AUSTRALIAN PRODUCT INFORMATION

TYRUKO® (NATALIZUMAB)

CONCENTRATED SOLUTION FOR INTRAVENOUS INFUSION

WARNING

TYRUKO is associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that may lead to death or severe disability. Healthcare professionals should closely monitor patients on TYRUKO for any new or worsening signs or symptoms that may be suggestive of PML.

TYRUKO dosing should be withheld immediately at the first signs or symptoms suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain, neurological assessment, and cerebrospinal fluid analysis for JC viral DNA is recommended (see section 4.3 CONTRAINDICATIONS and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Progressive Multifocal Leukoencephalopathy).

1 NAME OF THE MEDICINE

Natalizumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mL dose contains 300 mg natalizumab. The formulation also contains sodium chloride, histidine, histidine hydrochloride monohydrate, polysorbate 80 and water for injections, at pH 5.7.

TYRUKO (natalizumab) is a recombinant humanised IgG4 monoclonal antibody produced in Chinese hamster ovary (CHO) cells. Natalizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to α4-integrin. The molecular weight of natalizumab is 149 kilodaltons.

TYRUKO (natalizumab) is a biosimilar medicine to Tysabri®. The comparability of TYRUKO with Tysabri has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes [see section 5.1 Pharmacodynamic properties, Clinical trials and 4.8 Adverse effects (Undesirable effects)]. The evidence for comparability supports the use of TYRUKO for the listed indications.

3 PHARMACEUTICAL FORM

TYRUKO (natalizumab) concentrate for intravenous infusion is supplied as a sterile, colourless, clear to slightly opalescent solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TYRUKO is indicated as monotherapy for the treatment of patients with relapsing remitting multiple sclerosis (MS) to delay the progression of physical disability and to reduce the frequency of relapse.

4.2 DOSE AND METHOD OF ADMINISTRATION

TYRUKO therapy is to be initiated and supervised by neurologists, with timely access to MRI. Administration is to be performed by a healthcare professional and patients are to be monitored for early signs and symptoms of PML.

TYRUKO is not intended for subcutaneous administration.

Adults

The recommended dose of TYRUKO by intravenous infusion is 300 mg every four weeks. Dilute TYRUKO concentrate 300 mg/15 mL in 100 mL 0.9% Sodium Chloride and infuse over approximately one hour. Do not administer TYRUKO as an intravenous push or bolus injection (see Preparation Instructions).

Observe patients during the infusion and for 1 hour after the infusion is complete. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hypersensitivity). Staff and facilities should be available for treating anaphylaxis, in the unlikely event that this occurs. After the first 12 intravenous TYRUKO doses, patients should continue to be observed during infusion and observed after infusion according to clinical judgment.

Children and adolescents (<18 years)

Safety and effectiveness of natalizumab in MS patients below the age of 18 years of age have not been established. No recommendation on dosage can be made. Currently available data are described in section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials.

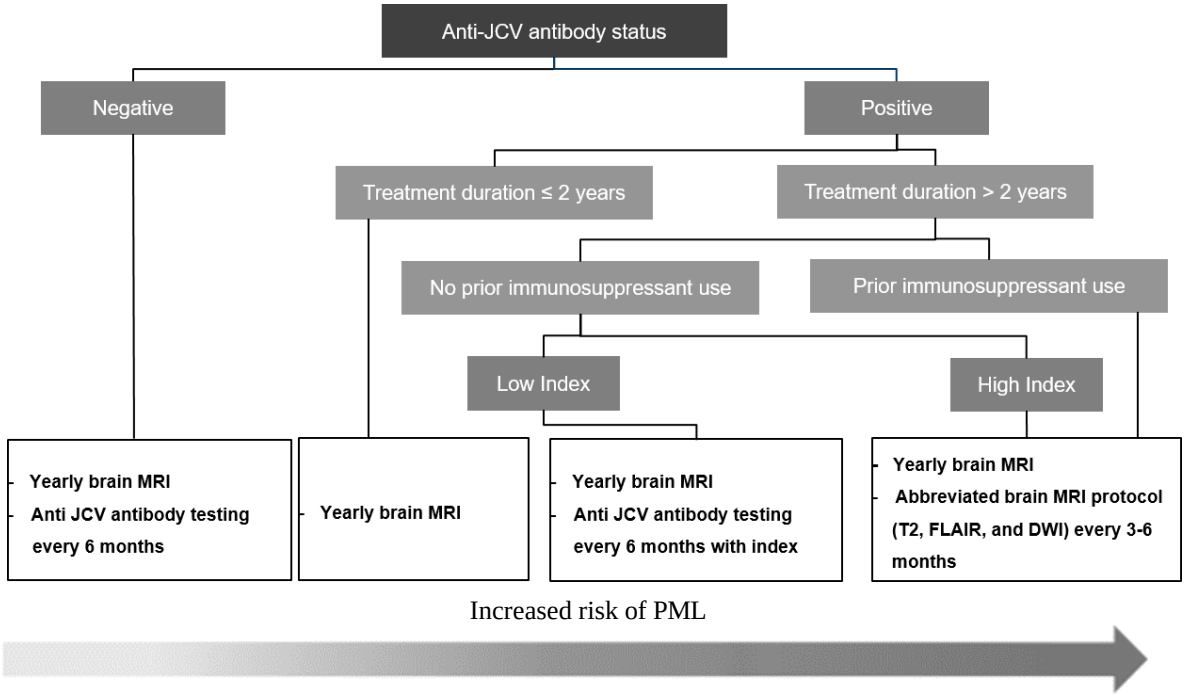
Renal and hepatic impairment

No formal pharmacokinetic studies have 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.

Monitoring advice

The information provided in the figure below is a graphical summary of guidance provided in section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE of the TYRUKO Product Information (PI) concerning patient monitoring, which is provided for information only and should not be used to make clinical decisions. It is important to refer to the full text in the PI and to the Physician Information and Management Guidelines to inform individual clinical decisions.

Figure 1: Guidance on patient monitoring according to anti-JCV antibody status



DWI= diffusion weighted imaging; FLAIR= fluid-attenuated inversion recovery, JCV= John Cunnigham Virus; MRI= magnetic resonance imaging

Index threshold values for low/high PML risk depend on the specific anti-JCV antibody test used (see Figure 2 of the PI and the Physician Information and Management Guidelines for further information).

Preparation Instructions

TYRUKO (natalizumab) is free of preservatives. Use aseptic technique when preparing TYRUKO solution for intravenous infusion. TYRUKO is for single use in one patient only. Discard any residue.

TYRUKO is a colourless, clear to slightly opalescent concentrate. Inspect the vial for particulate material prior to dilution and administration. If visible particulates are observed and/or the liquid in the vial is discoloured, the vial must not be used. Do not use TYRUKO beyond the expiration date on the carton or vial.

To prepare the solution, withdraw 15 mL of TYRUKO concentrate from the vial using a sterile needle and syringe. Inject the concentrate into 100 mL 0.9% Sodium Chloride. No other intravenous diluents may be used to prepare the TYRUKO solution.

Gently invert the TYRUKO solution to mix completely. Do not shake. Inspect for particulate material prior to administration.

Following dilution, infuse TYRUKO solution immediately or within 24 hours if stored at 2°C to 8°C. If stored at 2°C to 8°C, allow the solution to warm to room temperature prior to infusion. Do not freeze.

Administration Instructions

Infuse TYRUKO 300 mg in 100 mL 0.9% Sodium Chloride over approximately one hour. After the infusion is complete, flush with 0.9% Sodium Chloride.

Use of filtration devices during administration has not been evaluated. Other medications should not be injected into infusion set side ports or mixed with TYRUKO.

4.3 CONTRAINDICATIONS

TYRUKO should not be administered to patients with known hypersensitivity to natalizumab or any of the excipients, or to patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanised antibodies.

TYRUKO is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy.

TYRUKO should not be administered to patients with increased risk for opportunistic infections, including those immunocompromised due to current or recent immunosuppressive therapies (e.g. azathioprine, mitoxantrone), or systemic medical conditions resulting in significantly compromised immune system function (e.g. human immunodeficiency virus, organ transplant, active malignancy).

TYRUKO should not be administered in combination with immunomodulatory agents (e.g. beta interferons or glatiramer acetate).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Progressive Multifocal Leukoencephalopathy

Use of natalizumab has been associated with an increased risk of PML, an opportunistic infection caused by John Cunningham Virus (JCV), which may be fatal or result in severe disability (see BOXED WARNING). There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. Early diagnosis (from clinical and MRI monitoring), and stopping therapy are important factors in management of PML in patients on natalizumab. Natalizumab therapy is to be initiated and supervised by neurologists, with timely access to MRI. Prescribing neurologists must discuss the benefits and risks of natalizumab therapy with the patient, and provide them with the Consumer Medicine Information and a Patient Alert Card. After 2 years of treatment, patients should be re-informed about the risks, especially the increased risk of PML, and should be instructed together with their caregivers on early signs and symptoms of PML.

The Patient Alert Card reminds patients that because of the risks of PML and opportunistic infections with natalizumab, they must contact their doctor if they have unusual or prolonged new neurological symptoms or if they have severe or prolonged symptoms of infection. Patients should be instructed that they should inform all their healthcare providers that they are receiving treatment with natalizumab.

The neurologist should re-evaluate the patient 3 months after the first administration, 6 months after the first administration and every 6 months thereafter. Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months.

PML has been reported following discontinuation of natalizumab in patients who did not have findings suggestive of PML at the time of discontinuation. Patients and healthcare professionals should continue to be vigilant for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of natalizumab.

The following risk factors are associated with an increased risk of developing PML:

- **The presence of anti-JCV antibodies**
- **Treatment duration**, especially beyond 2 years in patients who are anti-JCV antibody positive
- **Immunosuppressant use** prior to receiving natalizumab.

Detection of PML

Patients should be instructed, together with their caregivers, on early signs and symptoms of PML. 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. Patients must be monitored at regular intervals to allow for early detection of any new or worsening neurological symptoms or signs that may be suggestive of PML. The treating clinician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive or psychiatric symptoms).

If new neurological symptoms suggestive of PML occur, further dosing must be suspended immediately until PML has been excluded. PML should be considered as a differential diagnosis in any MS patient taking natalizumab presenting with neurological symptoms and/or new brain lesions on MRI. If any doubt exists, further evaluation, including MRI scan (compared with pre-treatment and routine MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If initial investigations prove negative, but clinical suspicion for PML still remains, natalizumab should not be restarted and repeat investigations should be undertaken. Once the treating clinician has excluded PML, dosing of natalizumab may resume.

If a patient develops PML, the dosing of natalizumab must be permanently discontinued to enable reconstitution of the immune system.

MRI screening for PML

Before initiation of treatment with natalizumab, a recent (usually within 3 months) Magnetic Resonance Image (MRI) should be available as a reference and be routinely repeated at least yearly to update this reference. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML.

More frequent MRI monitoring, such as every 3-6 months, should be considered for patients at higher risk of PML. This includes:

- Patients who have all three risk factors for PML
- Patients with a high anti-JCV antibody index value without prior history of immunosuppressant therapy and more than 2 years of natalizumab treatment.

PML in the absence of symptoms can be detected on MRI and must be confirmed by the presence of JCV DNA in CSF or brain biopsy.

Anti-JCV antibody testing

Serum anti-JCV antibody testing provides supportive information for risk stratification for PML in patients treated with natalizumab. Therefore, testing should be carried out prior to initiating natalizumab therapy or in patients already receiving natalizumab in whom antibody status is unknown. In addition, anti-JCV antibody testing is recommended for patients with anti-JCV antibody negative status and for those anti-JCV antibody positive patients with lower index value, since the antibody status or index value may change. Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. Therefore six-monthly testing of patients who are anti-JCV antibody negative is recommended. Patients with lower index values who have not had prior immunosuppressant use

should also be retested periodically, for example every six months, once they reach the two year treatment point to inform on appropriate MRI monitoring.

Testing should be performed using an anti-JCV antibody assay that has been analytically validated in MS patients. Based on a Phase 4 study examining longitudinal antibody status over 18 months, there was approximately an 11% annual change in serostatus from anti-JCV antibody negative to positive.

Anti-JCV antibody assays should not be used to diagnose PML.

Use of plasmapheresis (plasma exchange, PLEX) or intravenous immunoglobulin (IVIG) can affect meaningful interpretation of serum anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies during or within 2 weeks of PLEX due to removal of antibodies from the serum, or within 6 months of IVIG (6 months being 5x half-life for immunoglobulins).

Estimates of PML Risk

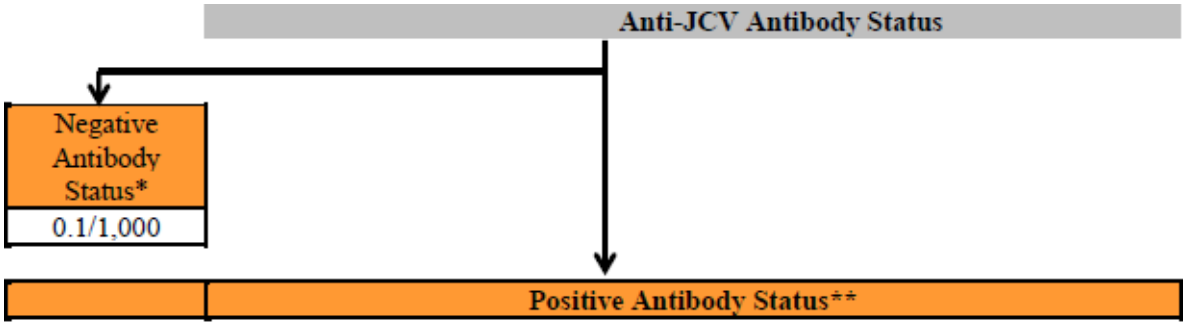
The PML Risk Estimates Algorithm (Figure 2) summarises PML risk by anti-JCV antibody status, prior immunosuppressant use and duration of treatment (by year of treatment) and stratifies this risk by anti-JCV antibody level (index value), as derived from the STRATIFY JCV assay, an anti-JCV antibody assay that has been analytically validated in MS patients. Index threshold values for low/high PML risk depend on the specific anti-JCV antibody test used.

Patients who have all three risk factors for developing PML (i.e., are anti-JCV antibody positive **and** have received more than 2 years of natalizumab therapy **and** have received prior immunosuppressant therapy) have a significantly higher risk of developing PML as determined during studies using a two-step ELISA anti-JCV antibody assay, although the relative risk may vary using other assays.

In patients not previously treated with immunosuppressants, the level of anti-JCV antibodies (index value) can further stratify the risk for developing PML (e.g. when using the STRATIFY JCV assay, index values equal to or below 0.9 are associated with a PML incidence of less than 1 per 1000 patients; PML risk increases substantially at index values above 1.5).

Figure 2: PML Risk Estimates (based on STRATIFY JCV assay)

This dataset may not exactly align with index values derived for other assays available for use.



Natalizumab exposure	PML risk estimates per 1,000 patients				
	Patients without prior IS use***				Patients with prior IS use
	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	No index value available	
1-12 months	0.1	0.1	0.2	0.1	0.3
13-24 months	0.1	0.3	0.9	0.6	0.4
25-36 months	0.2	0.8	3	2	4
37-48 months	0.4	2	7	4	8
49-60 months	0.5	2	8	5	8
61-72 months	0.6	3	10	6	6

*The risk of PML in anti-JCV antibody negative patients was estimated based on post marketing data from approximately 125,000 natalizumab exposed patients.
**PML risk estimates in anti-JCV antibody positive patients were based on the pooled cohort of 21,696 patients who participated in 3 observational studies and 1 clinical study.
***The majority of the prior IS use from these studies included the following 5 IS therapies: mitoxantrone, methotrexate, azathioprine, cyclophosphamide and mycophenolate.

For interpretation of index values obtained using alternative assays and the estimation of PML risk in the different patient subgroups, please refer to the Physician Information and Management Guidelines.

The risks and benefits of continuing treatment with natalizumab should be carefully considered in patients who have all three of these risk factors for PML or those patients who have no prior immunosuppressant use and have a high index value and more than two years of treatment with natalizumab.

Patients who are anti-JCV antibody negative are at a significantly lower risk of developing PML.

The risk of acquiring PML estimated from clinical trials is generally consistent with the risk estimated from post marketing data. Data on the safety and efficacy of natalizumab at two years were generated from controlled, double-blind studies. Post-marketing data are available from use up to six years, although data beyond 6 years are limited.

JCV Granule Cell Neuronopathy

JCV also causes granule cell neuronopathy (GCN) which has been reported in patients treated with natalizumab. Symptoms of JCV GCN are similar to symptoms of PML (i.e. cerebellar syndrome, although cerebellar atrophy may be a differential feature on MRI), and diagnosis and management of JCV GCN should follow guidance provided for PML (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Post-Marketing Experience).

PML, Plasma Exchange (PLEX) and IRIS (Immune Reconstitution Inflammatory Syndrome)

In natalizumab-treated patients that develop PML, IRIS occurs in almost all cases after withdrawal or removal of natalizumab, e.g. by plasma exchange (PLEX). IRIS is thought to result from the restoration of immune function in patients with PML. IRIS presents as a worsening in neurological status that may be rapid, 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 natalizumab-treated patients with PML, and appropriate treatment of the associated inflammation during recovery from PML should be undertaken.

Based on a retrospective analysis of natalizumab-treated patients since its approval, no difference was observed on 2-year survival after PML diagnosis between patients who received PLEX and those who did not. Physicians should use medical judgement when considering the use of PLEX to treat PML.

The impact of plasma exchange on the restitution of lymphocyte migration and ultimately its clinical usefulness is unknown (see section 5.2 PHARMACOKINETIC PROPERTIES).

Other Opportunistic Infections

Other opportunistic infections have been reported with the use of natalizumab, primarily in patients with Crohn's disease who were immunocompromised or where significant co-morbidity existed (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Infections). However increased risk of other opportunistic infections with use of natalizumab in patients without these co-morbidities cannot currently be excluded.

Serious, life-threatening and sometimes fatal reports of encephalitis and meningitis caused by herpes simplex or varicella zoster have been seen. The duration of treatment with natalizumab prior to onset ranged from a few months to several years. If herpes encephalitis or meningitis occurs, natalizumab should be discontinued and appropriate treatment for herpes encephalitis or meningitis should be administered.

Acute retinal necrosis (ARN) is a fulminant viral infection of the retina caused by the family of herpes viruses (e.g., varicella zoster). ARN has been observed in patients being administered natalizumab and can be potentially blinding (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Infections). Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN. Following clinical diagnosis of ARN and institution of antiviral therapy where appropriate, discontinuation of natalizumab should be considered in these patients.

Physicians should be aware of the possibility that other opportunistic infections may occur during natalizumab therapy and should include them in the differential diagnosis of infections that occur in natalizumab-treated patients. If an opportunistic infection is suspected, dosing with natalizumab is to be suspended until such infections can be excluded through further evaluations.

If a patient receiving natalizumab develops an opportunistic infection, dosing of natalizumab must be permanently discontinued.

Hepatotoxicity

Spontaneous suspect adverse drug reactions of liver injury, including severe liver injury, have been reported from the market. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose. Signs of liver injury

have also been reported for the first time after multiple doses, including cases with rechallenge. In these patients, recovery of liver function occurred following cessation of therapy.

If liver injury occurs during treatment with natalizumab the drug should be discontinued and investigation of cause undertaken. Natalizumab should be initiated with caution in patients with a history of liver disease and liver function tests should be regularly monitored in these patients.

Stopping natalizumab Therapy – Prolonged Pharmacodynamic Effects

If a decision is made to stop treatment with natalizumab, the physician needs to be aware that natalizumab remains in the blood, and may have pharmacodynamic effects (e.g. increased lymphocyte counts) for approximately 12 weeks following the last dose. Starting other therapies during this interval may 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. Also see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Progressive Multifocal Leukoencephalopathy.

Hypersensitivity

Natalizumab has been associated with hypersensitivity reactions, including anaphylactic/ anaphylactoid reactions, which occurred at an incidence of <1%. These reactions usually occurred during administration or up to 1 hour after completion of administration, but there have been occasional post-market reports of delays of up to 2 weeks in symptom onset. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypertension, hypotension, dyspnoea and chest pain. Generally, these reactions are associated with antibodies to natalizumab.

The risk for hypersensitivity was greatest with early infusions and in patients re-exposed to natalizumab following an initial short exposure (up to three infusions) and extended period (three months or more) without treatment. Neurologists should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment. However, the risk of hypersensitivity reactions should be considered for every administration.

Patients should be observed during administration and for 1 hour after the completion of administration (see also Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Resources for the management of hypersensitivity reactions should be available.

If a hypersensitivity reaction occurs, discontinue administration of natalizumab and initiate appropriate therapy. Patients who have experienced a hypersensitivity reaction should not be re-treated with natalizumab. The possibility of antibodies to natalizumab should be considered in patients who have hypersensitivity reactions (see section see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Immunogenicity).

Immunogenicity

Disease exacerbations or administration-related events may indicate the development of antibodies against natalizumab (see section see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). If, after approximately 6 months of therapy, persistent antibodies are suspected, they may be detected and confirmed with a subsequent test 6 weeks after the first positive test.

Antibodies detected early in the treatment course (e.g. within the first 6 months) may be transient and disappear with continued dosing. Given that efficacy may be reduced, or the incidence of hypersensitivity or administration-related reactions may be increased in a patient with persistent antibodies, physicians should consider the overall benefits and risks of continuing therapy with natalizumab and cessation of treatment may be appropriate. Patients who receive natalizumab for a short exposure followed by an extended period without treatment are at higher risk of developing anti-natalizumab antibodies and/or hypersensitivity reactions on re-exposure. Following a prolonged dose interruption (three months or more), consideration should be given to testing for the presence of persistent antibodies (detected on two occasions at least 6 weeks apart) prior to resuming treatment.

Use in hepatic impairment

Natalizumab has not been studied in patients with hepatic impairment in clinical trials.

Use in renal impairment

Natalizumab has not been studied in patients with renal impairment in clinical trials.

Use in the elderly

Clinical studies of natalizumab did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients.

Paediatric and adolescent use

Safety and effectiveness of natalizumab in paediatric and adolescent patients with multiple sclerosis below the age of 18 have not been established. Currently available data are described in section see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Paediatric and section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials.

Immunisations

In a randomised, open-label study of 60 patients with relapsing MS there was no significant difference in the humoral immune response to either a neoantigen (keyhole limpet haemocyanin) or a recall antigen (tetanus toxoid) between patients who were treated with natalizumab for 6-months compared to an untreated control group. Live vaccines have not been studied. No data are available on the secondary transmission of infection by live vaccines in patients receiving natalizumab.

Effects on laboratory tests

Natalizumab induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Elevations of neutrophils are not observed. Natalizumab induces mild decreases in haemoglobin levels that are frequently transient. Haematological changes persist during natalizumab exposure but are reversible, returning to baseline levels usually within 16 weeks after the last dose, and are not associated with clinical symptoms.

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, blood chemistry, including liver function tests, are recommended for patients with a history of liver disease or active liver disease, during treatment with natalizumab.

Extended Interval Dosing (EID)

Extended interval dosing of natalizumab (average dosing interval of approximately 6 weeks) has been used in the post-market setting. However, the efficacy of extended interval dosing has not been established and the associated benefit risk balance is currently unknown.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The safety and efficacy of natalizumab in combination with antineoplastic or immunosuppressive agents have not been established. Concurrent use of these agents with natalizumab may increase the risk of infections, including PML and other opportunistic infections (see section 4.3 CONTRAINDICATIONS and section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Infections).

In phase 3 clinical trials in multiple sclerosis (Studies 1 and 2), concomitant treatment of relapses with a short course of corticosteroids was associated with an increased rate of infection. However, the increase in infections was similar in natalizumab-treated patients who received steroids compared with placebo-treated patients who received steroids. Short courses of corticosteroids can be used in combination with natalizumab.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In guinea pigs, intravenous administration of natalizumab was associated with reduced female fertility at an estimated systemic exposure (serum AUC) of 18 times that in humans at the recommended clinical dose, but not at 3 times clinical exposure. Intravenous administration of natalizumab to male guinea pigs did not affect fertility at an estimated exposure 21 times clinical exposure (serum AUC).

Use in Pregnancy (Category C)

Studies in animals have shown reproductive toxicity. Natalizumab crossed the placenta in guinea pigs and monkeys, but there was no evidence of teratogenicity at respective maternal exposures up to 16 times and 100 times clinical exposure (based on AUC), including effects on early cardiac development (a process known to involve α4 integrins). Intravenous administration of natalizumab to pregnant monkeys during the period of organogenesis was associated with foetal changes (mild anaemia, thrombocytopaenia, increased spleen weights, and reduced liver and thymus weights associated with increased splenic extramedullary haematopoiesis, thymic atrophy and decreased hepatic haematopoiesis), at estimated maternal exposures of 17 times or greater (based on AUC) the clinical exposure at the recommended dose. At the no-effect dose, the extent of maternal exposure was uncertain. Offspring born to monkeys treated intravenously with high doses of natalizumab (100 times clinical exposure based on AUC) showed thrombocytopaenia (reversed upon clearance of natalizumab) and enlarged spleen, but there was no evidence of anaemia.

Intravenous administration of natalizumab to guinea pigs during late gestation and lactation was associated with reduced pup viability, with maternal exposure (based on AUC) estimated at 18-fold clinical exposure. At the no-effect dose, maternal exposure was 3-fold clinical exposure.

There are no adequate and well-controlled studies of natalizumab therapy in pregnant women. This drug should be used during pregnancy only if clearly needed. If a woman becomes pregnant while taking natalizumab, discontinuation of therapy should be considered.

Cases of thrombocytopenia in infants born to women exposed to natalizumab during pregnancy were reported in the post-marketing setting. Cases of increased white blood cell counts and transient mild to moderate anaemia, from published literature, were reported in infants born to women exposed to natalizumab in their third trimester. Therefore, monitoring for haematological abnormalities is recommended for neonates born to women exposed to natalizumab during pregnancy.

Use in Lactation

Natalizumab has been detected in human milk. Because of this, and because the potential for serious adverse reactions is unknown, a decision should be made whether to discontinue breast-feeding or natalizumab therapy.

Intravenous administration of natalizumab to guinea pigs during late gestation and lactation was associated with reduced pup viability, with estimated maternal exposure (AUC) 18-fold that in humans at the recommended clinical dose, and 3-fold clinical exposure at the no-effect dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of natalizumab on the ability to drive or use machines has not been studied.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

In placebo-controlled trials in 1617 MS patients treated with natalizumab for up to 2 years (placebo: 1135), 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 (an adverse event judged related to therapy by the investigating physician) (placebo: 39.6%).

Table 1 includes adverse events and selected laboratory abnormalities that occurred in Study 1 (Monotherapy Study) at an incidence of at least 1% higher in natalizumab-treated patients than was observed in placebo-treated patients.

Table 1 - Adverse Events in Study 1 (Monotherapy Study)

Adverse Events (Preferred Term)	Natalizumab n=627 %	Placebo n=312 %
General		
Headache	38	33
Fatigue	27	21
Arthralgia	19	14
Chest discomfort	5	3
Acute hypersensitivity reactions**	4	<1
Other hypersensitivity reactions**	5	2
Seasonal allergy	3	2
Rigors	3	<1
Weight increased	2	<1
Weight decreased	2	<1
Infection		
Urinary tract infection	21	17
Lower respiratory tract infection	17	16
Gastroenteritis	11	9
Vaginitis*	10	6
Tooth infections	9	7
Herpes	8	7
Tonsillitis	7	5

Adverse Events (Preferred Term)	Natalizumab n=627 %	Placebo n=312 %
Psychiatric		
Depression	19	16
Musculoskeletal/Connective Tissue Disorders		
Pain in extremity	16	14
Muscle cramp	5	3
Joint swelling	2	1
Gastrointestinal		
Abdominal discomfort	11	10
Diarrhoea NOS	10	9
Abnormal liver function test	5	4
Skin		
Rash	12	9
Dermatitis	7	4
Pruritus	4	2
Night sweats	1	0
Menstrual Disorders*		
Irregular menstruation	5	4
Dysmenorrhea	3	<1
Amenorrhea	2	1
Ovarian cyst	2	<1
Neurologic Disorders		
Somnolence	2	<1
Vertigo	6	5
Renal and Urinary Disorders		
Urinary incontinence	4	3
Urinary urgency/frequency	9	7
Injury		
Limb injury NOS	3	2
Skin laceration	2	<1
Thermal burn	1	<1

* Percentage based on female patients only
** Acute versus other hypersensitivity reactions are defined as occurring within 2 hours post infusion- versus more than 2 hours

Adverse drug reactions reported with natalizumab with an incidence of 0.5% greater than reported with placebo and not already included in Table 1 are shown below. The reactions are reported as MedDRA preferred terms under the MedDRA primary system organ class. Frequencies were defined as follows:

Very Common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100).

Infections and infestations	
Very Common	Nasopharyngitis
Immune system disorders	
Common	Urticaria
Nervous system disorders	
Very Common	Dizziness
Gastrointestinal disorders	
Very Common	Nausea
Common	Vomiting
General disorders and administration site conditions	
Common	Pyrexia

No trials were conducted directly comparing the adverse event profile of natalizumab plus Avonex® to natalizumab alone. When comparing across trials, in general, adverse events appeared to be more common in those receiving natalizumab in combination with Avonex than those receiving natalizumab alone (99.2% vs. 95.1%, natalizumab plus Avonex vs natalizumab, respectively). Many of these differences appeared to be attributable to adverse events often associated with beta-interferon (headache, fatigue, depression, arthralgia, flu-like symptoms). Peripheral oedema and herpes viral infections were slightly more common in those receiving natalizumab in combination with Avonex than those receiving natalizumab alone. The overall incidence of serious adverse events and serious infections were similar in those receiving natalizumab in addition to Avonex as compared with natalizumab alone, although appendicitis was slightly more common in those receiving combination treatment (0.8% vs. 0.2%).

Description of selected adverse effects

Infusion-Related Reactions

In 2-year controlled clinical trials in MS patients (Studies 1 and 2), an infusion-related event was defined as an adverse event occurring during the infusion or within 1 hour of the completion of the infusion. Approximately 24% of natalizumab-treated MS patients experienced an infusion-related reaction, compared to 18% of placebo-treated patients. Infusion-related reactions in natalizumab-treated patients included headache, dizziness, fatigue, rigors and localised or multi-symptomatic hypersensitivity reactions.

Hypersensitivity

The majority of hypersensitivity reactions are infusion-related. No delayed hypersensitivity reactions were seen in 2-year controlled clinical studies in MS patients receiving natalizumab intravenously (Studies 1 and 2). In Studies 1 and 2, hypersensitivity reactions occurred in up to 4% of patients. This includes acute urticaria, which was observed in approximately 2% of patients. Anaphylactic/anaphylactoid reactions occurred in <1% of patients. All patients recovered with treatment and/or discontinuation of the infusion.

Patients who became persistently positive for antibodies to natalizumab were more likely to have an infusion-related reaction than those who were antibody-negative (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Immunogenicity).

Immunogenicity

Patients in Study 1 and Study 2 were tested for antibodies to natalizumab every 12 weeks. Antibodies against natalizumab were detected in approximately 10% of multiple sclerosis patients receiving natalizumab 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. Approximately 90% of patients who became persistently antibody-positive by this assay had developed detectable antibodies by 12 weeks. Anti-natalizumab antibodies were neutralising *in vitro*.

Persistent antibodies to natalizumab were associated with a substantial decrease in the effectiveness of natalizumab and an increased incidence of hypersensitivity reactions. The risk of disability progression and the annualised relapse rate of persistently antibody-positive natalizumab-treated patients were similar to the rates in subjects who received placebo.

Infusion-related reactions most often associated with persistent antibody-positivity included urticaria, rigors, nausea, vomiting, and flushing. Additional adverse events more common in persistently antibody-positive patients included myalgia, hypertension, dyspnoea, anxiety, and tachycardia.

If, after approximately 6 months of therapy, persistent antibodies are suspected, 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, physicians should consider the overall benefits and risks of therapy with natalizumab and cessation of treatment may be appropriate.

Infections

In 2-year controlled clinical trials in MS patients, the rate of infection was approximately 1.5 per patient-year in both natalizumab-treated patients and placebo-treated patients. The nature of the infections were generally similar in natalizumab-treated and placebo-treated patients. The infections were predominately upper respiratory tract infections, influenza and urinary tract infections. Most patients did not interrupt treatment with natalizumab during the infection and recovery occurred with appropriate treatment.

Cases of PML have been reported in clinical trials. In the post-marketing setting, additional cases of PML in patients treated with natalizumab monotherapy have been reported (see BOXED WARNING and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Progressive Multifocal Leukoencephalopathy).

The only opportunistic infection in multiple sclerosis clinical trials was a case of cryptosporidial gastroenteritis with a prolonged course. In clinical studies for other indications, opportunistic infections (e.g. *pneumocystis carinii* pneumonia, pulmonary *mycobacterium avium intracellulare*, bronchopulmonary aspergillosis) were observed uncommonly in natalizumab-treated patients; the majority of these patients were either receiving concurrent immunosuppressants or had major co-morbidities.

In clinical trials, herpes infections occurred slightly more frequently in patients treated with natalizumab than in patients treated with placebo. In post-marketing experience, serious life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in multiple sclerosis patients receiving natalizumab (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Other Opportunistic Infections).

In post-marketing experience, acute retinal necrosis (ARN) has been observed at a higher incidence in patients receiving natalizumab. Some cases have occurred in patients with central nervous system herpes infections (e.g., herpes meningitis and encephalitis). Serious cases of ARN, affecting one or both eyes, led to blindness in some patients. The treatment reported in these cases included antiviral therapy and, in some cases, surgery.

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.

Post-Marketing Experience

Clinically significant liver injury has been reported in patients treated with natalizumab in the post-marketing setting (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hepatotoxicity).

PML has been reported in patients treated with natalizumab monotherapy in the post-marketing setting, including cases with onset in the absence of clinical symptoms (see BOXED WARNING and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Progressive Multifocal Leukoencephalopathy). Some cases have been reported up to 6 months following discontinuation of TSYABRI therapy. Cases of JCV granule cell neuronopathy (GCN) have also been reported during post-marketing use of natalizumab. Symptoms of JCV GCN are similar to PML.

In post-marketing experience, there have been reports of eosinophilia (eosinophil count > 1,500/mm^3) without clinical findings. In cases where natalizumab therapy was discontinued the elevated eosinophil levels resolved. There have also been reports of uncommon frequency of thrombocytopenia and immune thrombocytopenic purpura (ITP).

Serious, rare cases of haemolytic anaemia have been reported in patients treated with natalizumab in post- marketing observational studies.

Paediatric

Serious adverse events were evaluated in 621 MS paediatric patients from the meta-analysis study (see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). Within the limitations of these data, there were no new safety signals identified in this patient population. One case of herpes meningitis was reported in the meta-analysis. No cases of PML were identified in the meta-analysis, however PML has been reported in natalizumab-treated paediatric patients in the post-marketing setting. Safety and effectiveness of natalizumab in paediatric patients less than 18 years of age have not been established.

Comparability of TYRUKO with the reference medicine in terms of safety

The safety profiles of TYRUKO and Tysabri were similar in a single dose study in healthy subjects and in the target population of RRMS patients with treatment up to 48 weeks. Based on safety data from the entire TYRUKO clinical program, there do not appear to be any clinically meaningful differences in the safety of natalizumab occurring after the switch from Tysabri to TYRUKO.

Discussion of the adverse events (AEs) reported in the individual studies is provided below.

PB006-01-03: Single dose pivotal PK/PD study in healthy subjects

In this study, 149, 151, and 150 subjects received a single IV dose of 3 mg/kg TYRUKO, EU-Tysabri, and US-Tysabri, respectively. The percentage of patients with treatment emergent adverse events (TEAEs) and the AE profile were similar for TYRUKO and Tysabri. TEAEs related to the

study drug occurring in at least 2% of subjects in any treatment group are presented by system organ class (SOC) and preferred term (PT) in the following Table 2.

Table 2 - Study drug-related TEAEs in at least 2% of subjects by SOC and PT in study PB006-01- 03 (Safety population)

System organ class Preferred term	Number of subjects (%)		
	TYRUKO N=149	Tysabri[1] N=151	Tysabri[2] N=150
Any event	**55 (36.9)**	**52 (34.4)**	**52 (34.7)**
General disorders and administration site conditions	**32 (21.5)**	**32 (21.2)**	**29 (19.3)**
Injection site reaction	27 (18.1)	28 (18.5)	24 (16.0)
Infusion site reaction	4 (2.7)	1 (0.7)	1 (0.7)
Nervous system disorders	**20 (13.4)**	**23 (15.2)**	**18 (12.0)**
Headache	19 (12.8)	20 (13.2)	16 (10.7)
Gastrointestinal disorders	**5 (3.4)**	**10 (6.6)**	**9 (6.0)**
Nausea	4 (2.7)	8 (5.3)	6 (4.0)
Infections and infestations	**4 (2.7)**	**5 (3.3)**	**4 (2.7)**
Upper respiratory tract infection	1 (0.7)	3 (2.0)	1 (0.7)

N=number of subjects in group, n=number of subjects with event, PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event.
The three-arm PK/PD study compared TYRUKO to both US- and EU-Tysabri
Tysabri[1] = EU-Tysabri
Tysabri[2] = US-Tysabri

PB006-03-01: Multiple-dose pivotal Phase 3 study in RRMS patients

In this efficacy and safety study, natalizumab was administered as 300 mg IV infusions, at 4-week intervals, for a total of 12 infusions. A total of 131 patients were treated with TYRUKO starting at Week 0 and 133 patients were treated with Tysabri starting at Week 0; 30 of the 133 patients initially treated with Tysabri received TYRUKO from Week 24 to Week 48.

The percentage of patients with TEAEs and the AE profile were similar in the TYRUKO and the Tysabri groups. No subjects had any signs suggestive of PML during the study or in the 6-month PML follow-up. Results for laboratory findings, vital signs and ECG did not show any clinically meaningful differences between groups. Comparative results from the group switching treatment with Tysabri to TYRUKO after 24 weeks versus the Tysabri continuing group did not reveal any clinically meaningful differences in the AE profile.

In the following two tables, TEAEs related to the study drug are presented by SOC and PT, by preceding treatment and by SOC and PT, by treatment sequence.

Table 3 - Study drug-related TEAEs in at least 1% of patients by SOC and PT, by preceding treatment from Week 0 to Week 48 in study PB006-03-01 (Safety population)

System organ class Preferred term	TYRUKO 300 mg N=161	Tysabri 300 mg N=133
	Patients with event n (%)	Patients with event n (%)
Any event	**34 (21.1)**	**30 (22.6)**
Blood and lymphatic system disorders	**1 (0.6)**	**2 (1.5)**

Gastrointestinal disorders	**1 (0.6)**	**4 (3.0)**
Nausea	1 (0.6)	4 (1.5)
General disorders and administration site conditions	**6 (3.7)**	**7 (5.3)**
Hyperthermia	2 (1.2)	1 (0.8)
Pyrexia	1 (0.6)	2 (1.5)
Asthenia	2 (1.2)	0
Hepatobiliary disorders	**2 (1.2)**	**1 (0.8)**
Hyperbilirubinaemia	2 (1.2)	1 (0.8)
Infections and infestations	**9 (5.6)**	**12 (9.0)**
Cystitis	2 (1.2)	1 (0.8)
Oral herpes	2 (1.2)	2 (1.5)
Pharyngitis	1 (0.6)	2 (1.5)
Investigations	**4 (2.5)**	**4 (3.0)**
Musculoskeletal and connective tissue disorders	**4 (2.5)**	**2 (1.5)**
Muscle spasms	2 (1.2)	1 (0.8)
Nervous system disorders	**10 (6.2)**	**3 (2.3)**
Headache	7 (4.3)	2 (1.5)
Dizziness	2 (1.2)	2 (1.5)
Psychiatric disorders	**2 (1.2)**	**1 (0.8)**
Insomnia	2 (1.2)	1 (0.8)
Skin and subcutaneous tissue disorders	**6 (3.7)**	**4 (3.0)**
Urticaria	2 (1.2)	1 (0.8)
Pruritus	2 (1.2)	0
Vascular disorders	**3 (1.9)**	**0**
Hypotension	2 (1.2)	0

N=number of patients in group, PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event.
Note: AEs occurring after switch from Tysabri to TYRUKO were counted for both treatment arms.
131 patients were treated with TYRUKO starting at Week 0; 133 patients were treated with Tysabri starting at Week 0. 30 of the 133 patients treated with Tysabri received TYRUKO from Week 24 to Week 48.

Table 4 - TEAEs by SOC and PT, by treatment sequence, in at least 2% of patients in any group from Week 0 to Week 48 in study PB006-03-01 (Safety population)

System organ class **Preferred term**	**TYRUKO 300 mg N=131**	**TYRUKO after switch from Tysabri 300 mg N=30**	**Tysabri 300 mg N=103**
	Patients with event n (%)	**Patients with event n (%)**	**Patients with event n (%)**
Any event	**85 (64.9)**	**22 (73.3)**	**71 (68.9)**
Blood and lymphatic system disorders	**5 (3.8)**	**0**	**4 (3.9)**
Anaemia	4 (3.1)	0	0
Gastrointestinal disorders	**13 (9.9)**	**0**	**12 (11.7)**
Diarrhoea	3 (2.3)	0	5 (4.9)
Nausea	4 (3.1)	0	3 (2.9)
Constipation	2 (1.5)	0	3 (2.9)
General disorders and administration site conditions	**13 (9.9)**	**7 (23.3)**	**5 (4.9)**
Asthenia	5 (3.8)	1 (3.3)	1 (1.0)
Fatigue	5 (3.8)	0	1 (1.0)
Pyrexia	1 (0.8)	1 (3.3)	3 (2.9)

Hyperthermia	2 (1.5)	1 (3.3)	0
System organ class **Preferred term**	**TYRUKO 300 mg N=131**	**TYRUKO after switch from Tysabri 300 mg N=30**	**Tysabri 300 mg N=103**
	Patients with event n (%)	**Patients with event n (%)**	**Patients with event n (%)**
Feeling hot	0	2 (6.7)	0
Oedema peripheral	1 (0.8)	1 (3.3)	0
Discomfort	0	1 (3.3)	0
Infusion site pain	0	1 (3.3)	0
Hepatobiliary disorders	**2 (1.5)**	**1 (3.3)**	**1 (1.0)**
Hyperbilirubinaemia	1 (0.8)	1 (3.3)	0
Immune system disorders	**0**	**1 (3.3)**	**0**
Hypersensitivity	0	1 (3.3)	0
Infections and infestations	**39 (29.8)**	**15 (50.0)**	**34 (33.0)**
Nasopharyngitis	11 (8.4)	5 (16.7)	8 (7.8)
COVID-19	11 (8.4)	4 (13.3)	6 (5.8)
Upper respiratory tract infection	2 (1.5)	1 (3.3)	3 (2.9)
Pharyngitis	1 (0.8)	1 (3.3)	3 (2.9)
Pneumonia	3 (2.3)	0	1 (1.0)
Respiratory tract infection	2 (1.5)	1 (3.3)	1 (1.0)
Bronchitis	0	1 (3.3)	2 (1.9)
Oral herpes	1 (0.8)	1 (3.3)	1 (1.0)
Rhinitis	1 (0.8)	1 (3.3)	1 (1.0)
Respiratory tract infection viral	1 (0.8)	1 (3.3)	0
COVID-19 pneumonia	0	1 (3.3)	0
Laryngitis	0	1 (3.3)	0
Pyoderma streptococcal	0	1 (3.3)	0
Injury, poisoning and procedural complications	**2 (1.5)**	**1 (3.3)**	**3 (2.9)**
Contusion	0	1 (3.3)	1 (1.0)
Investigations	**8 (6.1)**	**2 (6.7)**	**9 (8.7)**
Weight decreased	2 (1.5)	1 (3.3)	3 (2.9)
Gamma-glutamyltransferase increased	1 (0.8)	1 (3.3)	0
Metabolism and nutrition disorders	**1 (0.8)**	**1 (3.3)**	**2 (1.9)**
Hyperlipidaemia	0	1 (3.3)	0
Musculoskeletal and connective tissue disorders	**17 (13.0)**	**1 (3.3)**	**9 (8.7)**
Back pain	7 (5.3)	1 (3.3)	3 (2.9)
Pain in extremity	2 (1.5)	0	4 (3.9)
Nervous system disorders	**33 (25.2)**	**8 (26.7)**	**24 (23.3)**
Headache	25 (19.1)	4 (13.3)	19 (18.4)
Dizziness	3 (2.3)	2 (6.7)	1 (1.0)
Hypoaesthesia	2 (1.5)	1 (3.3)	1 (1.0)

System organ class Preferred term	TYRUKO 300 mg N=131	TYRUKO after switch from Tysabri 300 mg N=30	Tysabri 300 mg N=103
	Patients with event n (%)	Patients with event n (%)	Patients with event n (%)
Paraesthesia	1 (0.8)	1 (3.3)	0
Presyncope	1 (0.8)	1 (3.3)	0
Tension headache	1 (0.8)	1 (3.3)	0
Psychiatric disorders	**7 (5.3)**	**4 (13.3)**	**2 (1.9)**
Depression	3 (2.3)	3 (10.0)	1 (1.0)
Insomnia	4 (3.1)	0	1 (1.0)
Sleep disorder	0	1 (3.3)	0
Renal and urinary disorders	**1 (0.8)**	**3 (10.0)**	**2 (1.9)**
Leukocyturia	0	1 (3.3)	1 (1.0)
Dysuria	0	1 (3.3)	0
Haematuria	0	1 (3.3)	0
Urinary retention	0	1 (3.3)	0
Reproductive system and breast disorders	**3 (2.3)**	**0**	**1 (1.0)**
Respiratory, thoracic and mediastinal disorders	**10 (7.6)**	**1 (3.3)**	**4 (3.9)**
Oropharyngeal pain	5 (3.8)	0	3 (2.9)
Rhinorrhoea	1 (0.8)	1 (3.3)	0
Skin and subcutaneous tissue disorders	**8 (6.1)**	**2 (6.7)**	**3 (2.9)**
Erythema	1 (0.8)	1 (3.3)	0
Hyperhidrosis	1 (0.8)	1 (3.3)	0
Vascular disorders	**4 (3.1)**	**1 (3.3)**	**0**
Hypertension	0	1 (3.3)	0

N=number of patients in group, PT=preferred term, SOC=system organ class, TEAE=treatment-emergent adverse event.
Note: AEs were summarised according to the randomised study drug sequence.
N=number of patients in group, PT=preferred term, PY=patient year, SAF=safety population, SOC=system organ class, TEAE=treatment-emergent adverse event.
Note: *Patient years calculated as the sum of (last day of follow-up – first day of exposure + 1)/365.25 for all patients in group. AEs were summarised according to the randomised study drug sequence.

Comparability of TYRUKO with the reference medicine in terms of immunogenicity

The observed incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADAs in the study described below with the incidence of ADAs in other studies.

The immunogenicity of TYRUKO was evaluated directly in comparison to the originator product, Tysabri, in a confirmatory efficacy and safety study (PB006-03-01) in patients with RRMS. In this study, natalizumab was administered as 300 mg IV infusions, at 4-week intervals, for a total of 12 infusions. A total of 131 patients were treated with TYRUKO starting at Week 0 and 133 patients were treated with Tysabri starting at Week 0; 30 of the 133 patients initially treated with Tysabri received TYRUKO from Week 24 to Week 48.

In this study, there was a strong concordance between the ADA and neutralising antibody (NAb) response dynamics in the TYRUKO treatment group compared to those for subjects treated with Tysabri. At the 24-week treatment timepoint corresponding to the primary efficacy endpoint, the incidence of treatment-emergent ADA was 79% for TYRUKO compared with 74% for Tysabri, allied to a NAb positive incidence of 69% for TYRUKO compared with 66% for Tysabri.

Despite slightly higher ADA and NAb levels in the TYRUKO compared to the Tysabri group, the impact on relevant clinical parameters (serum drug trough levels, and efficacy and safety parameters) was similar between groups during administration of natalizumab for 48 weeks.

Switching of 30 subjects from Tysabri to TYRUKO at Week 24 did not appear to affect the treatment-related humoral immune response to natalizumab or its clinical impact.

As TYRUKO and Tysabri demonstrated similar immunogenicity profiles, the same warnings and precautions are appropriate for TYRUKO as for Tysabri.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Safety of doses higher than 300 mg has not been adequately evaluated. The maximum amount of natalizumab that can be safely administered has not been determined.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Natalizumab binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leucocytes except neutrophils and inhibits the α4-mediated adhesion of leucocytes to their counter receptor(s). The receptors for the α4 family of integrins include vascular cell adhesion molecule-1 (VCAM-1), which is expressed on activated vascular endothelium, and mucosal addressin cell adhesion molecule-1 (MadCAM-1) present on vascular endothelial cells of the gastrointestinal tract. Disruption of these molecular interactions prevents transmigration of leucocytes across the endothelium into inflamed parenchymal tissue. *In vitro*, anti-α4-integrin antibodies also block α4-mediated cell binding to ligands such as osteopontin and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1).

The specific mechanism(s) by which natalizumab exerts its effects in multiple sclerosis have not been fully defined. In multiple sclerosis, lesions are believed to occur when activated inflammatory cells, including T-lymphocytes, cross the blood-brain barrier (BBB). Leucocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells, and their counter-receptors present on endothelial cells of the vessel wall. The clinical effect of natalizumab in multiple sclerosis may be secondary to blockade of the molecular interaction of α4β1-integrin expressed by inflammatory cells with VCAM-1 on vascular endothelial cells, and with CS-1 and/or osteopontin

expressed by parenchymal cells in the brain. Data from an experimental autoimmune encephalitis animal model of multiple sclerosis demonstrate reduction of leucocyte migration into brain parenchyma and reduction of plaque formation detected by magnetic resonance imaging (MRI) following repeated administration of natalizumab. The clinical relevance of these animal data is unknown.

Based on PK/α4β1 integrin binding relationships established in the updated population pharmacokinetic/pharmacodynamic model, the EC_{50} of natalizumab binding to α4β1 integrin is estimated to be 2.5 mg/L.

Natalizumab administration increases the number of circulating leucocytes, (including lymphocytes, monocytes, basophils, and eosinophils) due to inhibition of transmigration out of the vascular space. Natalizumab does not affect the number of circulating neutrophils (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Effects on laboratory tests).

Comparative non-clinical pharmacology

Pharmacodynamic comparability between TYRUKO and the reference medicine was demonstrated in *in vitro* studies. These included assessment of direct binding to α4β1-integrin, inhibition of α4β1-integrin binding to its cognate receptor VCAM-1, and inhibition of the adhesion of cells expressing α4β1-integrin to VCAM-1. As natalizumab also binds to α4β7 integrin, studies examining the α4β7-integrin/MAdCAM-1 interaction were also performed. These studies confirmed the similarity of TYRUKO to Tysabri in terms of the mechanisms of action.

Natalizumab does not exhibit any Fc-related effector functions. It was confirmed that TYRUKO, similarly to Tysabri, did not show any activity in ADCC, ADCP or CDC assays.

Clinical trials

Natalizumab was evaluated in two randomised, double-blind, placebo-controlled trials in patients with relapsing remitting multiple sclerosis. Both studies enrolled patients who experienced at least one clinical relapse during the prior year and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5.0. Patients with primary progressive, secondary progressive and progressive relapsing MS were excluded from these trials.

In both studies, neurological evaluations were performed every 12 weeks and at times of suspected relapse. Magnetic resonance imaging evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually.

Study 1 enrolled patients who had not received any interferon-beta or glatiramer acetate for at least the previous 6 months; approximately 94% had never been treated with these agents. Median age was 37, with a median disease duration of 5 years. Patients were randomised in a 2:1 ratio to receive natalizumab 300 mg intravenous infusion (n=627) or placebo (n=315) every 4 weeks for up to 28 months (30 infusions).

Study 2 enrolled patients who had experienced one or more relapses while on treatment with Avonex (interferon beta-1a) 30 µg intramuscularly (IM) once weekly during the year prior to study entry. Median age was 39, with a median disease duration of 7 years. Patients were evenly randomised to receive natalizumab 300 mg (n=589) or placebo (n=582) every 4 weeks for up to 28 months (30 infusions). All patients continued to receive Avonex 30 µg IM once weekly. In this study, natalizumab in combination with Avonex was compared with Avonex alone.

In both studies, there were two pre-specified primary endpoints, annualised clinical relapse rate at one year and disease progression, measured by Extended Disability Severity Scale (EDSS), at two years. Sustained increase in disability was defined as an increase of at least 1 point on the EDSS from

baseline EDSS ≥ 1.0 that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS = 0 that was sustained for 12 weeks. Results are shown in Table 5 and Table 6. Median time on study drug was 120 weeks in each study.

Time to onset of sustained increase in disability was longer in patients treated with natalizumab than in patients treated with placebo in Studies 1 (Figure 3) and 2. The proportions of patients with increased disability and annualised relapse rate were also lower in patients treated with natalizumab than in patients treated with placebo in Studies 1 and 2. Subgroup and sensitivity analyses showed results consistent with the primary analyses. The sensitivity analysis of increase in disability that was sustained for 24 weeks yielded a 54% reduction in the natalizumab group in Study 1 (p<0.001).

Changes in MRI findings often do not correlate with changes in the clinical status of patients (e.g. disability progression). The prognostic significance of the MRI findings in these studies has not been evaluated.

Table 5 - Clinical and MRI Endpoints in Study 1 (Monotherapy Study) at 2 Years

	Natalizumab n=627	**Placebo** n=315
Clinical Endpoints		
Percentage with sustained increase in disability	17%	29%
Relative Risk Reduction	42% (95% CI 23%, 57%)	
Annualised relapse rate	0.23	0.73
Relative reduction (percentage)	68% (95% CI 60%, 74%)	
Percentage of patients remaining relapse-free	67%	41%
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions	0	5
Median		
Percentage of patients with:*		
0 lesions	57%	15%
1 lesion	17%	10%
2 lesions	8%	8%
3 or more lesions	18%	68%
Gd-enhancing lesions		
Median	0	0
Percentage of patients with:		
0 lesions	97%	72%
1 lesion	2%	12%
2 or more lesions	1%	16%

All analyses were intent-to-treat. For each endpoint, p<0.001. Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS and age; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

* Values do not total 100% due to rounding.

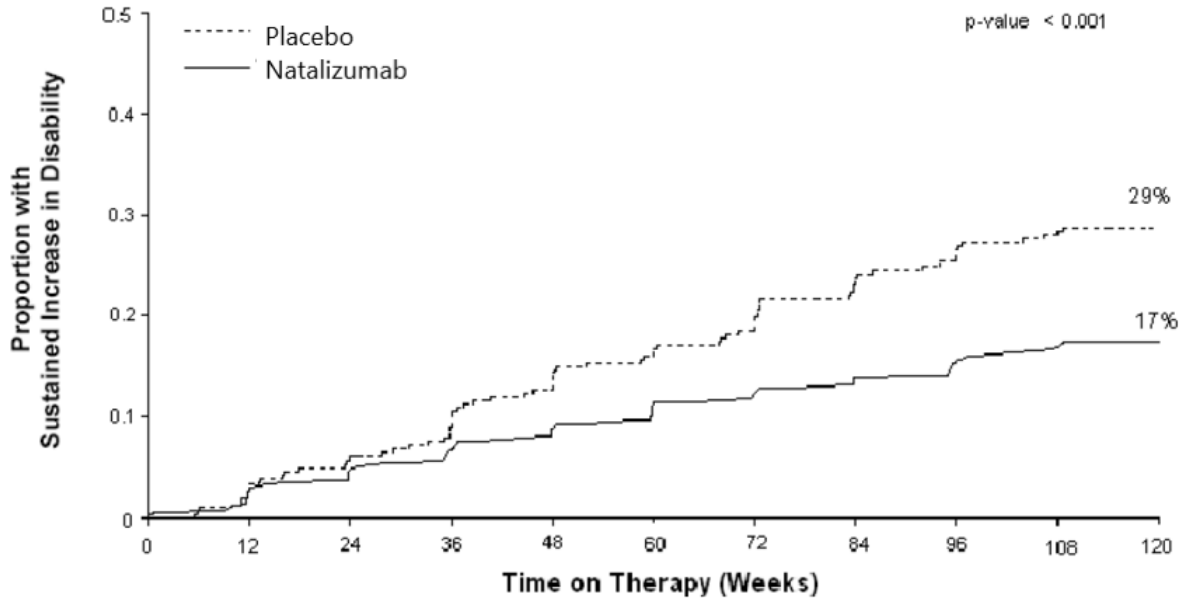
Table 6 - Clinical and MRI Endpoints in Study 2 (Add-On Study) at 2 Years

	Natalizumab plus Avonex n=589	**Placebo plus Avonex** n=582
Clinical Endpoints		
Percentage with sustained increase in disability	23%	29%
Relative Risk Reduction	24% (95% CI 4%, 39%)	
Annualised relapse rate	0.34	0.75
Relative reduction (percentage)	55% (95% CI 47%, 62%)	
Percentage of patients remaining relapse-free	54%	32%
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions	0	3
Median		
Percentage of patients with:*		
0 lesions	67%	30%
1 lesion	13%	9%
2 lesions	7%	10%
3 or more lesions	14%	50%
Gd-enhancing lesions		
Median	0	0
Percentage of patients with:		
0 lesions	96%	75%
1 lesion	2%	12%
2 or more lesions	1%	14%

All analyses were intent-to-treat. For disability progression p=0.024, for all other endpoints, p<0.001. Determination of p-values: increase in disability by Cox proportional hazards model adjusted for baseline EDSS; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd--enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

* Values do not total 100% due to rounding.

Figure 3: Time to Increase in Disability Sustained for 12 Weeks in Study 1



Study 101MS101 was an open-label, randomised, crossover study in 43 patients with relapsing forms of multiple sclerosis comparing the pharmacokinetic properties of natalizumab produced by the initial manufacturing process and natalizumab manufactured using the high titre process. As a secondary endpoint, the tolerability and safety of both manufacturing processes were assessed. No notable differences were observed in the overall incidence for any safety measures in patients receiving either natalizumab preparation. The safety profile over this 36-week study was similar to that described in other natalizumab studies.

Study 101MS201 was a multicentre, open-label, repeat-dose study of 113 natalizumab naïve patients with relapsing forms of multiple sclerosis assessing the immunogenicity of 300 mg of natalizumab manufactured using the high titre process. Natalizumab was administered intravenously over 60 minutes every 4 weeks for 9 months (a total of 9 doses). A secondary objective was to evaluate safety. All subjects received at least one dose of natalizumab. Natalizumab manufactured using the high titre process was well tolerated with an adverse event profile similar to that observed in previous clinical studies. Persistent anti-natalizumab antibodies formed in a small number of subjects which is comparable to the rate observed with previous clinical studies.

A meta-analysis was conducted using data from 621 paediatric MS patients treated with natalizumab (median age 17 years, range was 7-18 years, 91% aged ≥ 14 years). Within the meta-analysis, a limited subset of patients with data available prior to treatment (158 of the 621 patients) in the post-marketing setting demonstrated a reduction in annualised relapse rate (ARR) from 1.466 (95% CI 1.337, 1.604) prior to treatment to 0.110 (95% CI 0.094, 0.128).

Pharmacodynamic comparability of TYRUKO with the reference medicine

Pharmacodynamic comparability of TYRUKO was demonstrated in a comparative pharmacokinetic/ pharmacodynamic (PK/PD) clinical Phase I study (PB006-01-03) in 450 healthy subjects comparing TYRUKO with Tysabri. The study evaluated PK/PD after a single-dose, IV infusion of TYRUKO or Tysabri, at 3 mg/kg. Primary study endpoints included $AUEC_{0\text{-}12W}$ of CD19+ cell count and $AUEC_{0\text{-}12W}$ for a4-integrin receptor saturation (RS).

The results are shown in Table 7.

Table 7 - Study PB006-01-03: Statistical analysis of pharmacodynamic parameters for the comparison of TYRUKO with Tysabri

	Natalizumab injection 1 x 3 mg/kg From measured data			
	Geometric mean[1]			
Parameter (unit)	**TYRUKO**	**Tysabri**	**Ratio of means[2]**	**95% CI of ratio**
CD 19+ cell count $AUEC_{0-12W}$ baseline adjusted ($h*10^6/L$)	423080	416312	1.1063	0.8787, 1.1754
α4-integrin %RS $AUEC_{0-12W}$ (h*%)	99003	97616	1.0142	0.9667, 1.0641

LS= least square
[1] model-based data (from ANCOVA model) for the analysis of AUEC0-12w of baseline-adjusted CD19+
[2] ANCOVA was performed on the ln-transformed PD parameter baseline-adjusted AUEC0-12w of baseline adjusted CD19+; for the analysis of α4-integrin %RS, ANOVA model was used
α4-integrin %RS; percent of α4-integrin receptors saturated with natalizumab

Comparability of TYRUKO with the reference medicine in terms of efficacy

Study PB006-03-01 (Relapsing-remitting multiple sclerosis)

The efficacy of TYRUKO was compared to Tysabri in a randomised, double-blind clinical study in 264 adult patients (aged ≥18 to 60 years) with RRMS defined by the 2010 revised McDonald criteria. Eligible patients had at least 1 documented relapse within the previous year and either ≥ 1 gadolinium-enhancing (GdE) T1-weighted brain lesion or ≥9 T2-weighted brain lesions at screening. Also, patients had to have a Kurtzke's Expanded Disability Status Scale (EDSS) score from 0 to 5 (inclusive) at screening, and the John Cunningham virus (JCV) index was to be ≤ 1.5 (the assay used in the clinical trial may be different from the one used for clinical decision making for patients on TYRUKO). Prescribers should consider the index values relevant to the assay they are using.

Eligible patients were randomised in a 1:1 ratio to receive a total of 12 infusions of 300 mg TYRUKO or Tysabri every 4 weeks. Randomisation at baseline was stratified according to absence/presence of GdE lesions, presence of T2 lesions (≤15,>15) and JCV status (negative, positive).

The primary efficacy endpoint was the cumulative number of new active lesions over 24 weeks. The primary analysis was based on the per-protocol population.

The results are presented in Table 8.

Table 8 - Cumulative number of new active lesions over 24 weeks (PP population)

Least square means	Estimate (SE)	95% CI
TYRUKO Tysabri	0.34 (0.336) 0.45 (0.281)	
Exponentiated difference Tysabri - TYRUKO	0.17 (0.397)	-0.613; 0.944

CI=confidence interval, PP=per protocol, SE=standard error.
The analysis was based on 111 patients in the TYRUKO group and 118 patients in the Tysabri group.
For the primary analysis, a negative binomial generalised linear model with fixed effects for the treatment group and stratification factors with log link was used. Parameters were back-transformed to the original scale. Similarity was concluded if the 95% CI of the Tysabri – TYRUKO difference (exponentiated difference) was within the pre-specified similarity margins of -2.1 to 2.1.

5.2 PHARMACOKINETIC PROPERTIES

Following the repeat intravenous administration of a 300 mg dose of natalizumab to patients with multiple sclerosis (MS), the mean (± standard deviation) maximum observed serum concentration was 110 ± 52 µg/mL. Mean average steady-state trough concentrations ranged from 23 µg/mL to 29 µg/mL. The observed time to steady-state was approximately 24 weeks.

An updated population pharmacokinetic analysis was conducted consisting of 11 studies and data with serial PK sampling as measured by an industry standard assay. It included 1,286 subjects receiving doses ranging from 1 to 6 mg/kg and fixed doses of 150/300 mg. Population median estimate for linear clearance was 6.21 mL/h, (5.60-6.70 mL/h, 95% confidence interval), median steady-state volume of distribution was 5.58 L (5.27-5.92 L, 95% confidence interval) and the estimated median terminal half-life was 26.8 days.

The population analysis of 1,286 patients explored the effects of selected covariates including body weight, age, gender, presence of anti-natalizumab antibodies and formulation on natalizumab pharmacokinetics. Only body weight, the presence of anti-natalizumab antibodies and the formulation used in phase 2 studies were found to influence natalizumab disposition. Natalizumab clearance increased with body weight in a less than proportional manner, such that a +/-43% change in body weight resulted in a -38% to 36% change in clearance. Variation of clearance with body weight is not considered clinically relevant. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 2.54 fold, consistent with reduced serum natalizumab concentrations observed in persistently antibody-positive patients (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Immunogenicity). Clearance also increased by 2.17 fold for the phase 2 formulation compared to commercially used formulation.

Study 101MS101 was an open-label, randomised, crossover study in 43 subjects with relapsing forms of multiple sclerosis comparing the pharmacokinetic properties of natalizumab produced by the initial manufacturing process and natalizumab manufactured using the high titre process. Nearly identical concentration/time profiles were observed. Comparability of both manufacturing methods was well demonstrated.

The effect of plasma exchange on natalizumab clearance and pharmacodynamics was evaluated in a study of 12 MS patients. Estimates of the total drug 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 drug 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.

The pharmacokinetics of natalizumab in paediatric or adolescent MS patients younger than 18 years have not been established. Pharmacokinetics in patients over 65 years of age, or patients with renal or hepatic insufficiency have not been studied.

Pharmacokinetic comparability of TYRUKO with the reference medicine

Bioequivalence of TYRUKO was demonstrated in a comparative pharmacokinetic/ pharmacodynamic (PK/PD) clinical Phase I study (PB006-01-03) in 450 healthy subjects comparing TYRUKO with Tysabri. The study evaluated PK/PD after a single-dose, IV infusion of TYRUKO or Tysabri, at 3 mg/kg.

The results are shown in Table 9.

Table 9 - Study PB006-01-03: Statistical analysis of pharmacokinetic parameters for the comparison of TYRUKO with Tysabri

	Natalizumab (total) injection 1 x 3 mg/kg From measured data			
	Geometric mean[1] Arithmetic mean (CV%)			
Parameter (unit)	**TYRUKO**	**Tysabri**	**Ratio of means[3]**	**90% CI of ratio**
AUC_{0-t} (h*mg/L)	22014	22371	0.9840	0.9387, 1.0316
AUC_{inf} (h*mg/L)	22118	22424	0.9864	0.9410, 1.0340
C_{max} (mg/L)	68.6	71.7	0.9565	0.9215, 0.9929

LS= least square
[1] model-based data (from ANOVA model)
[2] expressed as median (range) only
[3] estimated using an analysis of variance model with treatment as a fixed effect

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Natalizumab was negative in genotoxicity assays *in vitro* (mouse lymphoma forward mutation assay, chromosomal aberration in human lymphocytes).

Carcinogenicity

Natalizumab showed no effects on *in vitro* assays of α4-integrin positive tumour line proliferation/cytotoxicity. Xenograft transplantation of two α4-integrin positive human tumour lines (leukaemia, melanoma) into immunodeficient mice demonstrated no increase in tumour growth rates or metastasis resulting from natalizumab treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Inactive ingredients include: 131.49 mg sodium chloride, 6.36 mg histidine, 22.86 mg histidine hydrochloride monohydrate, 3.0 mg polysorbate 80, and water for injections.

6.2 INCOMPATIBILITIES

Other medications should not be injected into infusion set side ports or mixed with TYRUKO.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

TYRUKO single-use vials must be stored between 2°C to 8°C. Do not use after the expiration date on the carton and label. DO NOT SHAKE OR FREEZE. Protect from light (store in carton).

If not used immediately, diluted solution for infusion can be stored at 2°C to 8°C. TYRUKO solution for infusion must be administered within 24 hours of preparation.

6.5 NATURE AND CONTENTS OF CONTAINER

TYRUKO concentrated injection solution for infusion contains 300 mg/15 mL natalizumab in a sterile, single-use vial (Type I glass) with a stopper (bromobutyl rubber) and a seal (aluminium) with a flip-off cap, free of preservatives (packs of 1 vial).

TYRUKO is for single use in one patient only.

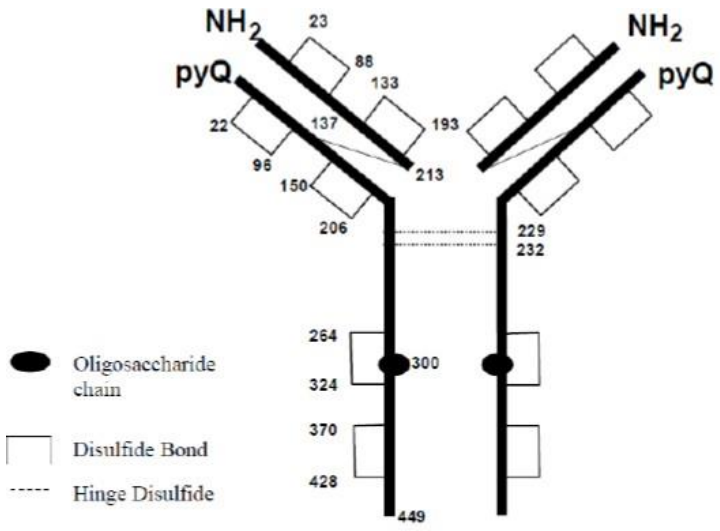
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Figure 4: Schematic Drawing of the Major Natalizumab Structure



Note: The assignment of the exact disulfide bonds between two H-chains is not possible.

CAS number

189261-10-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Sandoz Pty Ltd
100 Pacific Highway
North Sydney, NSW 2060
Australia

9 DATE OF FIRST APPROVAL

DD/MM/YYYY

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information