

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

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- α 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 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 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

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 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 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). For further information, refer to the Physician Information and Management Guidelines.

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/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 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.

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

PML and IRIS (Immune Reconstitution Inflammatory Syndrome)

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

Infections including other opportunistic infections

Other opportunistic infections have been reported with use of 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 very 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:

Very common ($\geq 1/10$), 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.

MedDRA System Organ Class	Adverse reaction	Frequency category
Infections and infestations	Urinary tract infection	Very common
	Nasopharyngitis	Very common
Immune system disorders	Urticaria	Common
	Hypersensitivity	Uncommon
Nervous system disorders	Headache	Very common
	Dizziness	Very common
	Progressive Multifocal Leukoencephalopathy (PML)	Uncommon
Gastrointestinal disorders	Vomiting	Common
	Nausea	Very common
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
General disorders and administration site conditions	Rigors	Common
	Pyrexia	Common
	Fatigue	Very 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 listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressive agents, ATC code: L04AA23

Pharmacodynamic effects

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α 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 α 4 β 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 α 4 β 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 α 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 α 4 β 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 α 4 β 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 α 4 β 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 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 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).

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 \geq 1 year prior to switching to EID. The interim analysis showed a lower risk of PML in patients treated with EID (hazard ratio = 0.06 95% CI of hazard ratio = 0.01- 0.22). The efficacy of TYSABRI when administered with EID has not been established, and therefore the benefit/risk balance of EID is unknown (see section 4.4).

Efficacy has been modelled for patients who switch to longer dosing after \geq 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 body weight >80kg or those with dosing intervals \geq 7 weeks. No prospective clinical studies have been completed to validate these findings.

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 μ g/ml. Mean average steady-state trough natalizumab concentrations over the dosing period ranged from 23 μ g/ml to 29 μ 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 ± 5.0 ml/h, with a mean \pm SD half-life of 16 ± 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.

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 α 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 (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 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

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/346/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th June 2006
Date of latest renewal: 18th April 2016

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Biogen Inc
5000 Davis Drive
Research Triangle Park
NC 27709-4627
USA

Biogen (Denmark) Manufacturing ApS
Biogen Allé 1
DK-3400 Hillerød
Denmark

Name and address of the manufacturers responsible for batch release

Biogen (Denmark) Manufacturing ApS
Biogen Allé 1
DK-3400 Hillerød
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

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

The Marketing Authorisation Holder must, following discussions and agreement with the National Competent Authorities in each Member State where TYSABRI is marketed, ensure that all physicians who intend to prescribe TYSABRI are provided with a physician pack containing the following elements:

- Summary of Product Characteristics and Package Leaflet
- Physician information about TYSABRI
- Patient alert card
- Treatment initiation and treatment continuation forms
- Treatment discontinuation form

The physician information about TYSABRI shall contain the following key elements:

- That 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.
- Information that atypical/opportunistic infections, in particular PML, may occur with TYSABRI and include:
 - Opportunistic infections (other than PML):
 - TYSABRI increases the risk of developing encephalitis, meningitis and acute retinal necrosis (ARN) caused by herpes simplex and varicella zoster viruses
 - Guidance on screening for ARN.
 - That the risk of PML increases with increasing duration of treatment and that treatment beyond 24 months carries additional risk and other factors associated with an increased risk for the development of PML
 - Presence of anti-JC virus antibodies
 - Level of the antibody response (index) for patients without a history of immunosuppressant treatment
 - Immunosuppressant treatment prior to the use of TYSABRI
 - A stratification of the risk of developing PML based on the identified risk factors and presentation of the PML risk in a given time interval of treatment as well as the cumulative PML risk
 - PML risk estimates algorithm summarizes PML risk by anti- John Cunningham virus (JCV) antibody status, prior IS use and duration of treatment (by year of treatment) and stratifies this risk by index value when applicable.
 - The recommendation that patients should have MRI scans at the following times:
 - Within 3 months prior to starting TYSABRI
 - Annually during treatment with TYSABRI
 - More frequent MRIs (e.g. on a 3 to 6 monthly basis) for patients at high risk for PML.

- At the first sign of any symptoms indicative of the possibility of PML.
- Description of MRI protocols for baseline, routine screening and in case of PML suspicion
- Anti-JCV antibody testing, frequency of testing, interpretation of qualitative and quantitative results, seroprevalence of JCV-antibodies and seroconversion rate over time
- Diagnosis and prognosis of symptomatic and asymptomatic PML
 - differentiation between PML and MS
 - early recognition and intervention may improve outcome

Discussion of PML in TYSABRI Treated Patients

During extended pre-registration trials, two cases of PML were reported in MS patients and a full safety evaluation revealed one further case in a clinical trial patient with Crohn's Disease. In the post-marketing setting, the risk of PML has been well characterized over the first 6 years of treatment with the identification of different levels of PML risk in different patient subgroups.

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 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 (i.e. the risk is greater in those with a high antibody index compared to those with a low index). Currently available 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.

Irrespective of the presence or absence of PML risk factors, heightened clinical vigilance for PML should be maintained in all patients treated with TYSABRI and for 6 months following discontinuation of therapy.

- Description of PML and incidence. Analysis of STRATIFY JCV showed the prevalence of anti-JCV antibodies to be approximately 55%. Anti-JCV antibody prevalence in the EU was reported as ranging from 48.8% to 69.5% in the EU in a cross sectional study of MS patients irrespective of treatment. In the MS population, anti-JCV antibody prevalence increased with age and was lower in women than in men in all cohorts tested. In general, anti-JCV antibody prevalence did not appear to be affected by prior immunosuppressant use, prior exposure to TYSABRI, or duration of TYSABRI exposure.
- Patients, their partners and care givers are advised of symptoms that may be indicative of early PML and the need for counseling on the need to be vigilant for these symptoms while on TYSABRI treatment, and also for approximately 6 months after the last dose of TYSABRI (PML has also been reported up to 6 months following the last dose of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation).
- Information provided regarding - In all cases where further investigation of change in neurological status or change in brain MRI is indicated, TYSABRI must be suspended and not restarted until non MS pathology has been confidently excluded. Suspension of TYSABRI therapy, for short duration (days or weeks), is not expected to compromise therapeutic efficacy based on the pharmacodynamics of the drug.

The decision to suspend TYSABRI at any stage may be based on the initial clinical presentation, MRI findings, the evolution of symptoms or signs and/or the response to corticosteroid treatment.

- Confirmation that TYSABRI should be permanently discontinued if PML is confirmed.
- Management of PML
- Monitoring strategy after discontinuation of TYSABRI treatment
- The need to inform patients about the benefits and risk of TYSABRI and provide them with:
 - A copy of the treatment initiation form
 - A patient alert card including a core text agreed by the CHMP
- If treatment is to be continued for longer than 24 months, the need to inform patients about the increased risk of PML and provide them with a copy of the treatment continuation form
- Description of Immune Reconstitution Inflammatory Syndrome (IRIS) is provided

Clinical neurologic deterioration in patients with PML and/or JCV GCN may be caused by JCV-mediated destruction of CNS tissue, or upon restoration of immune function, by an intracerebral immune inflammatory reaction known as immune reconstitution inflammatory syndrome (IRIS). IRIS is generally suspected when patients with PML exhibit signs of clinical worsening usually, but not always, accompanied by gadolinium enhancement of PML lesions with or without mass effect on brain MRI. The clinical worsening is a result of local inflammatory reaction, including oedema, and manifests as a worsening of neurological symptoms including hemiparesis, ataxia, speech abnormalities, visual disturbance, cognitive/behavioural changes and seizure (dependent on the site of IRIS). Severe sequelae can occur including coma and death. Although JC viral load in the CSF might be expected to decline in the setting of IRIS, it is also possible that due to the breakdown of the blood brain barrier (BBB) and release of JCV from cells lysed during IRIS, it can be increased.

In patients treated with TYSABRI, IRIS has occurred within days to several weeks after TYSABRI removal by plasma exchange (PLEX) or immunoabsorption (IA). Although the inflammatory reaction following immune reconstitution may be a necessary step to remove JCV-infected cells, it may become necessary to treat the active immune reaction to prevent potential damage caused by IRIS (Talan 2009; Elston and Thacker 2009) and can be life-threatening and may therefore require management in an intensive care unit. Therefore, following PLEX or IA, periodic clinical monitoring of patients, including MRI monitoring, may be useful for the early detection of IRIS. The diagnosis and management of IRIS is a controversial issue and there is no consensus concerning its treatment. However, it has recently been suggested that corticosteroids may be useful to treat IRIS, particularly in patients with severe to life-threatening IRIS (Tan *et al.*, 2009, Clifford *et al.*, 2010). The following steroid regimens have been reported for the treatment of IRIS in the literature:

- 1) Oral prednisone 1.5 mg/kg/d x 2 wks with taper over 2 months
- 2) Intravenous methylprednisolone (1 g/d for 3 or 5 d) with oral taper over 2 months

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

Prophylactic steroid treatment is currently not recommended. As scientific and medical knowledge, including both diagnostic criteria and management of IRIS is rapidly evolving, please contact Medical affairs in your country for the most up to date information on treatment recommendations.

- Possibility of other opportunistic infections
- The need to inform the National Competent Authority about any cases of PML
- Information about any registry or other monitoring system set up in the Member State and how to enter patients

Information about extended interval dosing (EID)

- Reminder of the approved dosing; cross reference to EU SmPC
- Present the results of the TOUCH analysis which showed clinically and statistically significant reduction in PML risk in patients who are treated with EID (dosing interval 6 weeks) compared to Standard interval dosing (dosing interval 4 weeks).
- Switching usually occurred after 1 year (median of 25 standard interval doses) in the secondary definition
- Inform about an ongoing study assessing the efficacy, tolerability and safety of switching to EID after at least 12 months on approved dosing.
- Present data from PK/PD/efficacy modelling from clinical trial data that suggests efficacy of 6 week dosing more similar to 4 weeks if occurs ≥ 1 year of 4 weekly treatment
- Present data from PK/PD/efficacy modelling from the RESTORE study which indicates that risk of return of MS disease activity more likely with increased body weight (≥ 80 kg) or longer dosing intervals (≥ 7 weeks). Monitoring for potential signs of return of MS disease activity in patients switching dosing intervals.

The treatment initiation form should contain the following elements:

- That the aim of the treatment initiation form is to provide patients with information on PML and IRIS
- Information on PML and IRIS including the risk of developing PML during TYSABRI treatment stratified by prior treatment with immunosuppressants and JCV infection.
- Confirmation that the doctor has discussed the risks of PML and the risk of IRIS if treatment is discontinued following suspicion of PML
- Confirmation of patient understanding of the risks of PML and that they have received a copy of the form and a patient alert card
- Patient details, signature and date
- Prescriber name, signature and date

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

The treatment discontinuation form

- Inform patient that PML has been reported up to 6 months after stopping Tysabri
- Reminder of PML symptoms
- When MRI imaging may be warranted

- Keep alert card with them after discontinuation
- Reporting of side effects

Patient alert card

- Reminder to show the card to any doctor involved with their treatment
- Reminder to read the package leaflet carefully before starting Tysabri
- Reminder to keep the card with them for 6 months after the last dose of Tysabri
- Reminder to show the card to patients and caregivers and provides a list of symptoms that may be associated with the development of PML
- Reminder not to start Tysabri if there is a serious problem with their immune system
- Reminder not to take any other long-term medicines for MS while receiving Tysabri
- A description of PML, potential symptoms and management of PML
- A reminder regarding serious infections and the need to speak to their doctor if they have severe persistent infection
- A reminder of where to report side effects
- Details of the patient, treating doctor and date Tysabri was started

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TYSABRI 300 mg concentrate for solution for infusion
natalizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

sodium phosphate, monobasic, monohydrate; sodium phosphate, dibasic, heptahydrate; sodium chloride; polysorbate 80 (E433) and water for injections.

See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion
1 x 15 ml vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Dilute before infusion.
After dilution, do not shake.

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/346/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TYSABRI 300 mg concentrate for solution for infusion
natalizumab
Intravenous use

2. METHOD OF ADMINISTRATION

Dilute before infusion. After dilution, do not shake.

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

15 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

TYSABRI 300 mg concentrate for solution for infusion natalizumab

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

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

In addition to this leaflet you will be given a Patient Alert Card, which contains important safety information that you need to know before you are given TYSABRI (pronounced tie-SA-bree) and during treatment with TYSABRI.

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

What is in this leaflet:

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

1. What TYSABRI is and what it is used for

TYSABRI contains the active substance (natalizumab). This active ingredient is called a monoclonal antibody. These antibodies work by binding to proteins in the body so that the harmful effect of that protein is removed.

TYSABRI is used to treat multiple sclerosis (MS). MS causes inflammation in the brain that damages the nerve cells. TYSABRI stops the cells that cause inflammation from going into your brain. This reduces nerve damage caused by MS.

What are the symptoms of multiple sclerosis?

The symptoms of MS vary from patient to patient, and you may experience some or none of them.

Symptoms can include; walking problems, numbness in the face, arms or legs, problems seeing things, tiredness, feeling off-balance or light headed, bladder and bowel problems, difficulty in thinking and concentrating, depression, acute or chronic pain, sexual problems, and stiffness and muscle spasms. When the symptoms flare up, it is called a relapse (also known as an exacerbation or an attack). When a relapse occurs, you may notice the symptoms suddenly, within a few hours, or slowly progressing over several days. Your symptoms will then usually improve gradually (this is called a remission).

In clinical trials, TYSABRI approximately halved the progression of the disabling effects of MS and also decreased the number of MS attacks by about two-thirds. When you receive TYSABRI you might not notice any improvement, but TYSABRI may still be working to prevent your MS becoming worse.

2. What you need to know before you use TYSABRI

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

Do not use TYSABRI

- If you are allergic to natalizumab or any of the other ingredients of this medicine (listed in section 6).
- If your doctor has told you that you have PML (progressive multifocal leukoencephalopathy). PML is a rare infection of the brain.
- If your doctor tells you that you have a serious problem with your immune system (due to disease for example, HIV or due to a medicine you are taking or have previously taken
- If you are taking medicines that suppress or modulate the immune system including other medicines used to treat MS disease. These medicines cannot be used with TYSABRI (see Using other medicines, below).
- If you have an active cancer (unless it is a type of skin cancer called basal cell carcinoma).

Warnings and precautions

Talk to your doctor before using TYSABRI.

Infections

Tell your doctor **immediately** if you have, or think you have, any sort of infection (see side effects). Some infections other than PML may also be serious and can be due to viruses, bacteria, or other causes.

There have been cases of a rare brain infection called PML (progressive multifocal leukoencephalopathy) that have occurred in patients who have been given TYSABRI. PML may lead to severe disability or death.

- The symptoms of PML may be similar to an MS relapse (e.g. weakness or visual changes). Therefore, if you believe your MS is getting worse or if you notice any new symptoms while you are on TYSABRI treatment or for up to 6 months after stopping TYSABRI treatment, it is very important that you speak to your doctor as soon as possible.
- Speak with your partner or caregivers and inform them about your treatment. Symptoms might arise that you might not become aware of by yourself, such as changes in mood or behaviour, memory lapses, speech and communication difficulties, which your doctor may need to investigate further to rule out PML. You should remain aware for symptoms that might arise for up to 6 months after stopping TYSABRI treatment.
- You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

PML is associated with an uncontrolled increase of the JC virus in the brain, although the reason for this increase in some patients treated with TYSABRI is unknown. A condition called JCV GCN (JC virus granule cell neuronopathy) is also caused by JC virus and has occurred in some patients who have been given TYSABRI. The symptoms of JCV GCN are similar to PML. JC virus is a common virus which infects many people but does not normally cause noticeable illness.

Your doctor may test your blood to check if you have antibodies to the JC virus before you start treatment with TYSABRI. These antibodies are a sign that you have been infected by JC virus. Your doctor may repeat this blood test while you are on TYSABRI treatment to check if anything has changed.

The risk of PML with TYSABRI is higher:

- If you have antibodies to the JC virus in your blood.
- The longer that you are on treatment especially if you have been on treatment for more than two years.
- If you have previously taken a medicine called an immunosuppressant. These medicines reduce the activity of your body's immune system.

If you have all three risks described above your chance of getting PML is higher.

If you have previously not been treated with immunosuppressants and have received TYSABRI for 2 years or longer, the level of your anti-JCV antibody response may be associated with the risk of getting PML.

For those with a lower risk of PML, your doctor may repeat the test regularly to check if anything has changed if:

- If you do not have antibodies to the JC virus in your blood OR
- If you have been treated for more than 2 years and you have a lower level of JCV antibodies in your blood.

You should discuss with your doctor if TYSABRI is the most suitable treatment for you before you start taking TYSABRI and when you have been taking TYSABRI for more than two years.

In patients with PML a reaction known as IRIS (Immune Reconstitution Inflammatory Syndrome) is likely to occur after treatment for PML, as TYSABRI is removed from your body. IRIS may lead to your condition getting worse, including worsening of brain function.

Allergic reactions

A few patients have had an allergic reaction to TYSABRI. Your doctor will check for allergic reactions during the infusion and for 1 hour afterwards.

Will TYSABRI always work?

In a few patients who use TYSABRI, over time the body's natural defence may stop TYSABRI from working properly (the body develops antibodies to TYSABRI). Your doctor can decide whether TYSABRI is not working properly for you by testing your blood and will stop TYSABRI, if necessary.

Other medicines and TYSABRI

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

- You **must not** use TYSABRI if you are being treated with other medicines to treat your MS disease
- You may not be able to use TYSABRI if you are currently receiving or have previously received medicines that affect your immune system

Pregnancy and breast-feeding

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

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

- Do not breast-feed whilst using TYSABRI. You should discuss with your doctor whether you choose to breast-feed or to use TYSABRI.

Driving and using machines

There are no studies on the effects of TYSABRI on the ability to drive and use machines. However, if you experience dizziness, a very common side effect, then you should not drive or use machines.

TYSABRI contains sodium

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

3. How to use TYSABRI

TYSABRI will be given to you by a doctor experienced in the treatment of MS. Your doctor may switch you directly from another medicine for MS to TYSABRI if there are no signs of abnormalities caused by your previous treatment. Your doctor should do a blood test in order to test for abnormalities and whether you have antibodies to the JC virus. To switch from some MS medicines, your doctor may advise you to wait for a certain time to ensure that most of the previous medicine has left your body. Initiating treatment with TYSABRI after alemtuzumab is generally not recommended. If you have been treated with alemtuzumab, a thorough evaluation and discussion with your doctor is required to decide if a switch to TYSABRI is appropriate for you.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

- The recommended dose for adults is 300 mg given once every 4 weeks.
- TYSABRI must be diluted before it is given to you. It is given as a drip into a vein (by intravenous infusion), usually in your arm. This takes about 1 hour.
- Information for medical or healthcare professionals on how to prepare and administer TYSABRI is provided at the end of this leaflet.
- It is important to continue with your medicine for as long as you and your doctor decide that it is helping you. Continuous dosing with TYSABRI is important, especially during the first few months of treatment. This is because patients who received one or two doses of TYSABRI and then had a gap in treatment of three months or more, were more likely to have an allergic reaction when resuming treatment.

If you miss your dose of TYSABRI

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

Always use this medicine exactly as described in this leaflet or as your doctor has told you. Check with your doctor if you are not sure.

If you have any further questions on TYSABRI, ask your doctor.

4. Possible side effects

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

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

Symptoms of serious infections including:

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

A group of symptoms caused by a serious infection of the brain including:

- Changes in personality and behaviour such as confusion, delirium or loss of consciousness, seizures (fits), headache, nausea / vomiting, stiff neck, extreme sensitivity to bright light, fever, rash (anywhere on the body).

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

Signs of allergy to TYSABRI, during or shortly after your infusion:

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

Signs of a possible liver problem:

- Yellowing of your skin or the whites of your eyes
- Unusual darkening of the urine.

TYSABRI can also have other side effects.

Side effects are listed below by how commonly they have been reported in clinical trials:

Very common side effects that may affect more than 1 in 10 people:

- Urinary tract infection
- Sore throat and runny or blocked up nose
- Headache
- Dizziness
- Feeling sick (nausea)
- Joint pain
- Tiredness

Common side effects that may affect up to 1 in 10 people:

- Shivering
- Itchy rash (hives)
- Being sick (vomiting)
- Fever

Uncommon side effects that may affect up to 1 in 100 people:

- Severe allergy (hypersensitivity)
- Progressive multifocal leukoencephalopathy (PML)

Rare side effects that may affect up to 1 in 1,000 people:

- Unusual infections (so-called “Opportunistic infections”)
- Severe anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy)

Speak to your doctor as soon as possible if you think you have an infection.

Show the Alert Card and this package leaflet to any doctor involved with your treatment, not only to your neurologist.

You will also find this information in the Patient Alert Card you have been given by your doctor.

Reporting of side effects

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

5. How to store TYSABRI

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

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

Unopened vial:

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.

Diluted solution:

After dilution, 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.

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

6. Contents of the pack and other information

What TYSABRI contains

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

The other ingredients are:

Sodium phosphate, monobasic, monohydrate,

Sodium phosphate, dibasic, heptahydrate,

Sodium chloride (see section 2 ‘TYSABRI contains sodium’),

Polysorbate 80 (E433)

Water for injections

What TYSABRI looks like and contents of the pack

TYSABRI is a clear, colourless to slightly cloudy liquid.

Each carton contains one glass vial.

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Manufacturer

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For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Other sources of information

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

The following information is intended for healthcare professionals only:

1. Inspect the 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.
2. Use aseptic technique when preparing TYSABRI solution for intravenous infusion. Remove flip-top from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 ml concentrate for solution for infusion.
3. Add the 15 ml concentrate for solution for infusion to 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection. Gently invert the TYSABRI solution to mix completely. Do not shake.
4. TYSABRI must not be mixed with other medicinal products or diluents.
5. Visually inspect the diluted medicinal product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.
6. The diluted medicinal product is to be used as soon as possible and within 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.
7. The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 ml/minute.
8. After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/ml (0.9%) solution for injection.

9. Each vial is for single-use only.
10. In order to improve traceability of biological medicinal products, the product name (Tysabri) and batch number of the administered product should be clearly recorded.
11. Any unused medicinal product or waste material must be disposed of in accordance with local requirements.