosis, yrs median (range)	2.0 (0-23)	2.0 (0-24)
Relapses in previous 12 months, median (range)	1.0 (0-5)	1.0 (0-12)
EDSS-baseline, median (range)	2 (0-6.0)	2 (0-6.0)
RESULTS		
Annual relapse rate		
After one year (primary endpoint)	0.805	0.261
After two years	0.733	0.235
One year	Rate ratio 0.33 $CI_{95\%}$ 0.26 ; 0.41	
Two years	Rate ratio 0.32 $CI_{95\%}$ 0.26 ; 0.40	
Relapse free		
After one year	53%	76%
After two years	41%	67%
Disability		
Proportion progressed[1](12-week confirmation; primary outcome)	29%	17%
	Hazard ratio 0.58, $CI_{95\%}$ 0.43; 0.73, p<0.001	
Proportion progressed[1](24-week confirmation)	23%	11%
	Hazard ratio 0.46, $CI_{95\%}$ 0.33; 0.64, p<0.001	

Table 2. AFFIRM study: Main features and results		
MRI (0-2 years)		
Median % change in T2-hyperintense lesion volume	+8.8%	-9.4% (p<0.001)
Mean number of new or newly-enlarging T2-hyperintense lesions	11.0	1.9 (p<0.001)
Mean number of T1-hypointense lesions	4.6	1.1 (p<0.001)
Mean number of Gd-enhancing lesions	1.2	0.1 (p<0.001)
[1] Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 or 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS = 0 sustained for 12 or 24 weeks.		

In the sub-group of patients indicated for treatment of rapidly evolving RRMS (patients with 2 or more relapses and 1 or more Gd+ lesion), the annualised relapse rate was 0.282 in the natalizumab-treated group (n = 148) and 1.455 in the placebo group (n = 61) (p <0.001). Hazard ratio for disability progression was 0.36 (95% CI: 0.17, 0.76) p = 0.008. These results were obtained from a *post hoc* analysis and should be interpreted cautiously. No information on the severity of the relapses before inclusion of patients in the study is available.

Natalizumab observational program

Interim analysis of results (as of May 2015) from an ongoing natalizumab observational program, a phase 4, multicentre, single-arm study (n = 5,770) demonstrated that patients switching from beta interferon (n = 3,255) or glatiramer acetate (n = 1,384) to natalizumab showed a sustained, significant decrease in annualised relapse rate (p <0.0001). Mean EDSS scores remained stable over 5 years. Consistent with efficacy results observed for patients switching from beta interferon or glatiramer acetate to natalizumab, for patients switching from fingolimod (n = 147) to natalizumab, a significant decrease in annualised relapse rate (ARR) was observed, which remained stable over 2 years, and mean EDSS scores remained similar from baseline to Year 2. The limited sample size and shorter duration of natalizumab exposure for this subgroup of patients should be considered when interpreting these data.

Paediatric population

A post-marketing meta-analysis was conducted using data from 621 paediatric MS patients treated with natalizumab (median age 17 years, range was 7 to 18 years, 91% aged ≥14 years). Within this analysis, a limited subset of patients with data available prior to treatment (158 of the 621 patients) demonstrated a reduction in ARR from 1.466 (95% CI 1.337, 1.604) prior to treatment to 0.110 (95% CI 0.094, 0.128).

Extended interval dosing

In a pre-specified, retrospective analysis of US anti-JCV antibody positive natalizumab patients intravenously administered, the risk of PML was compared between patients treated with the approved dosing interval and patients treated with extended interval dosing as identified in the last 18 months of exposure (EID, average dosing intervals of approximately 6 weeks). The majority (85%) of patients dosed with EID had received the approved dosing for ≥1 year prior to switching to EID. The analysis showed a lower risk of PML in patients treated with EID (hazard ratio = 0.06, 95% CI of hazard ratio = 0.01 to 0.22).

Efficacy has been modelled for patients who switch to longer dosing after ≥1 year of approved dosing with this medicinal product under intravenous administration and who did not experience a relapse in the year prior to switching. Current pharmacokinetic/pharmacodynamic statistical modelling and simulation indicate that the risk of MS disease activity for patients switching to longer dosing intervals

may be higher for patients with dosing intervals ≥7 weeks. No prospective clinical studies have been completed to validate these findings.

The efficacy of natalizumab when administered with EID has not been established, therefore the benefit/risk balance of EID is unknown (see *"Intravenous administration Q6W"*).

Intravenous administration Q6W

Efficacy and safety were evaluated in a prospective, randomized, interventional, controlled, open-label, rater-blinded, international phase 3 study (NOVA, 101MS329), involving subjects with relapsing-remitting MS according to the 2017 McDonald criteria dosed intravenously every six weeks with natalizumab. The study was designed to estimate an efficacy difference between Q6W and Q4W dosing regimens.

The study randomized 499 subjects aged 18-60, with an EDSS score ≤ 5.5 at screening, who received at least 1 year of natalizumab treatment IV Q4W and were clinically stable (no relapse in the last 12 months, no gadolinium (Gd) enhancing T1 lesions at screening). In the study, subjects who switched to Q6W after at least one year of IV Q4W treatment with natalizumab were evaluated in relation to subjects who continued on IV Q4W treatment.

Baseline demographic subgroups of age, sex, duration of natalizumab exposure, country, body weight, anti-JCV status and number of relapses in the year prior to the first dose, number of relapses while on natalizumab, number of prior DMTs, and type of prior DMT were similar between the Q6W and Q4W dosing treatment arms.

Table 3. NOVA study: Main features and results		
Design	Monotherapy; phase 3b prospective, randomized, interventional, controlled, open-label, rater-blinded, international study	
Subjects	RRMS (McDonald criteria)	
Treatment administration (part 1)	Natalizumab Q4W 300 mg I.V.	Natalizumab Q6W 300 mg I.V.
Randomized	248	251
RESULTS		
mITT[a] population for part 1 at week 72	242	247
New/newly enlarging (N/NE) T2 lesions from baseline to Week 72 Subjects with number of lesions = 0	189 (78.1%)	202 (81.8%)
= 1	7 (3.6%)	5 (2.0%)
= 2	1 (0.5%)	2 (0.8%)
= 3	0	0
= 4	0	0
≥ 5	0	2* (0.8%)
missing	45 (18.6%)	36 (14.6%)
Adjusted mean N/NE T2-hyperintense lesions (primary endpoint)* 95% CI[b,c]	0.05 (0.01, 0.22)	0.20 (0.07, 0.63)
	p = 0.0755	
Proportion of subjects that developed N/NE T2 lesions	4.1%	4.3%
Proportion of subjects who developed T1-hypointense lesions	0.8%	1.2%

Table 3. NOVA study: Main features and results		
Proportion of subjects who developed Gd-enhancing lesions	0.4%	0.4%
Adjusted annualized relapse rate	0.00010	0.00013
Proportion of subjects free of relapse**	97.6%	96.9%
Proportion free of 24-week confirmed EDSS worsening	92%	90%

[a] mITT population, which included all randomized participants who received at least 1 dose of study treatment (natalizumab SID or natalizumab EID) and had at least 1 postbaseline result from the following clinical efficacy assessments: MRI efficacy assessments, relapses, EDSS, 9-HPT, T25FW, SDMT, TSQM, CGI scale.

[b] Estimated using negative binomial regression with treatment as classification and baseline body weight (≤ 80 vs > 80 kg), duration of natalizumab exposure at baseline (≤ 3 vs > 3 years), and region (North America, the UK, Europe and Israel, and Australia) as covariates.

[c] Observed lesions are included for analysis regardless of intercurrent events, and missing values due to efficacy or safety (6 subjects switched to Q4W dosing and 1 subject each on Q6W and Q4W dosing discontinued treatment)are imputed by the worst case of subjects on treatment at the same visit in the same treatment group or otherwise via multiple imputation.

* The numerical difference seen in the N/NE lesions between the two treatment groups was driven by a high numberof lesions occurring in two subjects in the Q6W arm – one subject who developed lesions three months after treatment discontinuation and a second subject who was diagnosed with asymptomatic PML at week 72.

** Relapses – clinical relapses were assessed as defined by new or recurrent neurologic symptoms not associated with fever or infection having a minimum duration of 24 hours.

5.2 Pharmacokinetic properties

Following the repeat intravenous administration of a 300 mg dose of natalizumab to MS patients, the mean maximum observed serum concentration was 110 ± 52 µg/mL. Mean average steady-state trough natalizumab concentrations over the dosing period ranged from 23 µg/mL to 29 µg/mL in Q4W dosing. At any time, mean trough concentrations for the Q6W regimen were approximately 60 to 70% lower than for the Q4W regimen. The predicted time to steady state was approximately 24 weeks. Population pharmacokinetic analysis includes 12 studies and 1,781 subjects receiving doses ranging from 1 to 6 mg/kg and fixed doses of 150/300 mg.

Distribution

Median steady-state volume of distribution was 5.96 L (5.59-6.38 L, 95% confidence interval).

Elimination

Population median estimate for linear clearance was 6.08 mL/h (5.75-6.33 mL/h, 95% confidence interval) and the estimated median half-life was 28.2 days. The 95th percentile interval of the terminal half-life is from 11.6 to 46.2 days.

The population analysis of 1,781 patients explored the effects of selected covariates including body weight, age, gender, presence of anti-natalizumab antibodies and formulation on pharmacokinetics. Only body weight, the presence of anti-natalizumab antibodies and the formulation used in phase 2 studies were found to influence natalizumab disposition. Natalizumab clearance increased with body weight in a less-than-proportional manner, such that a +/-43% change in body weight resulted in only a -33% to 30% change in clearance. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 2.45-fold, consistent with reduced serum natalizumab concentrations observed in persistently antibody-positive patients.

Special populations

Paediatric population

The pharmacokinetics of natalizumab in paediatric MS patients has not been established.

Renal impairment

The pharmacokinetics of natalizumab in patients with renal insufficiency has not been studied.

Hepatic impairment

The pharmacokinetics of natalizumab in patients with hepatic insufficiency has not been studied.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Consistent with the pharmacological activity of natalizumab, altered trafficking of lymphocytes was seen as white blood cell increases as well as increased spleen weights in most *in vivo* studies. These changes were reversible and did not appear to have any adverse toxicological consequences.

In studies conducted in mice, growth and metastasis of melanoma and lymphoblastic leukaemia tumour cells was not increased by the administration of natalizumab.

No clastogenic or mutagenic effects of natalizumab were observed in the Ames or human chromosomal aberration assays. Natalizumab showed no effects on *in vitro* assays of α4-integrin-positive tumour line proliferation or cytotoxicity.

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility.

The effect of natalizumab on reproduction was evaluated in 5 studies, 3 in guinea pigs and 2 in *cynomolgus* monkeys. These studies showed no evidence of teratogenic effects or effects on growth of offspring. In one study in guinea pigs, a small reduction in pup survival was noted. In a study in monkeys, the number of abortions was doubled in the natalizumab 30 mg/kg treatment groups versus matching control groups. This was the result of a high incidence of abortions in treated groups in the first cohort that was not observed in the second cohort. No effects on abortion rates were noted in any other study. A study in pregnant *cynomolgus* monkeys demonstrated natalizumab-related changes in the foetus that included mild anaemia, reduced platelet counts, increased spleen weights and reduced liver and thymus weights. These changes were associated with increased splenic extramedullary haematopoiesis, thymic atrophy and decreased hepatic haematopoiesis. Platelet counts were also reduced in offspring born to mothers treated with natalizumab until parturition, however there was no evidence of anaemia in these offspring. All changes were observed at doses in excess of the human dose and were reversed upon clearance of natalizumab.

In *cynomolgus* monkeys treated with natalizumab until parturition, low levels of natalizumab were detected in the breast milk of some animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Histidine
Histidine monohydrochloride
Polysorbate 80 (E 433)
water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

No incompatibilities have been observed with polypropylene syringe, with polyvinyl chloride, polyethylene or polypropylene bags, and with polyvinyl chloride or polyurethane infusion lines.

6.3 Shelf life

Unopened vial

3 years

Diluted solution

From a microbiological point of view, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2 ˚C to 8 ˚C and infused within 24 hours of dilution. In-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 ˚C to 8 ˚C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product see section 6.3.

6.5 Nature and contents of container

15 mL concentrate in a vial (type I glass) with a stopper (bromobutyl rubber) and a seal (aluminium) with a flip-off cap.

Pack size of one vial per carton.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for use

- Inspect the vial for particles prior to dilution and administration. If particles are observed and/or the liquid in the vial is not colourless, clear to slightly opalescent, the vial must not be used.

- Use aseptic technique when preparing the solution for intravenous (IV) infusion. Remove flip-off cap from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 mL concentrate for solution for infusion.

- Add the 15 mL concentrate for solution for infusion to 100 mL sodium chloride 9 mg/mL (0.9%) solution for injection. Gently invert the solution to mix completely. Do not shake.

- This medicinal product must not be mixed with other medicinal products or diluents.

- Visually inspect the diluted medicinal product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.

- The diluted medicinal product is to be used as soon as possible and within 24 hours of dilution. If the diluted medicinal product is stored at 2 ˚C to 8 ˚C (do not freeze), allow the solution to warm to room temperature prior to infusion.

- The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 mL per minute.

- After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/mL (0.9%) solution for injection.

- Each vial is for single–use only.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER

EU/1/23/1745/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 September 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Polpharma Biologics S.A.
Ul. Trzy Lipy 3
80-172 Gdańsk
Poland

Name and address of the manufacturers responsible for batch release

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Based on how patients treated with Tyruko are currently monitored at national level, the MAH shall discuss and agree with the National Competent Authorities measures to enhance further this monitoring (e.g. registries, post-marketing surveillance studies) as appropriate. The MAH shall implement agreed measures for monitoring within a time frame agreed with the National Competent Authorities.

The educational programme is aimed at educating healthcare professionals and patients/carers of the potential and risk factors for the development of PML, its diagnosis and treatment, and the identification and management of possible sequelae.

The MAH shall ensure that in each Member State where Tyruko is marketed, all healthcare professionals and patients/carers who are expected to prescribe/use Tyruko have access to/are provided with the educational materials listed below. Prior to implementation, the MAH must agree on the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

- Educational materials for HCPs:

  - 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

These educational materials shall contain the following key elements:

Physician Information and Management Guidelines:

- Background information on the increased risk of atypical/opportunistic infections, in particular PML, which may occur with Tyruko therapy, including a detailed discussion of data (including **epidemiology, aetiology, and pathology**) pertaining to the development of PML in Tyruko-treated patients.

- Information relating to the **identification of risk factors** for Tyruko-associated PML, including details of the PML risk estimates algorithm summarising PML risk by risk factor (anti-John Cunningham virus [JCV] antibody status, prior IS use, and duration of treatment [by year of treatment]), and stratification of this risk by index value when applicable.

- **Information on extending the dosing interval for PML risk mitigation**, including a reminder of the approved dosing schedule.

- Inclusion of **monitoring guidance** for MRI and anti-JCV antibody based on PML risk,including recommended timing, protocols, and interpretation of results.

- Detail regarding the **diagnosis of PML**, including principals, clinical assessment (including MRI and laboratory testing), and differentiation between PML and MS.

- **Management** recommendations in the event of cases of suspected PML, including considerations on the effectiveness of PLEX treatment and the management of associated IRIS (immune reconstitution inflammatory syndrome).

- Detail on the **prognosis** on PML, including information on improved outcomes observed in asymptomatic PML cases.

- A reminder that irrespective of the presence or absence of PML risk factors, heightened clinical vigilance for PML should be maintained in all patients treated with Tyruko and for 6 months following **discontinuation of therapy**.

- A reminder on the need to discuss the benefit/risk profile of Tyruko treatment with the patient, and the requirement to provide the patient information pack.

Patient alert card:

- Reminder to patients to show the card to any doctor and/or caregiver involved with their treatment, and to keep the card with them for 6 months after the last dose of Tyruko treatment.

- Reminder to patients to read the package leaflet carefully before starting Tyruko, and not to start Tyruko if there is a serious problem with their immune system.

- Reminder to patients no to take any other long-term medicines for MS while receiving Tyruko.

- A description of PML, potential symptoms and management of PML.

- A reminder of where to report side effects.

- Details of the patient, treating doctor and date Tyruko was started.

Treatment initiation and treatment continuation forms:

- Information on PML and IRIS, including the risk of developing PML during Tyruko treatment stratified by prior treatment with immunosuppressants and JCV infection.

- Confirmation that the doctor has discussed the risks of PML and the risk of IRIS if treatment is discontinued following suspicion of PML, and confirmation of patient understanding of the risks of PML and that they have received a copy of the treatment initiation form and a patient alert card.

- Patient details and prescriber name.

The treatment continuation form should contain the elements of the treatment initiation form and, in addition, a statement that the risks of PML increase with duration of treatment and that treatment beyond 24 months carries additional risk.

Treatment discontinuation form

- Information for the patient that PML has been reported up to 6 months after stopping Tyruko, and to therefore keep the patient alert card with them after treatment discontinuation.

- Reminder of PML symptoms, and when MRI imaging may be warranted.

- Reporting of side effects.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tyruko 300 mg concentrate for solution for infusion
natalizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 15 mL vial of concentrate contains 300 mg natalizumab (20 mg/mL). When diluted the solution for infusion contains approximately 2.6 mg/mL of natalizumab.

3. LIST OF EXCIPIENTS

Sodium chloride, Histidine, Histidine monohydrochloride, Polysorbate 80 (E 433) and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion
300 mg/15 mL

1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use after dilution.
After dilution, do not shake.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/23/1745/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTEOF ADMINISTRATION

Tyruko 300 mg sterile concentrate
natalizumab

2. METHOD OF ADMINISTRATION

Intravenous use after dilution. Do not shake.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg/15 mL

6. OTHER

Additional information to appear on the fixed part of the label:
PC

Information to appear on peel-off label:
Tyruko 300 mg
natalizumab
15mL
PC
EXP
Lot

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tyruko 300 mg concentrate for solution for infusion
natalizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

In addition to this leaflet you will be given a patient alert card. This contains important safety information that you need to know before and during treatment with Tyruko.

- Keep this leaflet and the patient alert card. You may need to read them again. Keep the leaflet and patient alert card with you during treatment and for six months after the last dose of thismedicine , as side effects may occur even after you have stopped treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tyruko is and what it is used for
2. What you need to know before you receive Tyruko
3. How Tyruko is given
4. Possible side effects
5. How to store Tyruko
6. Contents of the pack and other information

1. What Tyruko is and what it is used for

Tyruko is used to treat multiple sclerosis (MS). It contains the active substance natalizumab. This is called a monoclonal antibody.

MS causes inflammation in the brain that damages the nerve cells. This inflammation happens when white blood cells get into the brain and spinal cord. This medicine stops the white blood cells getting through to the brain. This reduces nerve damage caused by MS.

Symptoms of multiple sclerosis
The symptoms of MS vary from patient to patient, and you 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, you may notice the symptoms suddenly, within a few hours, or slowly progressing over several days. Your symptoms will then usually improve gradually (this is called a remission).

How Tyruko can help
In trials, this medicine approximately halved the build-up of disability caused by MS, and decreased the number of MS attacks by about two-thirds. While you are treated with this medicine you might not notice any improvement, but it may still be working to prevent your MS becoming worse.

2. What you need to know before you receive Tyruko

Before you start treatment with this medicine, it is important that you and your doctor have discussed the benefits you could expect to receive from this treatment and the risks that are associated with it.

You must not be given Tyruko

- If you are **allergic** to natalizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have been **diagnosed with PML** (*progressive multifocal leukoencephalopathy*). PML is an uncommon infection of the brain.
- If your **immune system** has a serious problem. This may be due to disease (such as HIV), or to a medicine you are taking, or have taken in the past (see below).
- If you are taking **medicines that affect your immune system**, including certain other medicines used to treat MS. These medicines cannot be used with Tyruko.
- If you **have cancer** (unless it is a type of skin cancer called *basal cell carcinoma*).

Warnings and precautions

You need to discuss with your doctor whether Tyruko is the most suitable treatment for you. Do this before you start taking Tyruko, and when you have been receiving Tyruko for more than two years.

Possible brain infection (PML)

Some people receiving this medicine (fewer than 1 in 100) have had an uncommon brain infection called PML (*progressive multifocal leukoencephalopathy*). PML can lead to severe disability or death.

- Before starting treatment, **all patients will have blood tests** arranged by the doctor for JC virus infection. JC virus is a common virus that does not normally make you ill. However, PML is linked to an increase of JC virus in the brain. The reason for this increase in some patients treated with Tyruko is not clear. Before and during treatment, your doctor will test your blood to check if you have antibodies to the JC virus, which are a sign that you have been infected by the JC virus.
- Your doctor will arrange a **Magnetic Resonance Imaging (MRI) scan**, which will be repeated during treatment to rule out PML.
- **The symptoms of PML** may be similar to an MS relapse (see section 4, *Possible side effects*). You can also get PML up to 6 months after stopping Tyruko treatment.
- **Tell your doctor as soon as possible** if you notice your MS getting worse, if you notice any new symptoms while you are on Tyruko treatment or for up to 6 months afterwards.
- **Tell your partner or caregivers** about what to look out for (see also section 4, Possible side effects). Some symptoms might be difficult to spot by yourself, such as changes in mood or behaviour, confusion, speech and communication difficulties. If you get any of these, **you may need further tests**. Keep looking out for symptoms in the 6 months after stopping Tyruko.

- Keep the patient alert card you have been given by your doctor. It includes this information. Show it to your partner or caregivers.

Three things can increase your risk of PML with Tyruko. If you have two or more of these risk factors, the risk is increased further:

- **If you have antibodies to the JC virus** in your blood. These are a sign that the virus is in your body. You will be tested before and during Tyruko treatment.

- **If you are treated for a long time** with Tyruko, especially if it is more than two years.

- **If you have taken a medicine called an *immunosuppressant***, that reduces the activity of your immune system.

Another condition, called JCV GCN (*JC virus granule cell neuronopathy*), is also caused by JC virus and has occurred in some patients receiving Tyruko. The symptoms of JCV GCN are similar to PML.

For those with a lower risk of PML, your doctor may repeat the test regularly to check that:

- You still do not have antibodies to the JC virus in your blood.

- If you have been treated for more than 2 years, you still have a lower level of JC virus antibodies in your blood.

If someone gets PML
PML can be treated, and Tyruko treatment will be stopped. However, some people get a reaction as Tyruko is removed from the body. This reaction (known as IRIS or immune reconstitution inflammatory syndrome) may lead to your condition getting worse, including worsening of brain function.

Look out for other infections
Some infections other than PML may also be serious and can be due to viruses, bacteria, and other causes.

Tell a doctor or nurse immediately if you think you have an infection (see also section 4, *Possible side effects*).

Changes in blood platelets
Natalizumab may reduce platelets in the blood which are responsible for clotting. This may result in a condition called thrombocytopenia (see section 4) in which your blood may not clot quickly enough to stop bleeding. This can lead to bruising as well as other more serious problems such as excessive bleeding. You should talk to your doctor immediately if you have unexplained bruising, red or purple spots on the skin (called petechiae), bleeding from skin cuts that does not stop or oozes, prolonged bleeding from the gums or nose, blood in urine or stools, or bleeding in the whites of your eyes.

Children and adolescents
Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and Tyruko
Tell your doctor if you are taking, have recently taken or might take any other medicines.

- You **must not** be given this medicine if you are now being treated with medicines that affect your **immune system**, including certain other medicines to treat your MS.

- You **might** not be able to use this medicine if you have **previously** had any that affect your immune system.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

- **Do not use this medicine if you are pregnant,** unless you have discussed this with your doctor. **Be** sure to tell your doctor immediately if you get pregnant, think you may be pregnant, or if you are planning to become pregnant.

- **Do not breast-feed whilst using Tyruko.** Your doctor will help you decide whether you should choose to stop breast-feeding or stop using the medicine.

The risk to the baby and benefit to the mother will be taken into consideration by your doctor.

Driving and using machines
Dizziness is a very common side effect. If you are affected, do not drive or use machines.

Tyruko contains sodium
Each vial of this medicine contains 2.3 mmol (or 52 mg) of sodium. After dilution for use, this medicinal product contains 17.7 mmol (or 406 mg) sodium per dose. This should be considered if you are on a controlled sodium diet.

3. How Tyruko is given

Tyruko IV infusion will be given to you by a doctor experienced in the treatment of MS. Your doctor may switch you directly from another medicine for MS to Tyruko if there are no problems caused by your previous treatment.

- Your doctor will order **blood tests** for antibodies to the JC virus and other possible problems.

- Your doctor will arrange an **MRI scan**, which will be repeated during treatment.

- **To switch from some MS medicines,** your doctor may advise you to wait for a certain time to ensure that most of the previous medicine has left your body.

- For adults the recommended dose is 300 mg, given once every 4 weeks.

- Tyruko must be diluted before it is given to you. It is given as a drip into a vein (by intravenous infusion), usually in your arm. This takes about 1 hour.

- Information for medical or healthcare professionals on how to prepare and administer the medicine is provided at the end of this leaflet.

If you stop using Tyruko
Regular dosing with Tyruko is important, especially in the first few months of treatment. It is important to continue with your medicine for as long as you and your doctor decide that it is helping you. Patients who received one or two doses of Tyruko, and then had a gap in treatment of three months or more, were more likely to have an allergic reaction when restarting treatment.

Checking for allergic reactions
A few patients have had an allergic reaction to this medicine. Your doctor may check for allergic reactions during the infusion and for 1 hour afterwards. See also section 4, *Possible side effects*.

If you miss your dose of Tyruko
If you miss your usual dose of Tyruko, arrange with your doctor to receive it as soon as you can. You can then continue to receive your dose of Tyruko every 4 weeks.

Will Tyruko always work?
In a few patients receiving Tyruko, the body's natural defences may stop the medicine from working properly over time, as the body develops antibodies to the medicine. Your doctor can decide whether this medicine is not working properly for you from blood tests and will stop the treatment, if necessary.

If you have any further questions on Tyruko, ask your doctor. Always use this medicine exactly as described in this leaflet or as your doctor has told you. Check with your doctor if you are not sure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Speak to your doctor or nurse immediately if you notice any of the following.

Signs of a brain infection
- Changes in personality and behaviour such as confusion, delirium or loss of consciousness
- Seizures (fits)
- Headache
- Nausea / vomiting
- Stiff neck
- Extreme sensitivity to bright light
- Fever
- Rash (anywhere on the body)

These symptoms may be caused by an infection of the brain (*encephalitis or PML*) or its covering layer (*meningitis*).

Signs of other serious infections
- An unexplained fever
- Severe diarrhoea
- Shortness of breath
- Prolonged dizziness
- Headache
- Weight loss
- Listlessness
- Impaired vision
- Pain or redness of the eye(s)

Signs of an allergic reaction
- Itchy rash (*hives*)
- Swelling of your face, lips or tongue
- Difficulty breathing
- Chest pain or discomfort
- Increase or decrease in your blood pressure (your doctor or nurse will notice this if they are monitoring your blood pressure)

These are most likely during or shortly after the infusion.

Signs of a possible liver problem
- Yellowing of your skin or the whites of your eyes
- Unusual darkening of the urine
- Abnormal liver function test

Speak to a doctor or nurse immediately if you get any of the side effects listed above, or if you think you have an infection. **Show your patient alert card** and this package leaflet to any doctor or nurse who treats you, not only to your neurologist.

Other side effects

Very common (may affect more than 1 in 10 people)
- Urinary tract infection
- Sore throat and runny or blocked up nose
- Headache
- Dizziness
- Feeling sick (nausea)
- Joint pain
- Tiredness
- Dizziness, feeling sick (nausea), itching and chills during or shortly after infusion

Common (may affect up to 1 in 10 people)
- Anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy)
- Allergy (*hypersensitivity*)
- Shivering
- Itchy rash (*hives*)
- Being sick (*vomiting*)
- Fever
- Difficulty breathing (*dyspnoea)*
- Reddening of the face or body (*flushing*)
- Herpes infections
- Discomfort around the place you have had your infusion. You could experience bruising, redness, pain, itching or swelling

Uncommon (may affect up to 1 in 100 people)
- Severe allergy (*anaphylactic reaction*)
- Progressive multifocal leukoencephalopathy (PML)
- Inflammatory disorder after discontinuation of the medicinal product
- Facial swelling
- An increase in the number of white blood cells (*eosinophilia*)
- Reduction in blood platelets
- Easy bruising (purpura)

Rare (may affect up to 1 in 1 000 people)
- Herpes infection in the eye
- Severe anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy).
- Severe swelling under the skin
- High levels of bilirubin in the blood (*hyperbilirubinaemia*) which may cause symptoms such as yellowing of your eyes or skin, fever and tiredness

Not known (frequency cannot be estimated from the available data)
- Unusual infections (so-called "*opportunistic infections*")
- Damage to your liver

Speak to your doctor as soon as possible if you think you have an infection.
You will also find this information in the patient alert card you have been given by 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 this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tyruko

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

Unopened vial:
Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Diluted solution:
After dilution, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2 ˚C to 8 ˚C and infused within 24 hours of dilution.

Do not use this medicine if you notice particles in the liquid and/or the liquid in the vial is discoloured.

6. Contents of the pack and other information

What Tyruko contains
The active substance is natalizumab. Each 15 mL vial of concentrate contains 300 mg natalizumab (20 mg/mL). When diluted, the solution for infusion contains approximately 2.6 mg per mL of natalizumab.

The other ingredients are:
Sodium chloride (see section 2 'Tyruko contains sodium')
Histidine
Histidine monohydrochloride Polysorbate 80 (E 433)
water for injections

What Tyruko looks like and contents of the pack
Tyruko is a colourless, clear to slightly opalescent solution (sterile concentrate).
Each carton contains one glass vial.

Marketing Authorisation Holder and Manufacturer

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

1. Inspect the Tyruko vial for particles prior to dilution and administration. If particles are observed and/or the liquid in the vial is not colourless, clear to slightly opalescent, the vial must not be used.

2. Use aseptic technique when preparing the medicine. Remove flip-top from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 mL concentrate for solution for infusion.

3. Add the 15 mL concentrate for solution for infusion to 100 mL sodium chloride 9 mg/mL (0.9%) solution for injection. Gently invert the solution to mix completely. Do not shake.

4. Tyruko must not be mixed with other medicinal products or diluents.

5. Visually inspect the diluted medicinal product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.

6. The diluted medicinal product is to be used as soon as possible and within 24 hours of dilution. If the diluted medicinal product is stored at 2 to 8 °C (do not freeze), allow the solution to warm to room temperature prior to infusion.

7. The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 mL per minute.

8. After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/mL (0.9%) solution for injection.

9. Each vial is for single-use only.

10. In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

11. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.