PACKAGE INSERT

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 2.6mg/ml of natalizumab.

Natalizumab is a recombinant humanised anti-α4-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. (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.

Colourless, clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tysabri 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 relapsing remitting multiple sclerosis 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 Patient Information Leaflet). After 2 years of treatment, patients should be re-informed about the risks of the medicinal product, 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 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 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 this medicinal product in children and adolescents up to 18 years have not been established. Currently available data are described in sections 4.8 and 5.1.

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 Tysabri 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.

Tysabri 300 mg concentrate for solution 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

Traceability

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

Progressive Multifocal Leukoencephalopathy (PML)

Use of this medicinal product 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 this medicinal product. 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 this medicinal product **and** have received prior immunosuppressant therapy) have a significantly higher risk of PML.

In anti-JCV antibody positive natalizumab treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response (index) is associated with the level of risk for PML.

In anti-JCV antibody positive patients, extended interval dosing of Tysabri (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.

In 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).

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),

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- 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 an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with this medicinal product 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 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 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 natalizumab-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 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 this medicinal product 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 six months following discontinuation of Tysabri.

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.

<u>PML and IRIS (Immune Reconstitution Inflammatory Syndrome)</u>
IRIS occurs in almost all PML patients treated with this medicinal product 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).

<u>Infections including other opportunistic infections</u>

Other opportunistic infections have been reported with use of this medicinal product, 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 this medicinal product 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 postmarketing 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 this medicinal product 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 this medicinal product, 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 this medicinal product 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 Package Insert 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 this medicinal product and an increased incidence of hypersensitivity reactions (see section 4.8).

Since patients who have received an initial short exposure to this medicinal product 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 this medicinal product 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 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 this medicinal product.

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 postmarketing setting. Monitoring of platelet counts and haemoglobin is recommended in neonates born to women exposed to natalizumab during pregnancy.

This drug 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 newborn/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

Tysabri has a minor influence on the ability to drive and use machines. Dizziness may occur following administration of this medicinal product (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 6786 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 Necrotising herpetic retinopathy
Immune system disorders		Hypersensitivity	Anaphylactic reaction Immune reconstitution inflammatory syndrome		
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia, Immune thrombocytopenic purpura (ITP) Eosinophilia	Haemolytic anaemia Nucleated red cells	
Hepatobiliary disorders				Hyperbilirubinaemia	Liver injury
Investigations		Hepatic enzyme increased Drug specific antibody present			
Injury, poisoning and procedural complications	Infusion related reaction				
Respiratory, thoracic and mediastinal disorders		Dyspnoea			
Gastrointestinal disorders	Nausea	Vomiting			
General disorders and administration site conditions	Fatigue	Pyrexia Chills Infusion site reaction Injection site reaction	Face oedema		
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria		Angioedema	
Vascular disorders		Flushing			
Nervous system disorders	Dizziness Headache				

MedDRA System Organ Class	Frequency of adverse reactions				
	Very Common	*Common*	*Uncommon*	*Rare*	*Not known*
Musculoskeletal and connective tissue disorders	Arthralgia				

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 this medicinal product. 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 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 postmarketing experience, rare cases of ARN have been observed in patients receiving this medicinal product. 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 this medicinal product 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. During treatment with IV form of this medicinal product, 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 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 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.

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: Selective Immunosuppressive Agent, ATC code: L04AA23

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 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 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	
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 relapsing remitting MS (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.

Tysabri Observational Program (TOP)

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 this medicinal product, 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 Tysabri patients (TOUCH registry), 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 Tysabri dosing 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%
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 number of 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.

**Percentages are calculated based on the number of subjects with available N/NE T2 lesion data at Week 72.

*** Percentages are calculated based on the number of subjects in the mITT population.

**** 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 (4.59-6.38 L, 95% confidence interval).

Elimination

Population median estimate for linear clearance was 6.21 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 & Hepatic Impairment

The pharmacokinetics of natalizumab in patients with renal or 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 phosphate, monobasic, monohydrate
Sodium phosphate, dibasic, heptahydrate
Sodium chloride
Polysorbate 80 (E433)

Water for injections.

6.2 Incompatibilities

Tysabri 300 mg concentrate for solution for infusion 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 to 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 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 (chlorobutyl 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 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 8 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/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 (Singapore) Pte Ltd
152 Beach Road,
#15-07 to 08 Gateway East,
Singapore 189721

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th June 2006

9. DATE OF REVISION OF THE TEXT

April 2023