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IMPORTANT SAFETY INFORMATION

Dear Health Care Professional,

The content of this letter has been agreed with the European Authorities, following the EMEA's Press Release of 20 March 2008 and with the Irish Medicines Board.

Summary

• Reports of serious liver injury in patients receiving TYSABRI have been received from the market.
• Signs of liver injury including elevated serum hepatic enzymes and total bilirubin occurred as early as six days after the first dose but have also been reported later during treatment.
• In a small number of cases, liver dysfunction that had resolved after cessation of therapy reoccurred upon resumption of dosing with TYSABRI.
• Patients treated with TYSABRI should be monitored as appropriate for signs of liver dysfunction and be instructed to contact their physician in case of signs and symptoms suggestive of liver injury.
• Treatment should be discontinued in cases of significant liver injury.

Further information on the safety concern

Serious hepatic events have been reported in which a contributory role for TYSABRI could not be excluded. None of the reported cases led to death or liver transplantation.

In the clinical trials of TYSABRI in MS and Crohn's disease, although serious hepatic events consistent with liver injury were reported, the proportions of affected individuals was comparable in patients receiving active drug or placebo. The post-marketing data has prompted the Marketing Authorisation Holder to amend the Summary of Product Characteristics. The incidence of these serious events is not precisely known as the reports arise from post-marketing surveillance, however they are likely to be rare, since they were not observed in the clinical studies involving over 3000 patients studied for up to 2 years or longer. Details of the changes to the Summary of Product Characteristics and patient leaflet are attached as Annex 1.

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Further information on recommendations to healthcare professionals

• Patients treated with TYSABRI should be monitored as appropriate for signs of liver dysfunction and be instructed to contact their physician in case of signs and symptoms suggestive of liver injury.
• In cases of significant liver injury, treatment should be discontinued.
• The Marketing Authorisation Holder will be updating the educational information, which is supplied to healthcare professionals as part of the risk minimisation for TYSABRI.

Call for reporting
Please remember that any suspect adverse reaction following the use of TYSABRI should be reported to the marketing authorisation holder at 1800 409 676 or to the Irish Medicines Board, in the usual way.

Communication information
For further information please contact: -

Medical Information on 1800 409 676

Annexes:
Text of the revised Product Information (with changes made visible)

Yours faithfully,

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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

Concentrate: Each ml of concentrate contains 20 mg of natalizumab.

Natalizumab is a recombinant humanised anti-α4-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.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colourless, clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Patients with high disease activity despite treatment with a beta-interferon (see section 5.1);

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis (see section 5.1).

4.2 Posology and method of administration

TYSABRI therapy is to be initiated and 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.

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

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.

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 medications (e.g. mitoxantrone, cyclophosphamide, azathioprine). These drugs 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.

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 beyond 2 years are not available. Continued therapy beyond this time should be considered only following a reassessment of the potential for benefit and risk.

Adults

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

Elderly

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

Children and adolescents

TYSABRI is contraindicated in children and adolescents (see section 4.3).

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.

Readministration

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

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.

4.4 Special warnings and precautions for use

Progressive Multifocal Leukoencephalopathy (PML)

Use of TYSABRI has been associated with an increased risk of PML.

Before initiation of treatment with TYSABRI, a recent (usually within 3 months) Magnetic Resonance Image should be available. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If new neurological symptoms occur, further dosing is to 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 they are suggestive of PML, or if any doubt exists, further evaluation, including MRI scan (compared with pre-treatment MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. Once the clinician has excluded PML, 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, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of TYSABRI therapy may lead to similar stabilisation or improved outcome.

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

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, including cyclophosphamide and mitoxantrone, may experience prolonged immunosuppression and therefore may be 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 drugs 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 medicines 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.

4.5 Interaction with other medicinal products and other forms of interaction

See section 4.3.

4.6 Pregnancy and lactation

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

It is not known whether TYSABRI is excreted in human milk, but it has been observed in animal studies (see section 5.3). Patients receiving TYSABRI should not breastfeed their infants.

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. Based on the pharmacological mechanism of action of natalizumab, the use of TYSABRI is not expected to affect patient's ability to drive and use machines.

4.8 Undesirable effects

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 drug reactions (placebo: 39.6%)[1]. Adverse drug 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, undesirable effects are presented in order of decreasing seriousness.

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

Nervous system disorders

Common	Headache
	Dizziness

Gastrointestinal disorders

Common	Vomiting
	Nausea

Musculoskeletal and connective tissue disorders

Common	Arthralgia

Infections and infestations

Common	Urinary tract infection
	Nasopharyngitis

General disorders and administration site conditions

Common	Rigors
	Pyrexia
	Fatigue

Immune system disorders

Common	Urticaria
Uncommon	Hypersensitivity

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. See section 4.4.

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.

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.

In clinical trials, cases of PML have been reported. PML usually leads to severe disability or death (see section 4.4). In pivotal clinical trials, two cases, including one fatality, occurred in MS patients who were being treated with concomitant interferon beta-1a therapy for more than 2 years. In another trial, one patient with Crohn's disease, who had a long history of treatment with immunosuppressants and associated lymphopenia also developed PML and died.

Although each case of PML occurred in patients either with concomitant use of immune modulating drugs or with evidence of immunosuppression, it remains possible that the risk of PML is associated with natalizumab alone.

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 x 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 properties

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

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

Clinical efficacy

TYSABRI is indicated as a single disease modifying therapy in relapsing remitting multiple sclerosis to prevent relapses and delay progression of disability. Due to safety concerns (see sections 4.4 and 4.8) treatment is restricted to the following patient groups:

- Patients who have failed to respond to a full and adequate course of a 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 MRI or at least 1 Gadolinium-enhancing lesion.

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.

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 ± SD steady-state clearance was 13.1 ± 5.0 ml/h, with a mean ± 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.

5.3 Preclinical safety data

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

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

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

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

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

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

evidence of anaemia in these offspring. All changes were observed at doses in excess of the human dose and were reversed upon clearance of natalizumab.

In *cynomolgus* monkeys treated with natalizumab until parturition, low levels of natalizumab were detected in the breast milk of some animals, indicating the possibility for transfer of natalizumab into breast milk in humans (see section 4.6).

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

Concentrate

2 years.

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. 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 TYSABRI 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 product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.

6. The diluted product is to be used as soon as possible and within 8 hours of dilution. If the diluted 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 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

27th June 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

ANNEX III

LABELLING AND PACKAGE LEAFLET

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 or pharmacist.
- This leaflet will explain about side effects that some patients experience on TYSABRI. If you have any worrying side effects, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. WHAT TYSABRI IS AND WHAT IT IS USED FOR

TYSABRI is used to treat multiple sclerosis (MS).

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).

MS causes inflammation in the brain that damages the nerve cells. In TYSABRI the active ingredient is natalizumab, a protein similar to your own antibodies. It stops the cells that cause inflammation from going into your brain. This reduces nerve damage caused by MS.

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.

It is important to continue with your medicine for as long as you and your doctor decide that it is helping you.

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, leukaemia or HIV or due to a medicine you are taking or have previously taken).
- If you are taking medicines that cannot be used with TYSABRI (see Using other medicines, below).
- If you have 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

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 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.

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.

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 may not be able to use TYSABRI with some medicines that affect your immune system.

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.

Ask your doctor or pharmacist for advice before taking any other medicine with 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.

3. HOW TO USE TYSABRI

TYSABRI will be prepared and given to you by a doctor.

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

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.

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.

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.

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.

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.

Signs of a possible liver problem:

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

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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 occur in less than 10 in 100 patients:
- 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 occur in less than 1 in 100 patients:
- Severe allergy (hypersensitivity).

Rare side effects:
- Unusual infections (so-called "Opportunistic infections")
- Progressive multifocal leukencephalopathy (PML), a rare brain infection.

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 as soon as possible.
- Discuss your treatment with your partner or caregivers. They might see new symptoms that you might not notice.

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 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.

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.

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.

TYSABRI must be diluted before it is given to you.

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

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.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 product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.

6. The diluted product is to be used as soon as possible and within 8 hours of dilution. If the diluted 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 product or waste material must be disposed of in accordance with local requirements.