



## 1. NAME OF THE MEDICINAL PRODUCT

TYSABRI 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/ml of natalizumab.

Natalizumab is a recombinant humanised anti- $\alpha$ 4-integrin antibody produced in a murine cell line by recombinant DNA technology.

### Excipient with known effect

Each vial contains 2.3 mmol (or 52 mg) sodium. When diluted in 100 ml sodium chloride 9 mg/ml (0.9%) the medicinal product contains 17.7 mmol (or 406 mg) sodium.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colourless, clear to slightly opalescent solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

TYSABRI is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis 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 relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

## 4.2 Posology and method of administration

TYSABRI 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 TYSABRI 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 of TYSABRI, 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 with TYSABRI (see also section 4.4).

### Posology

TYSABRI 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 TYSABRI 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*

TYSABRI 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 TYSABRI in children and adolescents up to 18 years have not been established. No recommendation on a posology can be made. Currently available data are described in sections 4.8 and 5.1.

### Method of Administration

TYSABRI 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.

TYSABRI must not be administered as a bolus injection.

### 4.3 Contraindications

Hypersensitivity to natalizumab 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

#### Progressive Multifocal Leukoencephalopathy (PML)

Use of TYSABRI 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 TYSABRI 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 TYSABRI. 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 TYSABRI.
- Immunosuppressant use prior to receiving TYSABRI.

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 TYSABRI therapy, **and** have received prior immunosuppressant therapy) have a significantly higher risk of PML.

In anti-JCV antibody positive TYSABRI 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 patients considered at high risk treatment with TYSABRI 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 TYSABRI treatment. Testing for serum anti-JCV antibody prior to initiating TYSABRI 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 (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).

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

### MRI screening for PML

Before initiation of treatment with TYSABRI, 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 TYSABRI therapy, **and** have received prior immunosuppressant therapy),
- or
- Patients with a high anti-JCV antibody index who have received more than 2 years of TYSABRI therapy and without prior history of immunosuppressant therapy.

Current evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with TYSABRI for longer than 2 years (see the Physician Information and Management Guidelines for further information).

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

PML should be considered as a differential diagnosis in any MS patient taking TYSABRI 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 TYSABRI-treated patients.

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

The clinician 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 of TYSABRI 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 TYSABRI 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 TYSABRI.

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

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

PML and IRIS (Immune Reconstitution Inflammatory Syndrome)

IRIS occurs in almost all TYSABRI PML patients after withdrawal or removal of the medicinal product, e.g. by plasma exchange (see section 5.2). 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, which has occurred within days to several weeks after plasma exchange in TYSABRI treated patients with PML, 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 TYSABRI, 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 TYSABRI as a monotherapy (see section 4.8).

TYSABRI increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving TYSABRI (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 TYSABRI 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 TYSABRI should be considered in these patients.

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

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

#### Educational guidance

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

Physicians must discuss the benefits and risks of TYSABRI 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 TYSABRI.

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 TYSABRI, 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 TYSABRI 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.

Discontinue administration of TYSABRI and initiate appropriate therapy at the first symptoms or signs of hypersensitivity.

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

#### Concurrent treatment with immunosuppressants

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

In Phase 3 MS clinical trials, 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 TYSABRI.

#### 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 TYSABRI when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to TYSABRI have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to TYSABRI, 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 with TYSABRI (see section 4.3).

When switching patients from another DMT to TYSABRI, 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 TYSABRI 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 TYSABRI 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 with TYSABRI 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 with TYSABRI 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 TYSABRI.

Alemtuzumab has profound prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with TYSABRI 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 TYSABRI and an increased incidence of hypersensitivity reactions (see section 4.8).

Since patients who have received an initial short exposure to TYSABRI 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 TYSABRI.

### Hepatic Events

Spontaneous serious adverse reactions of liver injury have been reported during the post marketing phase. These liver injuries may occur at any time during treatment, even after the first dose. In some instances, the reaction reoccurred when TYSABRI was reintroduced. Some patients with a past medical history of an abnormal liver test have experienced an exacerbation of abnormal liver test while on TYSABRI. 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 TYSABRI should be discontinued.

#### Stopping TYSABRI 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 in TYSABRI

TYSABRI contains 2.3 mmol (or 52 mg) sodium per vial of medicinal product. When diluted in 100 ml sodium chloride 9 mg/ml (0.9%) this medicinal product contains 17.7 mmol (or 406 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

TYSABRI 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 TYSABRI for 6 months compared to an untreated control group. Live vaccines have not been studied.

#### **4.6 Fertility, pregnancy and lactation**

##### 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 TYSABRI exposure on pregnancy outcomes.

The completed prospective TYSABRI 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 TYSABRI.

Cases from published literature reported transient mild to moderate thrombocytopenia and anaemia observed in infants born to women exposed to TYSABRI in their third trimester of pregnancy. Therefore, it is recommended that newborns of women exposed to the medicinal product during the third trimester of pregnancy are monitored for potential haematological abnormalities.



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

#### Breast-feeding

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

#### 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**

No studies on the effects on the ability to drive and use machines have been performed with TYSABRI. However, given that dizziness has been commonly reported, patients who experience this adverse reaction should be advised not to drive or use machines until it has resolved.

#### **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%).

The highest incidence of adverse reactions identified from placebo-controlled trials in multiple sclerosis patients with natalizumab given at the recommended dose, are reported as dizziness, nausea, urticaria and rigors associated with infusions.

##### Tabulated list of adverse reactions

Adverse reactions reported with natalizumab with an incidence of 0.5% greater than reported with placebo are shown below.

The reactions are reported as MedDRA preferred terms under the MedDRA primary system organ class. Frequencies were defined as follows:

Common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<b>MedDRA System Organ Class</b>	<b>Adverse reaction</b>	<b>Frequency category</b>
Infections and infestations	Urinary tract infection	Common
	Nasopharyngitis	Common
Immune system disorders	Urticaria	Common
	Hypersensitivity	Uncommon
Nervous system disorders	Headache	Common
	Dizziness	Common

	Progressive Multifocal Leukoencephalopathy (PML)	Uncommon
Gastrointestinal disorders	Vomiting	Common
	Nausea	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Rigors	Common
	Pyrexia	Common
	Fatigue	Common

### Description of selected adverse reactions

#### Infusion reactions

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 TYSABRI. 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

In 10% of patients antibodies against natalizumab were detected in 2-year controlled clinical trials in MS patients. Persistent anti-natalizumab antibodies (one positive test reproducible on retesting at least 6 weeks later) developed in approximately 6% of patients. Antibodies were detected on only one occasion in an additional 4% of patients. Persistent antibodies were associated with a substantial decrease in the effectiveness of TYSABRI 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 TYSABRI. The duration of treatment with TYSABRI prior to onset ranged from a few months to several years (see section 4.4).

In postmarketing experience, rare cases of ARN have been observed in patients receiving TYSABRI. 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 postmarketing use of TYSABRI. 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 TYSABRI 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 TYSABRI treatment 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. During treatment with TYSABRI, small reductions in haemoglobin (mean decrease 0.6 g/dl), haematocrit (mean decrease 2%) and red blood cell counts (mean decrease  $0.1 \times 10^6/l$ ) were seen. All changes in haematological variables returned to pre-treatment values, usually within 16 weeks of last dose of the medicinal product 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 TYSABRI therapy was discontinued the elevated eosinophil levels resolved.

#### 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.

#### **4.9 Overdose**

No case of overdose has been reported.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Selective Immunosuppressive Agent, ATC code: L04AA23

#### Pharmacodynamic effects

Natalizumab is a selective adhesion-molecule inhibitor and binds to the  $\alpha 4$ -subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the  $\alpha 4\beta 1$  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  $\alpha 4\beta 7$  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  $\alpha 4$ -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  $\alpha 4\beta 1$  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  $\alpha 4\beta 1$  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  $\alpha 4\beta 1$  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

Efficacy as monotherapy has been evaluated in one randomised, double-blind, placebo-controlled study lasting 2 years (AFFIRM study) in relapsing-remitting MS 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 TYSABRI 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 below.

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 year	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)
<b>RESULTS</b>		
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 <sub>95%</sub> 0.26 ; 0.41	
Two years	Rate ratio 0.32 CI <sub>95%</sub> 0.26 ; 0.40	
Relapse free		
After one year	53%	76%
After two years	41%	67%
Disability		
Proportion progressed <sup>1</sup> (12-week confirmation; primary outcome)	29%	17%
	Hazard ratio 0.58, CI <sub>95%</sub> 0.43; 0.73, p<0.001	
Proportion progressed <sup>1</sup> (24-week confirmation)	23%	11%
	Hazard ratio 0.46, CI <sub>95%</sub> 0.33; 0.64, p<0.001	
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)
<sup>1</sup> Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS $\geq 1.0$ 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 relapsing remitting MS (patients with 2 or more relapses and 1 or more Gd+ lesion), the annualised relapse rate was 0.282 in the TYSABRI 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.

Interim analysis of results (as of May 2015) from the ongoing TYSABRI Observational Program (TOP), a phase 4, multicentre, single-arm study (n=5770) demonstrated that patients switching from beta interferon (n= 3255) or glatiramer acetate (n= 1384) to TYSABRI 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 TYSABRI, for patients switching from fingolimod (n=147) to TYSABRI, 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 TYSABRI exposure for this subgroup of patients should be considered when interpreting these data.

A post-marketing meta-analysis was conducted using data from 621 paediatric MS patients treated with TYSABRI (median age 17 years, range was 7-18 years, 91% aged  $\geq$ 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).

## 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  $110 \pm 52$   $\mu$ g/ml. Mean average steady-state trough natalizumab concentrations over the dosing period ranged from 23  $\mu$ g/ml to 29  $\mu$ g/ml. The predicted time to steady-state was approximately 36 weeks.

A population pharmacokinetics analysis was conducted on samples from over 1,100 MS patients receiving doses ranging from 3 to 6 mg/kg natalizumab. Of these, 581 patients received a fixed 300 mg dose as monotherapy. The mean  $\pm$  SD steady-state clearance was  $13.1 \pm 5.0$  ml/h, with a mean  $\pm$  SD half-life of  $16 \pm 4$  days. The analysis explored the effects of selected covariates including body weight, age, gender, hepatic and renal function, and presence of anti-natalizumab antibodies upon pharmacokinetics. Only body weight and the presence of anti-natalizumab antibodies were found to influence natalizumab disposition. Body weight was found to influence clearance in a less-than-proportional manner, such that a 43% change in body weight resulted in a 31% to 34% change in clearance. The change in clearance was not clinically significant. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 3-fold, consistent with reduced serum natalizumab concentrations observed in persistently antibody-positive patients, (see section 4.8).

The pharmacokinetics of natalizumab in paediatric MS patients has not been established. The pharmacokinetics of natalizumab in patients with renal or hepatic insufficiency has not been studied.

The effect of plasma exchange on natalizumab clearance and pharmacodynamics was evaluated in a study of 12 MS patients. Estimates of the total natalizumab removal after 3 plasma exchanges (over a 5-8 day interval) was approximately 70-80%. This compares to approximately 40% seen in earlier studies in which measurements occurred after natalizumab discontinuation over a similar period of observation. The impact of plasma exchange on the restitution of lymphocyte migration and ultimately its clinical usefulness is unknown.

### 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  $\alpha$ 4-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 phosphate, monobasic, monohydrate  
Sodium phosphate, dibasic, heptahydrate  
Sodium chloride  
Polysorbate 80 (E433)  
Water for injections.

### 6.2 Incompatibilities

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



### **6.3 Shelf life**

#### Unopened vial

4 years

#### Diluted solution

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 - 8°C and infused within 8 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 - 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**

Instructions for use:

- Inspect the TYSABRI 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 TYSABRI 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 TYSABRI solution to mix completely. Do not shake.
- TYSABRI 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 8 hours of dilution. If the diluted medicinal product is stored at 2°C - 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/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.

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

**7. MARKETING AUTHORISATION HOLDER**

Eisai (Thailand) Marketing Co., Ltd., Bangkok

**8. MARKETING AUTHORISATION NUMBER(S)**

1C 66/60 (NBC)

**9. DATE OF AUTHORISATION**

26 December 2017

**10. DATE OF REVISION OF THE TEXT**

23 April 2019