

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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.

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

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

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%) the medicinal product contains 17.7 mmol (or 406 mg) sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colourless, clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TYSABRI is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups:

- Adult patients aged 18 years and over with high disease activity despite treatment with a beta-interferon.

These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial Magnetic Resonance Image (MRI) or at least 1 Gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

or

- Adult patients aged 18 years and over 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 TYSABRI (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.

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. If there are signs of treatment-related abnormalities these must return to normal before treatment with natalizumab is started.

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

Adults

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-JCV antibodies (see Section 4.4.).

Readministration

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

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

TYSABRI is contraindicated in children and adolescents below the age of 18 years (see section 4.3).

Method of Administration

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.

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, e.g. mitoxantrone or cyclophosphamide, see also sections 4.4 and 4.8).

Combination with beta-interferons or glatiramer acetate.

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

Children and adolescents below the age of 18 years.

4.4 Special warnings and precautions for use

Progressive Multifocal Leukoencephalopathy (PML)

Use of TYSABRI has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of TYSABRI treatment should be individually reconsidered by the specialist physician and the patient.

Patients should be instructed together with their caregivers on early signs and symptoms of PML.

Each of the following independent risk factors is associated with an increased risk of PML.

- Treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 4 years of TYSABRI treatment therefore the risk of PML in these patients cannot currently be estimated.
- Immunosuppressant use prior to receiving TYSABRI.
- The presence of anti-JCV antibodies.

Anti-JCV antibody status identifies different levels of risk for PML in TYSABRI treated patients. 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., have received more than 2 years of TYSABRI therapy, **and** have received prior immunosuppressant therapy **and** are anti-JCV antibody positive) have the highest risk of PML at approximately 9 in 1,000 patients treated. Patients

should be informed about this increased risk for developing PML before continuation of treatment after 2 years.

For risk stratification prior or during the treatment with TYSABRI anti-JCV antibody testing may provide supportive information.

Before initiation of treatment with TYSABRI, a recent (usually within 3 months) MRI should be available as a reference, and be repeated on a yearly routine basis to update this reference. Patients must be monitored at regular intervals throughout. After 2 years the patient should be re-informed about the risk of PML with TYSABRI.

If PML 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. If any doubt exists, further evaluation, including MRI scan preferably with contrast (compared with pre-treatment 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 (if necessary, by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains), dosing of natalizumab may resume.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive or psychiatric symptoms). 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.

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

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

PML and IRIS (Immune Reconstitution Inflammatory Syndrome)

IRIS occurs in almost all TYSABRI PML patients after withdrawal or removal of TYSABRI, e.g. by plasma exchange (see section 5.2). IRIS is thought to result from the restoration of immune function in patients with PML, which can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS, which has occurred within days to several weeks after plasma exchange in TYSABRI treated patients with PML, and appropriate treatment of the associated inflammation during recovery from PML should be undertaken (see the Physician Information and Management Guidelines for further information).

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 TYSABRI 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).

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 TYSABRI 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 or prior 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).

Patients with a treatment history of immunosuppressant medications are at increased risk 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).

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.

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 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 more at risk for hypersensitivity upon redosing, the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after 6 weeks treatment should not be resumed.

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 beta-interferons or glatiramer acetate (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

There are no adequate data from the use of natalizumab in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Natalizumab should not be used during pregnancy unless the clinical condition of the women requires treatment with TYSABRI.

If a woman becomes pregnant while taking TYSABRI, discontinuation of TYSABRI should be considered.

Breast-feeding

TYSABRI 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

Based on the pharmacological mechanism of action of natalizumab, the use of TYSABRI has no or negligible influence on the ability to drive and use machines.

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%)¹.

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.

List of adverse reactions

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

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

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

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

¹ An adverse event judged related to therapy by the investigating physician.

Infections and infestations

Common Urinary tract infection
 Nasopharyngitis

Immune system disorders

Common Urticaria
Uncommon Hypersensitivity

Nervous system disorders

Common Headache
 Dizziness
Uncommon Progressive Multifocal Leukoencephalopathy (PML)

Gastrointestinal disorders

Common Vomiting
 Nausea

Musculoskeletal and connective tissue disorders

Common Arthralgia

General disorders and administration site conditions

Common Rigors
 Pyrexia
 Fatigue

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. 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, there have been reports of serious cases, including one fatal case of herpes encephalitis. See section 4.4.

The majority of patients did not interrupt natalizumab therapy during infections and recovery occurred with appropriate treatment.

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).

Hepatic Events

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

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

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 TYSABRI and the changes were not associated with clinical symptoms.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective Immunosuppressive Agent, ATC code: L04AA23

Pharmacodynamic effects

Natalizumab is a selective adhesion-molecule inhibitor and binds to the $\alpha 4$ -subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the $\alpha 4\beta 1$ integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of $\alpha 4\beta 7$ integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of $\alpha 4$ -expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

In MS, lesions are believed to occur when activated T-lymphocytes cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and endothelial cells of the vessel wall. The interaction between $\alpha 4\beta 1$ and its targets is an important component of pathological inflammation in the brain and disruption of these interactions leads to reduced inflammation. Under normal conditions, VCAM-1 is not expressed in the brain parenchyma. However, in the presence of pro-inflammatory cytokines, VCAM-1 is upregulated on endothelial cells and possibly on glial cells near the sites of inflammation. In the setting of central nervous system (CNS) inflammation in MS, it is the interaction of $\alpha 4\beta 1$ with VCAM-1, CS-1 and osteopontin that mediates the firm adhesion and transmigration of leukocytes into the brain parenchyma and may perpetuate the inflammatory cascade in CNS tissue. Blockade of the molecular interactions of $\alpha 4\beta 1$ with its targets reduces inflammatory activity present in the brain in MS and inhibits further recruitment of immune cells into inflamed tissue, thus reducing the formation or enlargement of MS lesions.

Clinical efficacy

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

Study features and results are presented in the table below.

AFFIRM study: Main features and results		
Design	Monotherapy; randomised double-blind placebo-controlled parallel-group trial for 120 weeks	
Subjects	RRMS (McDonald criteria)	
Treatment	Placebo / Natalizumab 300 mg i.v. every 4 weeks	
One year endpoint	Relapse rate	
Two year endpoint	Progression on EDSS	
Secondary endpoints	Relapse rate derived variables / MRI-derived variables	
Subjects	Placebo	Natalizumab
Randomised	315	627
Completing 1 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.

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. 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 or in patients with renal or hepatic insufficiency has not been studied.

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

5.3 Preclinical safety data

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

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

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

No clastogenic or mutagenic effects of natalizumab were observed in the Ames or human chromosomal aberration assays. Natalizumab showed no effects on *in vitro* assays of 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

4 years

Diluted solution

After dilution with 0.9 % sodium chloride, 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

Concentrate

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 of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

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

Pack size of one vial per carton.

6.6 Special precautions for disposal and other handling

Instructions for use:

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

7. MARKETING AUTHORISATION HOLDER

Elan Pharma International Ltd., Monksland, Athlone, County Westmeath, Ireland

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 first renewal:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURING AUTHORISATION
HOLDERS RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

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

Name and address of the manufacturers responsible for batch release

Biogen Idec Denmark Manufacturing ApS
Biogen Idec Allé 1
DK-3400 Hillerød
Denmark

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

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

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:
 - o That the risk of PML increases with increasing duration of treatment and that treatment beyond 24 months carries additional risk

- o Other factors associated with an increased risk for the development of PML
 - Immunosuppressant treatment prior to the use of Tysabri
 - Presence of anti-JC virus antibodies
 - o A stratification of the risk of developing PML based on the three identified risk factors
 - o Diagnosis of PML including differentiation between PML and MS relapse
 - o PML management algorithm
 - o Possibility of other opportunistic infections
 - o The recommendation that patients should have MRI scans at the following times
 - Within 3 months prior to starting TYSABRI
 - Annually during treatment with TYSABRI
 - At the first sign of any symptoms indicative of the possibility of PML.
 - o 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
 - o 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
 - o The need to inform the National Competent Authority about any cases of PML
- Information about the following adverse reactions:
 - o Infusion reactions
 - o Hypersensitivity reactions
 - o Antibody formation
 - Information about any registry or other monitoring system set up in the Member State and how to enter patients

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 JC virus 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
- Date treatment started

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.

- **OTHER CONDITIONS**

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 11 of the Risk Management Plan (RMP) presented in

Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

The MAH will submit PSURs on a 6 monthly basis until otherwise agreed by the CHMP.

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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

Elan Pharma International Ltd.
Monksland
Athlone
County Westmeath
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/346/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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 USER

TYSABRI 300 mg concentrate for solution for infusion natalizumab

Read all of this leaflet carefully before you start using this medicine.

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.
- It is important that you keep the 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 have any worrying side effects, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse

In this leaflet:

1. What TYSABRI is and what it is used for
2. Before you use TYSABRI
3. How to use TYSABRI
4. Possible side effects
5. How to store TYSABRI
6. Further information

1. WHAT TYSABRI IS AND WHAT IT IS USED FOR

In TYSABRI the active ingredient is natalizumab, a protein similar to your own antibodies. 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 is 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. However, TYSABRI cannot repair the damage that has already been caused by MS. When you receive TYSABRI you might not notice any improvement, but TYSABRI may still be working to prevent your MS becoming worse.

2. 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 (hypersensitive) to natalizumab or any of the other ingredients of TYSABRI (see section 6 for the ingredients).
- 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, e.g. mitoxantrone or cyclophosphamide).
- If you are taking either beta-interferon or glatiramer acetate. These medicines are for MS and 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).
- If you are under 18 years of age.

Take special care with TYSABRI

Infections

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.

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. JC virus is a common virus which infects many people but does not normally cause noticeable illness.

The risk of PML with TYSABRI is higher:

- The longer that you are on treatment especially if you have been on treatment for more than two years. It is not known if the chance of getting PML continues to rise, remains the same, or falls after you have been on TYSABRI for more than three 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 antibodies to the JC virus in your blood. These antibodies are a sign that you have been infected by JC virus.

Your doctor may test your blood to check if you have antibodies to the JC virus before you start treatment with TYSABRI. The risk of PML is higher in patients who have antibodies to the JC virus compared to patients who do not have antibodies to the JC virus. If you do not have antibodies to the JC virus, then your doctor may repeat the test regularly to check if anything has changed.

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

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, it is very important that you speak to your doctor as soon as possible.

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.

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 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.

Serious infections may occur with TYSABRI. If you develop any infection, or if you develop symptoms like an unexplained fever, severe diarrhoea, prolonged dizziness / headache / stiff neck, weight loss, or listlessness, or other symptoms potentially associated with an infection whilst receiving TYSABRI, speak to your doctor as soon as possible and show the Patient Alert Card and this package leaflet to him.

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.

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.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines you may have obtained without a prescription.

You must not use TYSABRI if you are being treated with beta-interferons or glatiramer acetate.

You may not be able to use TYSABRI if you are currently receiving or have previously received medicines that affect your immune system, e.g. mitoxantrone or cyclophosphamide.

Pregnancy and breast-feeding

You should 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

TYSABRI is not expected to have an effect on your ability to drive or to operate machines. If you are concerned, discuss this with your doctor.

Important information about some of the ingredients of TYSABRI

After dilution for use, 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.

3. HOW TO USE TYSABRI

TYSABRI will be given to you by a doctor experienced in the treatment of MS.

Always take TYSABRI exactly as your doctor has told you. You should check with your doctor if you are not sure.

The adult dose 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.

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

4. POSSIBLE SIDE EFFECTS

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

If you have any worrying side effects, including any not listed in this leaflet, please tell your doctor, nurse or pharmacist as soon as possible.

What to do if your MS gets worse or you notice new symptoms

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

The symptoms of PML may be similar to an MS relapse.

- Therefore, if you believe your MS is getting worse or if you notice any new symptoms, it is important that you speak to your doctor immediately
- Discuss your treatment with your partner or caregivers. They might see new symptoms that you might not notice 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.
- Show the Alert Card and this package leaflet to any doctor involved with your treatment, not only to your neurologist.

Serious infections may occur with TYSABRI. The symptoms of infections include:

- an unexplained fever
- severe diarrhoea
- shortness of breath
- prolonged dizziness
- headache
- stiff neck
- weight loss
- listlessness.

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

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:

Common side effects that may affect 1 to 10 users in 100:

- Urinary tract infection
- Sore throat and runny or blocked up nose
- Shivering
- Itchy rash (hives)
- Headache
- Dizziness
- Feeling sick (nausea)
- Being sick (vomiting)
- Joint pain
- Fever
- Tiredness

Uncommon side effects that may affect 1 to 10 users in 1,000:

- Severe allergy (hypersensitivity).
- Progressive multifocal leukoencephalopathy (PML), a rare brain infection.

Rare side effects that may affect 1 to 10 users in 10,000:

- Unusual infections (so-called “Opportunistic infections”)
- 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.

5. HOW TO STORE TYSABRI

Keep out of the reach and sight of children.

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.

Do not use TYSABRI after the expiry date stated on the label and carton.

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 TYSABRI if you notice particles in the liquid and/or the liquid in the vial is discoloured.

6. FURTHER INFORMATION

What TYSABRI contains

Each 15 ml vial of concentrate contains 300 mg natalizumab (20 mg/ml).

The other ingredients are:

Sodium phosphate, monobasic, monohydrate

Sodium phosphate, dibasic, heptahydrate

Sodium chloride

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.

Marketing Authorisation Holder

Elan Pharma International Ltd.

Monksland

Athlone

County Westmeath

Ireland

Manufacturer

Biogen Idec Denmark Manufacturing ApS

Biogen Idec Allé 1

DK-3400 Hillerød

Denmark

For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder. This information is provided at the end of the leaflet.

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Biogen Idec Limited
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Lietuva

Gedeon Richter Plc.
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This leaflet was last approved in {MM/YYYY}.

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 medical or 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 (IV) 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. Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

ANNEX IV

GROUND S FOR ONE ADDITIONAL RENEWAL

Grounds for one additional renewal

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of TYSABI remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

The currently available information from the post-marketing experience (ongoing observational trials, registries and ongoing clinical trials) does not provide a complete picture of evidence on how the risk factors could combine and interfere on the benefit-risk balance in long-term exposed patients.

Therefore, based on the safety profile of TYSABRI, which requires the submission of 6-monthly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.