PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

PROPRIETARY NAME (AND DOSAGE FORM)

TYSABRI (concentrate for solution for infusion)

WARNING

TYSABRI is associated with an increased risk of progressive multifocal leucoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for John Cunningham (JC) viral DNA are recommended (see CONTRA-INDICATIONS and WARNINGS, Progressive Multifocal Leukoencephalopathy)

COMPOSITION

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

List of excipients:

Sodium phosphate, monobasic, monohydrate

Sodium phosphate, dibasic, heptahydrate

Sodium chloride

Polysorbate 80

Water for Injections

PHARMACOLOGICAL CLASSIFICATION

A.30.1 Antibodies

PHARMACOLOGICAL ACTION

Natalizumab is a recombinant humanised anti-α4-integrin antibody produced in a murine cell line by recombinant DNA technology.

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.

Pharmacokinetic properties

Following the repeat intravenous administration of a 300 mg dose of natalizumab to multiple sclerosis 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 581 patients who 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.

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) were 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.

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.

The percentage of patients who experienced relapses over the 2 years was 33 % for patients on natalizumab and 59 % for patients on placebo. The MRI after 0 – 2 years demonstrated significantly fewer changes in the T_2-hyperintensive lesion volume number of new or newly emerging T_2-hyperintensive lesion, T_1-hypointensive lesions and mean number of gadolinium-enhancing lesions.

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.

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.

  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 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

- 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.

CONTRA-INDICATIONS

Hypersensitivity to natalizumab or to any of the excipients of TYSABRI.

Progressive multifocal leukoencephalopathy (PML) (see BOXED WARNING and WARNINGS).

Pregnancy and breastfeeding .

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 WARNINGS).

Combination with beta-interferons or glatiramer acetate.

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

Children and adolescents.

WARNINGS

Progressive Multifocal Leukoencephalopathy (PML)

Use of TYSABRI has been associated with an increased risk of PML which may be fatal or result in severe disability. The risk of PML increases with longer treatment duration, and is significantly higher at and beyond 2 years. There is limited experience in patients who received more than 3 years of TYSABRI treatment therefore the risk of PML in these patients cannot currently be estimated. The risk of PML is at least tripled in patients who have been treated with an immunosuppressive therapy prior to receiving TYSABRI. Due to this increased risk of developing PML, the benefits and risks of TYSABRI treatment should be individually reconsidered by the specialist medical practitioner and the patient. The patient should be re-informed about the risks of TYSABRI treatment annually with regard

to the increased risk of PML, and should be instructed together with their caregivers on early signs and symptoms of PML.

Before initiation of treatment with TYSABRI, a recent (usually within 3 months) Magnetic Resonance Image (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 treatment for any new or worsening neurological symptoms or signs that may be suggestive of PML.

If PML is suspected, further dosing must be suspended until PML has been excluded.

The medical practitioner 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 John Cunningham (JC) Viral DNA and repeat neurological assessments, should be considered as described in the Medical Practitioner Information and Management Guidelines (see educational guidance). Once the medical practitioner has excluded PML (if necessary, by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains), dosing of TYSABRI may resume.

The medical practitioner 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 Pharmacokinetic properties). 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 Medical Practitioner 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 SIDE-EFFECTS AND SPECIAL PRECAUTIONS).

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 medical practitioners who intend to prescribe TYSABRI must ensure they are familiar with the Medical Practitioner Information and Management Guidelines.

Medical practitioners 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 medical practitioner that they are being treated with TYSABRI.

Medical practitioners 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 SIDE-EFFECTS AND SPECIAL PRECAUTIONS). 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 (up to three 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. 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 immunosuppressant's

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 contra-indicated (see CONTRA-INDICATIONS).

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 immunosuppressant's to allow sufficient time for immune function recovery to occur.

Medical practitioners must evaluate each individual case to determine whether there is evidence of an immunocompromised state prior to commencing treatment with TYSABRI.

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 TYSABRI. 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 SIDE-EFFECTS AND SPECIAL PRECAUTIONS).

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 medical practitioner 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 TYSABRI, the medical practitioner needs to be aware that TYSABRI 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 TYSABRI. For medicines, 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 TYSABRI may lead to an additive immunosuppressive effect. This should be carefully considered on a case-by-case basis, and a wash-out period of TYSABRI might be appropriate. Short courses of steroids used to treat relapses were not associated with increased infections in clinical trials.

INTERACTIONS

See CONTRA-INDICATIONS and WARNINGS, Concurrent or prior treatment with immune-suppressant's.

PREGNANCY AND LACTATION

TYSABRI should not be used during pregnancy. If a woman becomes pregnant while taking TYSABRI, it should be discontinued.

TYSABRI is excreted in human milk. The effect of TYSABRI on newborn/infants is unknown. Breastfeeding should be discontinued during treatment with TYSABRI.

DOSAGE AND DIRECTIONS FOR USE

TYSABRI therapy is to be initiated and continuously supervised by specialised medical practitioners 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 patient information leaflet). Patients should be re-informed about the risks of TYSABRI, especially the increased risk of PML annually, 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.

After dilution (see Instructions for Use), 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 TYSABRI 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 TYSABRI is started.

Some patients may have been exposed to immunosuppressive medications (e.g. mitoxantrone, cyclophosphamide, azathioprine). These medicines have the potential to cause prolonged immunosuppression, even after dosing is discontinued. Therefore, the medical practitioner 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 TYSABRI at 2 years were generated from controlled, double-blind studies. 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 contra-indicated in children and adolescents (see CONTRA-INDICATIONS).

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 and safety of readministration have not been established.

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.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-Effects

In placebo-controlled trials in 1 617 MS patients treated with TYSABRI for up to 2 years (placebo: 1 135), adverse events leading to discontinuation of therapy occurred in 5,8 % of patients treated with TYSABRI (placebo: 4,8 %). Over the 2-year duration of the studies, 43,5 % of patients treated with TYSABRI reported adverse reactions (placebo: 39,6 %)[1]. Adverse reactions reported with TYSABRI with an incidence of 0,5 % greater than reported with placebo are shown below. Frequencies were defined as follows: Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 TYSABRI (placebo: 18,7 %). Events reported more commonly with TYSABRI 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 WARNINGS. 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 patient's antibodies against TYSABRI 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 WARNINGS).

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 TYSABRI- and placebo-treated patients. The nature of the infections was generally similar in TYSABRI- 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 occurred slightly more frequently in TYSABRI-treated patients than in placebo-treated patients. In post marketing experience, there have been rare reports of serious cases, including one fatal case of herpes encephalitis.
See WARNINGS.

The majority of patients did not interrupt TYSABRI 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 WARNINGS). 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 immunosuppressant's and associated lymphopenia also developed PML and died.

PML has been reported in post-marketing experience in patients treated with TYSABRI monotherapy.

Hepatic Events

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

Malignancies

No differences in incidence rates or the nature of malignancies between TYSABRI- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of TYSABRI on malignancies can be excluded. See CONTRA-INDICATIONS.

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.

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No case of overdose has been reported.

IDENTIFICATION

Colourless, clear to slightly opalescent solution. No visible particles.

PRESENTATION

15 ml TYSABRI is filled in a type I clear glass vial with a grey bromobutyl rubber stopper and an aluminium seal with a royal blue plastic flip-off cap. Pack size is one vial per carton.

STORAGE INSTRUCTIONS

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.

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.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

42/30.1/0765

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