

Medicines Adverse Reactions Committee

Meeting date	7 December 2017	Agenda item	3.2.5
Title	Natalizumab (Tysabri) and haematological abnormalities in newborns whose mothers were treated with natalizumab during pregnancy		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent	Medicines	Sponsors	
Natalizumab	Tysabri	Biogen NZ Biopharma Limited	
Funding	Tysabri is funded by PHARMAC by special authority		
Previous MARC meetings	None		
Prescriber Update	None		
Schedule	Prescription medicine		
Advice sought	<p>The Committee is asked to advise whether:</p> <ul style="list-style-type: none"> – is there a potential for blood abnormalities to occur in newborns whose mothers were treated with natalizumab during pregnancy – a statement regarding haematological abnormalities in newborns whose mothers were treated with natalizumab during pregnancy is required <ul style="list-style-type: none"> ○ if required, should the statement be in Section 4.6: Fertility, pregnancy and lactation or Section 4.8: Undesirable effects (or both) – any of the additional information in the United Kingdom's Summary of Product Characteristics section on pregnancy should be included in the New Zealand data sheet – is any communication to healthcare professionals warranted? 		

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1.0 PURPOSE

In June 2017, Health Canada published a summary safety review on haematological abnormalities in newborns whose mothers were treated with natalizumab (Tysabri) during pregnancy following the publication of reports of newborns having anaemia, thrombocytopenic and leucocytosis. The review included reports provided by the manufacturer and from published literature.

Health Canada concluded there is a potential for haematological abnormalities in newborns whose mothers were treated with natalizumab and updated the Canadian product information to include this potential risk.

2.0 BACKGROUND

2.1 Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune condition that affects the central nervous system (CNS). Individuals with MS display diffuse and focal areas of inflammation, demyelination, and neuronal injury in the brain and spinal cord (1).

Over 2.5 million individuals worldwide have MS and 80 % have relapsing-remitting MS (RRMS) characterised by periods of exacerbation followed by substantial remission (2). MS has an average age of onset of about 30 years with a 2–3-fold greater occurrence in women versus men (3).

In RRMS, relapses occur once every few years and may last for days or weeks (2). Relapses are followed by remission often with some residual disability (2). Symptoms may include visual, motor, sensory disturbances or autonomic disturbances of bowel and bladder depending on where the inflammatory attack occurs in the CNS (2). As RRMS continues, one third of patients develop substantial disability (2).

Disease-modifying drugs aim to reduce the frequency of relapses as well as reducing the severity of relapses to reduce the build-up of disability. Approved and currently funded disease-modifying drugs for RRMS in New Zealand include interferon β -1a, interferon β -1b, glatiramer acetate, dimethyl fumarate, natalizumab, teriflunomide and fingolimod. The efficacy of these treatments versus placebo is shown in Table 1.

Table 1: Efficacy of disease-modifying medicines versus placebo in pivotal trials in RRMS (1)

Drug (generic name)	Year of first approval	Relapse rate reduction (%)	Confirmed EDSS disability reduction	MRI activity reduction (new lesions, Gd+ lesions) (%)
Interferon- β	1993–1998	~ 30	Inconsistent	~ 60–80
Glatiramer acetate	1996	~ 30	Inconsistent	~ 30
Mitoxantrone	2000	~ 60	~ 64 %	~ 85
Natalizumab	2004	~ 68	~ 42 %	~ 80–90
Fingolimod	2011	~ 50	~ 37 %	~ 75–80
Teriflunomide	2012	~ 30	Inconsistent	~ 70
Dimethyl fumarate	2013	~ 50	~ 38%	~ 80–90
Alemtuzumab ^a	2013	~ 40–50	~ 30 %	~ 70

EDSS Expanded Disability Status Scale, Gd+ gadolinium-enhancing, MRI magnetic resonance imaging

^a The data are versus interferon- β 1a 44 μ g three times weekly

2.1.1 Pregnancy

MS can affect women of childbearing age and disease-modifying therapies are widely used by women of childbearing age. Women are typically advised to discontinue disease-modifying drugs on becoming pregnancy due to the unknown risk of foetal harm. There are limited treatment options for women with MS on disease-modifying therapies who wish to become pregnant and continue treatment. Table 2 shows the disease-modifying therapies that are approved for use in New Zealand and the pregnancy recommendations included on the data sheet. Australian categories for prescribing medicines in pregnancy are shown in Table 3.

Table 2: Options for women wanting to become pregnant on disease-modifying therapies from New Zealand data sheets

Medicine	Pregnancy recommendation
Interferon β -1a (Avonex)	Initiation of treatment is contraindicated during pregnancy. Pregnancy category D.
Interferon β -1b (Betaferon)	Contraindicated during pregnancy. Pregnancy category D.
Glatiramer acetate (Copaxone)	Pregnancy Category B1. Should be used during pregnancy only if clearly needed.
Teriflunomide (Aubagio)	Contraindicated in pregnant women and women of childbearing potential who are not using reliable contraception. Pregnancy category X.
Dimethyl fumarate (Tecfidera)	Pregnancy Category B1. Should be used during pregnancy only if clearly needed.
Natalizumab (Tysabri)	Pregnancy category C. Should be used during pregnancy only if clearly needed. Consider discontinuation if pregnancy occurs.
Fingolimod (Gilenya)	Pregnancy category D. Consider risks and benefits in pregnancy.
Alemtuzumab (Lemtrada)*	Pregnancy category B3. Consider risks and benefits in pregnancy.

* Approved but not funded

Table 3: Australian categories for prescribing medicines in pregnancy

Category	Description
Category A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.
Category B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.
Category B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are

	inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.
Category B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.
Category C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
Category D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
Category X	Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

2.2 Natalizumab

Natalizumab is a recombinant humanised IgG4 monoclonal antibody indicated as a monotherapy for the treatment of patients with RRMS to delay the progression of physical disability and to reduce the frequency of relapse (4). Tysabri has been approved in New Zealand since September 2007.

2.2.1 Efficacy

In a two year randomised, double-blind, placebo-controlled trial of natalizumab in patients with RRMS, natalizumab reduced the annualised rate of relapse by 68 % and reduced the risk of sustained progression of disability by 42 % (5). In addition, the number of new or enlarged T2-hyperintense lesions were reduced by 83 % compared with placebo and gadolinium-enhanced lesions were reduced by 92 % compared to placebo (5).

In another two year randomised, double-blind, placebo-controlled trial in patients with RRMS who despite IFN β -1a treatment experienced one or more relapses, the combination of natalizumab and IFN β -1a significantly reduced the annualised relapse rate by 55 % and reduced the risk of sustained progression of disability by 24 % when compared to IFN β -1a and placebo (6). In addition, the accumulation of new or enlarged T2-hyperintense lesions was reduced by 83 % with combination therapy and the mean number of gadolinium-enhancing lesions was reduced by 89 % (6).

2.2.2 Mechanism

Natalizumab binds to the α 4-subunit of α 4 β 1 and α 4 β 7 integrins expressed on the surface of all leucocytes except neutrophils, and inhibits the α 4-mediated adhesion of leucocytes to their receptor(s)(4). The receptors for the α 4 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 (4). Disruption of these molecular interactions prevents transmigration of leucocytes across the endothelium into inflamed parenchymal tissue (4) (Figure 1).

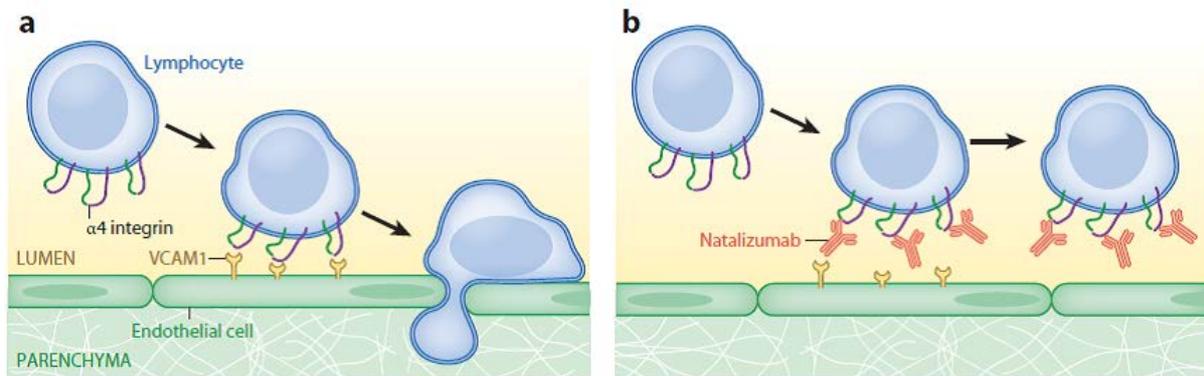


Figure 1: Natalizumab blocks lymphocyte homing in MS. (a) $\alpha 4$ integrin binds to vascular cell adhesion molecule 1 (VCAM-1) and to osteopontin (a second binding partner of $\alpha 4$ integrin, not depicted) on inflamed brain endothelium. This interaction gives lymphocytes access to the central nervous system (CNS). The presence of immune cells in the brain is a prominent feature of MS. (b) Natalizumab, a humanized antibody to $\alpha 4$ integrin, blocks binding of lymphocytes to VCAM and osteopontin on inflamed brain endothelium, thereby preventing lymphocyte entry into the CNS(2).

The specific mechanism(s) by which natalizumab exerts its effects in MS have not been fully defined (4). However, the homing of immune cells to the CNS is one of the major events leading to a relapse in RRMS (2). In 1992, while analysing a frozen section binding assay from the experimental autoimmune encephalomyelitis model (a rat model of MS), it was discovered that antibodies to $\alpha 4$ and $\beta 1$ integrin completely blocked the adhesion of lymphocytes (rat, mouse and human) to inflamed brain endothelium (2). The primary receptor on the inflamed endothelium for $\alpha 4\beta 1$ integrin was subsequently identified as vascular cell adhesion molecule 1 (VCAM-1), although $\alpha 4\beta 1$ integrin also binds to osteopontin (2).

2.2.3 Haematological

Haematological abnormalities have been reported in adult patients treated with natalizumab. Natalizumab induces circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells but elevations of neutrophils are not observed (4, 6). Natalizumab induces mild decreases in haemoglobin levels that are frequently transient (4). Haematological changes persist during natalizumab exposure but are reversible, returning to baseline levels usually within 16 weeks after the last dose (4, 6). In addition, there has been a case of natalizumab-induced immune thrombocytopenia (drug-induced thrombocytopenic purpura) reported (7).

2.2.4 Pregnancy

Natalizumab has been categorised as a pregnancy category C medication as there are no adequate and well-controlled studies in pregnant women (4). The data sheet recommends that natalizumab should be used during pregnancy only if clearly needed and if a woman becomes pregnant while taking natalizumab, discontinuation of therapy should be considered (4).

Pregnancy has been shown to have a short-term reduction of relapse rate (8, 9). In a prospective study of 254 women with MS, the rate of relapse was 07 ± 0.9 per woman per year in the year before pregnancy, 0.5 ± 1.3 ($P=0.03$) in the first trimester, 0.6 ± 1.6 ($P=0.17$) in the second trimester, and 0.2 ± 1.0 ($P<0.001$) in the third trimester (8). However, after delivery there was a rebound increase in relapse rate to 1.2 ± 2.0 ($P<0.001$) during the first three months postpartum that then returned to the pre-pregnancy rate (8).

Medsafe comment

The women with MS in this study did not appear to be on any medication for MS prior to pregnancy (none indicated) and only short courses of glucocorticoids were allowed during pregnancy.

There are concerns over potential risks of stopping natalizumab treatment during pregnancy because of the possibility of a return of disease activity. Verhaeghe *et al.* describe the case of a woman on natalizumab with stable disease who stopped treatment due to pregnancy and experienced reactivation of disease activity with new pseudotumoral lesions (10). This case is described in more detail in Section 3.1.2.8 as treatment with natalizumab was restarted one month before delivery due to the disease reactivation. In a case series of four pregnant women who interrupted natalizumab treatment to become pregnant, all four presented a return of disease activity during gestation and two of the women displayed a worsening of disability by the end pregnancy (11). In addition, there is a case report of a young woman with recurrent rebound activity after natalizumab discontinuation for pregnancy planning that forced her to restart treatment (three attempts) without a successful pregnancy (12).

Natalizumab is an IgG4 antibody. Immunoglobulins in the foetal circulation are almost exclusively maternal IgG (13). Maternal antibodies are transported to the foetus at increasing rates during pregnancy (13). During the first trimester the level of IgG in the foetus as compared to the maternal concentration is quite low, increasing from 17–22 gestational weeks and 28–32 gestational weeks to 10 % and 50 % of the maternal concentration respectively (13). Levels of IgG continue to increase resulting in the neonate having antibody levels at or in excess of those in the mother (13). Concentrations of the four subclasses of IgG in foetal sera showed the preferential transport was IgG1>IgG3>IgG4>IgG2 (13).

Natalizumab has also been detected in human breast milk and a decision should be made whether to continue breast-feeding during natalizumab treatment (4).

2.3 Data sheets

2.3.1 New Zealand

Tysabri (natalizumab, rmc), 11 November 2016

2.3.1.1 Pharmacology>Pharmacodynamics

TYSABRI administration increases the number of circulating leucocytes, (including lymphocytes, monocytes, basophils, and eosinophils) due to inhibition of transmigration out of the vascular space. TYSABRI does not affect the number of circulating neutrophils (see PRECAUTIONS, Effect on Laboratory Tests).

2.3.1.2 Precautions>Stopping TYSABRI Therapy – Prolonged Pharmacodynamic Effects

If a decision is made to stop treatment with TYSABRI, 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.

2.3.1.3 Precautions>Use in Pregnancy (Category C)

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

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 $\alpha 4$ integrins). Intravenous administration of natalizumab to pregnant monkeys during the period of organogenesis was associated with foetal changes (mild anaemia, thrombocytopenia, 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 thrombocytopenia (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.

2.3.1.4 Precautions>Effect on Laboratory Tests

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

2.3.1.5 Adverse Effects>Post-marketing Experience

In post-marketing experience, there have been reports of eosinophilia (eosinophil count > 1,500/mm³) without clinical findings. In cases where TYSABRI therapy was discontinued the elevated eosinophil levels resolved.

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

2.3.2 Canada

2.3.2.1 Warnings and Precautions>Hematologic

In clinical trials, TYSABRI was observed to induce increases in circulating lymphocytes, monocytes, eosinophils and nucleated red blood cells. During phase 3 clinical trials, cell counts were measured every 12 weeks. The largest cell increases were seen in lymphocytes, which were found to be elevated within 12 weeks after initiating TYSABRI treatment, reaching a plateau by 24 weeks. Although elevated, mean cell counts remained within the normal range. Observed increases persisted during TYSABRI exposure, but were reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils were not observed. TYSABRI may induce mild decreases in hemoglobin levels (mean decrease of 6.0 g/L) that are frequently transient. Hemoglobin

levels returned to pretreatment values, usually within 16 weeks of last dose of TYSABRI and the changes were not associated with clinical symptoms.

2.3.2.2 Special Populations>Pregnant Women

There are no adequate and well-controlled studies of TYSABRI therapy in pregnant women. In premarketing clinical trials, the extent of exposure is very limited. Because animal reproduction studies are not always predictive of human response, this drug should only be used during pregnancy if clearly needed. If a woman becomes pregnant while taking TYSABRI, discontinuation of TYSABRI should be considered.

In reproductive studies in monkeys and guinea pigs, there was no evidence of teratogenic effects or effects on survival or growth of offspring at doses up to 30 mg/kg (7 times the human clinical dose based on body weight comparison). In one of five studies that exposed monkeys or guinea pigs during pregnancy, the number of abortions in treated (30 mg/kg) monkeys was 33% vs. 17% in controls. No effects on abortion rates were noted in any other study. A study in pregnant cynomolgus monkeys treated at 2.3-fold the clinical dose demonstrated natalizumab-related changes in the fetus. These changes included mild anemia, reduced platelet count, increased spleen weights, and reduced liver and thymus weights associated with increased splenic extramedullary hematopoiesis, thymic atrophy and decreased hepatic hematopoiesis. In offspring born to mothers treated with natalizumab at 7-fold the clinical dose, platelet counts were also reduced. This effect was reversed upon clearance of natalizumab. There was no evidence of anemia in these offspring.

2.3.2.3 Post-market Adverse Drug Reactions>Hematologic

In post-marketing experience, there have been reports of eosinophilia (eosinophil count > 1,500/mm³) without clinical findings. In cases where TYSABRI therapy was discontinued the elevated eosinophil levels resolved. Rare serious cases of anemia and hemolytic anemia have been reported in patients treated with TYSABRI in post-marketing observational studies.

Cases from published literature reported transient mild to moderate thrombocytopenia and anemia observed in infants born to women exposed to TYSABRI in their third trimester of pregnancy. Therefore, it is recommended that newborns of women exposed to the medicinal product during the third trimester of pregnancy are monitored for potential hematological abnormalities.

2.3.2.4 Action and Clinical Pharmacology>Pharmacodynamics

Treatment with TYSABRI (natalizumab) led to an increase in circulating white blood cells and total lymphocytes that was maintained throughout the treatment period. This is due to the ability of natalizumab to inhibit adhesion of leukocytes to endothelial cells and diminish transmigration of these cells from the vascular space into inflamed tissues. These increases were not clinically significant and once treatment was discontinued, counts returned to baseline levels. Consistent with the mechanism of action of natalizumab and the lack of $\alpha 4$ on the surface of this cell type, there was no change in the number of circulating neutrophils.

Duration of Effect

TYSABRI has pharmacodynamic effects (e.g. increased lymphocyte counts) for approximately 12 weeks following the last dose.

2.3.3 Australia

Tysabri (natalizumab, rmc), 8 November 2016

The Australian Product Information contains the same information as the NZ data sheet above.

2.3.4 United Kingdom

Tysabri 300mg concentrate for solution for infusion Summary of Product Characteristics (SPC), February 2017

2.3.4.1 4.4 Special Warnings and Precautions for Use>Stopping TYSABRI Therapy

If a decision is made to stop treatment with natalizumab, the physician needs to be aware that natalizumab remains in the blood, and has pharmacodynamic effects (e.g increased lymphocyte counts) for approximately 12 weeks following the last dose.

2.3.4.2 4.6 Fertility, Pregnancy and Lactation>Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3).

Data from clinical trials, a prospective pregnancy registry, post-marketing cases and available literature do not suggest an effect of TYSABRI exposure on pregnancy outcomes.

The completed prospective TYSABRI pregnancy registry contained 355 pregnancies with available outcomes. There were 316 live births, 29 of which were reported to have birth defects. Sixteen of the 29 were classified as major defects. The rate of defects corresponds to the defect rates reported in other pregnancy registries involving MS patients. There is no evidence of a specific pattern of birth defects with TYSABRI.

Cases from published literature reported transient mild to moderate thrombocytopenia and anaemia observed in infants born to women exposed to TYSABRI in their third trimester of pregnancy. Therefore, it is recommended that newborns of women exposed to the medicinal product during the third trimester of pregnancy are monitored for potential haematological abnormalities.

If a woman becomes pregnant while taking TYSABRI, discontinuation of the medicinal product should be considered. A benefit-risk evaluation of the use of TYSABRI during pregnancy should take into account the patient's clinical condition and the possible return of disease activity after stopping the medicinal product.

Medsafe comment

The UK SPC differs from the New Zealand, Canada and Australia data sheets as it includes information regarding the Tysabri pregnancy registry and other information that should be included in a benefit-risk evaluation. In addition, the animal studies are not included in this section but are included in Section 5.3: Pharmacological Properties>Preclinical Safety Data

2.3.4.3 4.8 Undesirable Effects>Effects of Laboratory Tests

In 2-year controlled clinical trials in MS patients TYSABRI treatment was associated with increases in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells. Elevations in neutrophils were not seen. Increases from baseline for lymphocytes, monocytes, eosinophils and basophils ranged from 35% to 140% for individual cell types but mean cell counts remained within normal ranges. During treatment with TYSABRI, small reductions in haemoglobin (mean decrease 0.6 g/dl), haematocrit (mean decrease 2%) and red blood cell counts (mean decrease 0.1 x 10⁶/l) were seen. All changes in haematological variables returned to pre-treatment values, usually within 16

weeks of last dose of the medicinal product and the changes were not associated with clinical symptoms. In post-marketing experience, there have also been reports of eosinophilia (eosinophil count $>1,500/\text{mm}^3$) without clinical symptoms. In such cases where TYSABRI therapy was discontinued the elevated eosinophil levels resolved.

2.3.4.4 5.3 Pharmacological Properties>Preclinical Safety Data

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

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

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

In cynomolgus monkeys treated with natalizumab until parturition, low levels of natalizumab were detected in the breast milk of some animals.

2.3.5 United States

2.3.5.1 8.1 Use in Specific Populations>Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of TYSABRI in pregnant women. In animal studies, administration of natalizumab during pregnancy produced fetal immunologic and hematologic effects in monkeys at doses similar to the human dose and reduced offspring survival in guinea pigs at doses greater than the human dose. These doses were not maternally toxic but produced the expected pharmacological effects in maternal animals [see Data]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Animal Data

In developmental toxicity studies conducted in guinea pigs and monkeys, at natalizumab doses up to 30 mg/kg (7 times the recommended human dose based on body weight [mg/kg]), transplacental transfer and in utero exposure of the embryo/fetus was demonstrated in both species.

In a study in which pregnant guinea pigs were administered natalizumab (0, 3, 10, or 30 mg/kg) by intravenous (IV) infusion on alternate days throughout organogenesis (gestation days [GD] 4-30), no effects on embryo fetal development were observed.

When pregnant monkeys were administered natalizumab (0, 3, 10, or 30 mg/kg) by IV infusion on alternative days throughout organogenesis (GDs 20-70), serum levels in fetuses at delivery were approximately 35% of maternal serum natalizumab levels. There were no effects on embryofetal development; however, natalizumab-related immunological and hematologic changes were observed in the fetuses at the two highest doses. These changes included decreases in lymphocytes (CD3+ and CD20+), changes in lymphocyte subpopulation percentages, mild anemia, reduced platelet count, increased spleen weights, and reduced liver and thymus weights associated with increased splenic extramedullary hematopoiesis, thymic atrophy, and decreased hepatic hematopoiesis.

In a study in which monkeys were exposed to natalizumab during pregnancy (IV infusion of 30 mg/kg) on alternate days from GD20 to GD70 or GD20 to term, abortions were increased approximately 2-fold compared to controls. In offspring born to mothers administered natalizumab on alternate days from GD20 until delivery, hematologic effects (decreased lymphocyte and platelet counts) were also observed. These effects were reversed upon clearance of natalizumab. There was no evidence of anemia in these offspring. Offspring exposed in utero and during lactation had a normal immune response to challenge with a T-cell dependent antigen.

In a study in which pregnant guinea pigs were exposed to natalizumab (30 mg/kg IV) on alternate dates during GDs 30-64, a reduction in pup survival was observed.

2.3.5.2 5.7 Warnings and Precautions>Laboratory Test Abnormalities

In clinical trials, TYSABRI was observed to induce increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persisted during TYSABRI exposure, but were reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils were not observed. TYSABRI induces mild decreases in hemoglobin levels (mean decrease of 0.6 g/dL) that are frequently transient.

2.3.5.3 6.3 Adverse Reactions>Postmarketing experience

Blood disorders: hemolytic anemia

2.3.5.4 12.3 Clinical Pharmacology>Pharmacodynamics

TYSABRI administration increases the number of circulating leukocytes (including lymphocytes, monocytes, basophils, and eosinophils) due to inhibition of transmigration out of the vascular space. TYSABRI does not affect the absolute count of circulating neutrophils.

Medsafe comment

The Product Information for Tysabri in Canada and the Summary of SPC for Tysabri in the United Kingdom both include the following information regarding infants born to women exposed to Tysabri. *'Cases from published literature reported transient mild to moderate thrombocytopenia and anaemia observed in infants born to women exposed to Tysabri in their third trimester of pregnancy. Therefore, it is recommended that newborns of women exposed to the medicinal product during the third trimester of pregnancy are monitored for potential haematological abnormalities.'* The only difference being that in the United Kingdom SPC this information is in Section 4.6 Fertility, Pregnancy and Lactation and in the Canadian Product Information this is in the Post-market Adverse Drug Reactions>Hematologic section. The United Kingdom SPC also contains additional information regarding pregnant women.

2.4 Recent Reviews by International Regulators

2.4.1 Health Canada (14)

Summary Safety Review

TYSABRI (natalizumab) — Blood (haematological) Abnormalities in Newborns whose Mothers were treated with Tysabri during Pregnancy (22 June 2017)

Health Canada conducted a review of the potential risk of blood abnormalities in newborns whose mothers were treated with Tysabri during pregnancy. The review included reports provided by the manufacturer and from published literature. Blood (haematological) abnormalities have been reported in adult patients treated with Tysabri and this was already written in the product information.

At the time of the review, Health Canada had received, from the manufacturer, 15 reports of blood abnormalities in newborns whose mothers were treated with Tysabri during pregnancy.

It was determined that in 14 of the 15 reports the abnormalities in the newborns' blood was potentially related to the Tysabri treatment, while the remaining one case could not be assessed due to missing information. The blood abnormalities included anaemia, thrombocytopenia and leucocytosis.

In three of the 15 cases it was reported that the newborns' umbilical cord blood was found to contain Tysabri. This suggests that Tysabri can cross from the mother's blood into the foetus and may contribute to a blood abnormality in the newborn.

Health Canada's safety review concluded that there is a potential for blood abnormalities to happen in newborns whose mothers were treated with Tysabri during pregnancy. The Canadian product information has been updated to reflect this potential risk in the post-marketing section.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Animal Studies

Natalizumab does not bind to $\alpha 4$ integrin in rats, mice and rabbits and therefore guinea pigs and cynomolgus monkeys have been used to study the reproductive safety as natalizumab binds their $\alpha 4$ integrins with an affinity similar to binding in humans and result in similar pharmacologic effects (15).

3.1.1.1 Guinea Pigs (15)

Female Hartley guinea pigs were treated with intravenous injections of natalizumab every other day from gestational day four to 30 or starting at least 28 days prior to mating though to gestational day 30. Natalizumab was administered at dose levels up to 30 mg/kg every other day, a dose level resulting in 25–36-fold greater exposure than the measured mean human exposure for a similar time period.

Natalizumab treatment had no effect on number of implantation sites, resorptions, live foetuses or dead foetuses. No effects of natalizumab treatment were observed in the total number of male and

female foetuses, litter weights, and foetal weights. Foetal external, skeletal, and visceral findings were similar across treatment groups. The incidence of external and visceral variations and malformations was low. There were no natalizumab-related histological changes in the heart, thymus, spleen, and intestinal tract observed.

Natalizumab was detected in approximately 75 % of females and foetuses at the terminal necropsy, indicating maternal exposure not just during organogenesis but throughout the entire pregnancy.

3.1.1.2 Cynomolgus Monkeys (16, 17)

Cynomolgus monkeys were treated with either 0, 3, 10, or 30 mg/kg of natalizumab (up to 191-fold greater than human exposure) on alternative days from gestational day 20 to 70 (16). This includes the period of organogenesis in cynomolgus monkeys which occurs gestational day 20–50. Pregnancies were terminated at gestational day 100 by Caesarean section.

Natalizumab treatment was not associated with increased abortions at any dose. No significant differences were seen in foetal weight, placental morphology or weight, amniotic fluid or foetal external measurements. No external, visceral abnormalities or skeletal abnormalities were observed that were considered to be related to natalizumab treatment.

White blood cells in the gestational day 100 foetuses from the dams treated with 10 and 30 mg/kg natalizumab groups were increased 6.8–7.5 fold compared to the control group. This was primarily due to increased lymphocytes counts (6.8–7.2 increased). Monocytes at the 10 mg/kg dose and neutrophils at the 30 mg/kg dose were significantly increased. Mild anaemia was observed at in the 10 and 30 mg/kg groups with decreased red blood cells counts and haemoglobin concentration along with significant increases in mean corpuscular volume and mean corpuscular haemoglobin. The percentage of nucleated red blood cells from a cord blood smear was significantly increased in the 10 and 30 mg/kg groups. Histological changes included slight atrophy of the thymus, increased extramedullary haematopoiesis in the spleen and decreased haematopoiesis in the liver.

In a second study, cynomolgus monkeys were treated with 0 or 30 mg/kg natalizumab on alternative days throughout pregnancy at a greater exposure than the measured mean human exposure following monthly 300 mg dosing (17). Treatment was either during and just beyond organogenesis (gestational day 20 to 70), or through the full pregnancy (gestational day 20 to term).

In the first cohort, abortions were observed more frequently in the natalizumab treated groups than in control groups. However, this was not observed in the second cohort where abortions occurred at a slightly higher incidence in the control groups.

Natalizumab treatment of dams had no effect on infant body weights, body weight gains or clinical observations and no external malformations were observed in any infants. Statistically significant increases in white blood cell counts were observed in infants from dams treated with natalizumab from gestational day 20 to term. White blood cell increases were 1.2- to 1.6-fold greater than controls and this was primarily attributable to increases in lymphocyte counts, which were 1.2- to 2.1-fold that of controls. In this same group, statistically significant increases in the presence of nucleated red blood cells were observed as well as statistically significant decreases in platelet counts. These were all reversible following natalizumab clearance. Infants in the term treatment group had significantly increased spleen weights at 12 months but not at 18 months.

3.1.3 Case Reports

3.1.3.1 Hellwig *et al.* 2011 (18)

This paper analysed disease activity during pregnancy and pregnancy outcome in patients with RRMS who became accidentally pregnant during natalizumab treatment in comparison with pregnancies of women with RRMS who were not exposed to disease-modifying treatments.

There were 35 pregnancies in women exposed to natalizumab during the early stages of pregnancy. Six of these women received the last infusion prior to last menstrual period and the remaining 29 after last menses. All stopped natalizumab treatment as soon as they knew they were pregnant. Of the 35 natalizumab-exposed pregnancies, there were five spontaneous abortions in the first trimester (14.3%) and one pregnancy was terminated electively. The general population abortion rates are between 10–20%. The remaining 29 pregnancies resulted in 28 healthy babies and one boy with hexadactyly born in gestational week 35 after natalizumab exposure five days after last menstrual period.

In the control group of 23 women without disease-modifying treatment during pregnancy, 20 healthy babies were born. One girl suffered from trisomy 21 with ventricular septum defect. There was one spontaneous abortion in the first trimester (4.3 %) and one stillbirth in the 36th gestational week with unknown cause. The lower abortion rate in this group compared to the mothers exposed to natalizumab is likely due to the later recruitment, as the concerns about safety lead to women exposed to natalizumab contacting the database at an earlier stage of pregnancy. The characteristics of the newborns in both groups are shown in Table 4.

Table 4: Characteristics of newborns born to women with RRMS exposed to natalizumab during the early stages of pregnancy and to women with women with RRMS who were not exposed to disease-modifying treatment (18)

	Age (years, mean ± SD)	Study enrolment (gestational week (gw) mean ± SD)	Birth weight (grams, mean ± SD)	Birth length (cm, mean ± SD)	Gestational week of birth (mean ± SD)
Natalizumab mothers	30.6 ± 5.6	15.4 ± 12.6	3159 ± 403	50 ± 2.4	38.8 ± 1.9
Control mothers	32 ± 6	18.7 ± 10.6	3406 ± 509	51.4 ± 2.3	39.3 ± 1.3

The authors note that they did not find any adverse events on pregnancy outcome which could be attributed to natalizumab exposure during early pregnancy compared to non-disease-modifying treatment exposed pregnancies in patients with RRMS.

3.1.3.2 Hoevenaren *et al.* 2011 (19)

This is a report of two cases of two babies born to mothers who were treated during the periconceptual period with natalizumab. The first patient was treated with natalizumab during the periconceptual period and the second patient was treated with natalizumab in both the periconceptual period and throughout gestation.

Case 1

A 28-year-old woman who had RRMS for nine years that was not responding to interferon β -1a. The woman was started on natalizumab and despite the risks being explained, the woman intentionally became pregnant. She received her last dose of natalizumab on day nine of the menstrual cycle in

which she became pregnant. The pregnancy developed normally with normal growth curves and with normal foetal movements. During pregnancy the woman had an episode of hyperemesis gravidarum at 22 weeks that was treated with intravenous fluid and tube feeding for 11 days. At 36 weeks gestation, the woman experienced an exacerbation of MS. For this reason, labour was induced with prostaglandins. A health baby girl was born at 37 weeks and three days weighing 3,160 g. The APGAR post birth score that is performed 1 min, 5 min and 10 min following birth looks at the baby's appearance, pulse, grimace response, activity, respiration was 10/10 (10/10/10 is the highest score possible) and clinical examination by a paediatrician revealed no abnormalities. A white blood cell count was not performed. The woman restarted treatment with natalizumab 10 days postpartum.

Case 2

A 34-year-old woman with RRMS for eight years became pregnant while on natalizumab treatment. She was aware of the unknown risks but felt she needed the medicine to remain free of relapsing MS. She did not inform her neurologist until she was 20 weeks pregnant. It was the patient's first child. She continued to use natalizumab throughout the pregnancy. The patient did not experience any MS relapses during pregnancy. Her general history revealed allergy for latex, penicillin, azithromycin, and various metals, and borderline lupus erythematosus with positive antinuclear antibodies but all specific tests negative. On advanced ultrasound examination at 20 and 22 weeks, the head circumference was on the fifth percentile, while the other biometric data and Doppler flow in the umbilical artery were normal. Amniocentesis was performed, quantitative PCR and karyotyping were normal, 46 XX, tests for TORCH Syndrome (infection of a developing foetus), and parvovirus B19 were negative. The pregnancy developed normally with normal foetal movements, absence of oligohydramnios and biometry following normal growth curves. At 39 weeks' gestation, she was started on methyldopa for pregnancy-induced hypertension (maximum 140/100 mmHg, no proteinuria). At 41 weeks, induction of labour with prostaglandins resulted in caesarean section because of suspected foetal distress. She had a baby girl of 2,940 g with APGAR score 5/8 with no abnormalities. The placenta was 10th percentile with no infarcts or other signs of placental insufficiency. A white blood count was not performed.

3.1.3.3 Bayas *et al.* 2011 (20)

This is a case report of a 17-year-old patient with MS treated with natalizumab from age of 16, who was diagnosed as pregnant in the 31 gestational week of pregnancy after 17 natalizumab infusions, seven while pregnant. The patient was diagnosed with MS at 14 years of age and after interferon β -1a treatment was ineffective at controlling disease activity was started on natalizumab. The pregnancy was not realised until the patient was 31 gestation weeks and the natalizumab was immediately stopped with the last infusion being at gestational week 28. The patient had intermittent use of paracetamol, ibuprofen, hydrotalcite and decongestant spray and smoked throughout the pregnancy. An ultrasound at gestational week 33 + 6 was normal.

A healthy baby girl was delivered at gestational week 38 + 3 with an APGAR score of 10/10/10. The newborn was 2,830 g, with a head circumference of 33 cm and a birth length of 48 cm. An abdominal ultrasound at two days of age revealed normal findings for spleen and liver. Neonatal laboratory findings at the day of delivery revealed:

- normal liver enzymes (AST, ALT,GGT,LDH)
- basophils 0.19 Giga/L (normal 0.0–0.1)
- relative lymphocyte count 22.2 % (22.3–49.9)
- Mean platelet volume 10.4 fL (normal 6.8–10).

At three days after delivery blood count was normal with the exception of:

- haemoglobin 14.6 g/dL (normal 15–24)

- platelet volume 10.3 fL (normal 6.8–10).

The child at 10 months of age was developing normally.

Medsafe comment

This was the first report of abnormal blood results in a newborn following treatment with natalizumab during pregnancy with low relative lymphocyte count, high basophils and low haemoglobin. Blood abnormalities were observed in the newborn even though the mother had not had a natalizumab infusion since gestational week 28.

3.1.3.4 Schneider *et al.* 2013 (21)

This is a report of two cases of newborns whose mothers were treated with natalizumab until the 34th weeks of pregnancy for severe RRMS. Prior to pregnancy, natalizumab was the only effective medicine in reducing disease activity of the mothers.

Case 1

The patient developed severe rebound like relapse that did not respond to corticosteroids after stopping natalizumab for a planned pregnancy. She was restarted on natalizumab at pregnancy week 21 with no further relapses. She had a baby girl at that was born pregnancy week 38. The APGAR score was 9/10/10. The baby's birth parameters were within the normal range: weight 2,640 g, length 49 cm, head circumference 34 cm. The baby was screened for congenital malformations and organomegaly. A small unspecific cystic formation was detected in the caudothalamic region. A follow up ultrasound was normal and so a minor intracerebral haemorrhage was a possible explanation. A full blood count detected anaemia (haemoglobin: 105 g/L) and moderate thrombocytopenia (149,000/ μ L). An analysis of lymphocytes detected an enhancement of B cells and CD4/CD8 T cell ratio. T cell chemotaxis was also assessed in the absence and presence of the T cell chemoattractant, CXCL12. CXCL12 stimulated chemotaxis of T cells was reduced to 3 % in the newborn compared to 7 % in an age-matched healthy neonate control.

A six weeks of age the baby girl was admitted for two days with respiratory syncytial virus bronchiolitis. A full blood count revealed anaemia (haemoglobin: 78 g/L) and a restored platelet count (499,000/ μ L). Infection resolved within a few days with symptomatic treatment. At 12 weeks of age the baby was developing normally and her haemoglobin was 99 g/L and platelets 423,000/ μ L. She still had an enhanced CD4/CD8 T cell ratio. However, her reduced CXCL12 stimulated chemotaxis rate was the same as an age-matched healthy neonate control.

Case 2

The patient was changed from natalizumab treatment to interferon β -1a treatment because of a planned pregnancy. After conception, the mother was treated with methylprednisolone because of two relapses. Following another relapse in the second trimester, the mother was restarted on natalizumab at pregnancy week 21 and stopped at pregnancy week 34. The baby was born at pregnancy week 38. The APGAR post birth score was 9/10/10 and the baby's birth parameters were within the normal range: weight 2755 g, length 48 cm, head circumference 32.5 cm. CXCL12 induced chemotaxis was reduced in the newborn to 3.4 % compared to 7 % in an age-matched healthy neonate control. At 12 weeks of age the CXCL12 induced chemotaxis had been restored compared with an age-matched healthy neonate control.

Medsafe Comment

In both of these cases, the patient's last natalizumab treatment was four weeks before birth and both newborns displayed impaired T cell chemotaxis in addition to other haematological abnormalities including an increase in white blood cell counts in case 2 (22). These two cases are also included in the Haghikia *et al.* 2014 case series below. Schneider case 1 is Haghikia NB8 and Schneider case 2 is Haghikia NB3.

3.1.3.5 Haghikia *et al.* 2014 (22)

This case series describes the hematological and birth outcomes of 13 infants born to 12 mothers with highly active MS who were treated with natalizumab during the third trimester of pregnancy.

The women were recruited through a MS pregnancy registry in Germany and the characteristics of the mothers with MS are described in Table 5. Of the 12 women treated, 10 became pregnant while taking natalizumab. Five of these women stopped treatment with natalizumab in the first trimester but experienced severe relapses during pregnancy requiring treatment (M1, M3, M6, M7, M8). The remaining five women who became pregnant while taking natalizumab continued treatment throughout the pregnancy due to previous natalizumab-withdrawal relapsed prior to pregnancy (M4, M5², M10, M11, M12). Three additional cases that required natalizumab during the third trimester had stopped treatment prior to pregnancy but suffered severe relapses during the first trimester (M2, M5¹, M9).

Table 5: Clinical characteristics of the mothers with highly active MS who were treated with natalizumab during pregnancy (22)

Patient	At Pregnancy Onset				During Pregnancy	
	Age, y	Disease Duration, y	Natalizumab Infusions, No.	Natalizumab Infusion at Conception	Relapses, Trimester (No.)	Relapse Treatment (Excluding Natalizumab)
M1	32	4.6	24	Yes, stopped 1st trimester	1st (1)	Steroids, 5 g
M2	37	3.9	27	No, stopped prior to pregnancy	1st and 2nd (2)	Steroids, 13 g; intrathecal TCA (2 d); PLEX (5 d); immunoadsorption (4 d)
M3	29	5.2	33	Yes, stopped 1st trimester	2nd (1)	Steroids, 5 g
M4	37	5.1	29	Yes, continuously during pregnancy	NA	None
M5	27	6.1	31	No, stopped prior to pregnancy	1st (2)	Steroids, 8 g; IVIG, 30 g
	28	4.5	45	Yes, continuously during pregnancy	NA	None
M6	34	10.1	38	Yes, stopped 1st trimester	2nd and 3rd (3)	Steroids, 9 g
M7	31	12.5	25	Yes, stopped 1st trimester	2nd (1)	Steroids, 8 g; IVIG, 30 g
M8	38	18.0	44	Yes, stopped 1st trimester	2nd (1)	Steroids, 10 g
M9	26	8.8	24	No, stopped prior to pregnancy	1st (1)	Steroids, 5 g
M10	27	2.6	16	Yes, continuously during pregnancy	NA	None
M11	27	10.2	49	Yes, continuously during pregnancy	NA	None
M12	25	1.8	16	Yes, continuously during pregnancy	NA	None

Abbreviations: IVIG, intravenous immunoglobulin; M, mother; NA, not applicable; PLEX, plasma exchange; TCA, triamcinolone acetate.

The clinical characteristics of the infants of the women with highly active MS who were treated with natalizumab during the third trimester and or longer are shown in Table 6. Laboratory abnormalities and/or medical conditions were observed in 11 of the 13 newborns. Haematological abnormalities were observed in 10 of the newborns including anaemia (8 newborns) and thrombocytopenia (6 newborns). The mother of **Newborn 2** experienced a catastrophic relapse that required intense treatment and the child was born small for gestational age and at one year of age displayed developmental delay. **Newborn 8** had a cystic formation in the caudothalamic region (potentially an intracranial haemorrhage) that by 12 weeks of age was no longer detectable. **Newborn 12** was born with an atrioventricular septal defect that required surgical intervention. However, this child was also exposed to sodium valproate during pregnancy due to the mother's epilepsy, hereditary proximal myotonic myopathy and tumour necrosis factor receptor 10-associated periodic syndrome.

Table 6: Clinical characteristics of the infants of women with highly active MS who were treated with natalizumab during pregnancy (22)

Patient	Natalizumab Infusions During Pregnancy		Hematological Abnormalities at Birth ^b	Birth Outcomes					
	No.	Gestational Wk ^a		Time to Normalization, wk	Gestational Wk	Length, cm	Weight, g	Mode of Delivery	Outcome
NB1	2	30 and 34	RBC count: $3.91 \times 10^6/\mu\text{L}$ (4.8-8.2); WBC count: 27 670/ μL (8800-18 000); LDH: 660 U/L (<451)	NA	38	52	2855	Natural	Normal
NB2	5	14-34	RBC count: $3.57 \times 10^6/\mu\text{L}$ (3.97-5.01); WBC count: 15 500/ μL (<13 200); platelet count: 77 000/ μL (>247 000); bilirubin: 14.8 mg/dL (<8.7); LDH: 1726 U/L (<225); IgG: 190 mg/dL (>300)	14	39	45	1830	Cesarean	Bradycardia; icterus; hypoxia; small for gestational age
NB3	3	4, 8, and 33	WBC count: 22 180/ μL (<15 400)	NA	38	48	2755	Cesarean	Normal
NB4	9	1-36	No abnormalities		41	50	3290	Cesarean	Normal
NB5	4	17-32	RBC count: 2.8×10^6 (>3.45); hb: 11.1 g/dL (15.1); platelet count: 171 000/ μL (>247 000); bilirubin: 4.7 mg/dL (<8.7); LDH: 678 U/L (<600)	16	38	52	2730	Cesarean	Normal
NB6	6	1-36	No abnormalities		38	52	3270	Natural	Normal
NB7	2	31-35	RBC count: $4.1 \times 10^6/\mu\text{L}$ (>4.7)	1	37	51	2550	Vacuum	Normal
NB8	4	18-34	hb: 10.5 g/dL (>12.7); platelet count: 149 000/ μL	>12 6	38	49	2640	Natural	Subclinical ICH ^c
NB9	1	34	No abnormalities		38	50	3100	Natural	Pylorusstenosis
NB10	1	33	RBC count: $3 \times 10^6/\mu\text{L}$ (>4.2); hb: 11 g/dL (>12)	NA	38	52	3040	Cesarean	Normal
NB11	6	1-36	WBC count: 25.2/ μL (<24.3); platelet count: 133/ μL (>150); γ -glutamyltransferase: 297 U/L (<203)	NA	37	47	2120	Cesarean	Normal
NB12	9	1-36	RBC count: $3.15 \times 10^{12}/\text{L}$ (>4.3); hb: 12.8 g/dL (>15); WBC count: $39.4 \times 10^9/\text{L}$ (<38); platelet count: $71 \times 10^9/\text{L}$ (>150)	16	39	48	2575	Natural	ASD I and II; coloboma
NB13	9	1-36	RBC count: $2.9 \times 10^6/\mu\text{L}$ (>4.5); hb: 11.5 g/dL (>14); WBC count: 21 000/ μL (<10 000); platelet count: 92 000/ μL (>140 000)	4	40	48	2620	Natural	Normal

Abbreviations: ASD, atrial septal defect; hb, hemoglobin; ICH, intracranial hemorrhage; LDH, lactate dehydrogenase; NA, not applicable; NB, newborn; RBC, red blood cell; WBC, white blood cell.

SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.104; γ -glutamyltransferase to microkatal per liter, multiply by 0.01667; hb to grams per liter, multiply by 10.0; IgG to grams per liter, multiply by 0.01; LDH to microkatal per liter, multiply by 0.0167; RBC count to $\times 10^{12}$ per liter, multiply by 1.0; WBC count to $\times 10^9$ per liter, multiply by 0.001.

^a Gestational weeks at time of natalizumab infusions; for those with more than 3 infusions, it was typically administered every 4 to 6 weeks.

^b Abnormalities in RBC, WBC, and platelet counts with normal ranges in parentheses; if not indicated, these laboratory values were within normal limits.

^c Initial screening cerebral ultrasonography after showed a small cystic formation in the caudothalamic region that was no longer detected on follow-up ultrasonography at 12 weeks, compatible with a minor ICH.

There was one mother who contributed two pregnancies to the case series. Her first child (**Newborn 5**) was found to have anaemia while her second child (**Newborn 6**) who was exposed to more natalizumab infusions due to the mother not stopping natalizumab treatment did not display any haematological abnormalities.

Five newborns cord blood was tested for natalizumab and in all five newborns detectable natalizumab was found in the cord blood.

In the majority of the newborns, the haematological abnormalities resolved during the four months following birth and no newborn required specific treatment for the haematological abnormalities.

The authors note that this case series was limited by sample size, not designed to identify risk factors for rebound or severe relapses after natalizumab treatment, the infants natalizumab levels were not analysed after birth, and there is no long-term developmental outcomes of the children.

Medsafe comment

Of the 13 newborns identified and examined, 10 were found to have haematological abnormalities (although two of these were previously reported in Schneider *et al.* 2013). These ten cases included six reports of increased white blood cell counts, six reports of thrombocytopenia and eight reports of

anaemia. All five of the newborn cord blood that was tested were found to have detected natalizumab.

3.1.3.6 Ebrahimi *et al.* 2014 (23)

This is an observation study that compared pregnancy outcomes in women with RRMS exposed to natalizumab in early pregnancy to disease-matched and healthy control women.

Women were recruited from a pregnancy registry for MS in Germany. Women with RRMS were deemed to have been exposed to natalizumab during pregnancy if the last treatment was eight weeks or less prior to the start of the last menstrual period. Women were followed until six months postpartum. Thirty-five outcomes in this group were previously reported in Hellwig *et al.* 2011. The disease-matched and healthy control groups were recruited from the Motherisk programme in Canada. The disease-matched group were pregnant women with RRMS who were not treated with natalizumab. The healthy group were recruited after contacting the Motherisk lines to ask about the safety of non-terogenic medicines.

There were 276 women included in this study: 101 natalizumab exposed, 78 disease-matched, and 97 healthy controls. Baseline characteristics are presented in Table 7. The disease-matched controls were significantly older compared to the healthy and exposed groups.

Table 7: Maternal characteristics in each of the study groups (23)

Maternal characteristics	Natalizumab exposed	Disease matched	Healthy controls	<i>p</i> values
Maternal age (years) Mean±SD (Median)	30.5±5.3 ^d (30.2)	33.9±4.7 ^{c,d} (33.3)	30.6 ± 4.9 ^c (30.5)	<0.0001
Pre-pregnancy BMI Mean±SD (Median)	<i>N</i> = 61 24.4±5.3 (23.8)	<i>N</i> = 56 24.9±4.6 (24.2)	<i>N</i> = 69 23.8±4.5 (23.3)	0.47
Gestational age at call (Weeks) Mean±SD (Median)	<i>N</i> = 97 12.5±9.5 (8.7)	<i>N</i> = 79 9.4±9.5 (6.0)	<i>N</i> = 97 12.2±9.1 (8.9)	0.07
Gravidity	1.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	1.0 ^a
Parity	0.0 (0.0–1.0)	0.0 (0.0–1.0)	1.0 (0.0–1.0)	
Spontaneous abortions	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	
Terminations	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	
Alcohol exposure	1/90 (1.1%) ^e	4/94 (4.3%)	11/86 (12.8%) ^e	0.003 ^b
Smoking exposure	8/86 (9.3%)	8/94(8.5%)	10/85 (11.8%)	0.75

^aKruskal Wallis Test; ^bFisher Exact; ^{c,d}Matching pairs differ significantly as identified by Tukey's test; ^ematching pairs differ sig. as identified by Bonferonni's test.

The women who were exposed to natalizumab during pregnancy were divided into four groups: those exposed eight weeks prior to last menstrual period (20), those exposed zero to nine weeks of gestation (76), those exposed 10-13 weeks of gestation (4) and one who was exposed until the 31st week of gestation (reported in Bayas *et al.* 2011). There were 21 women from the exposed group who experienced a relapse during pregnancy that required at least one course of steroid treatment. There was one woman included with a twin pregnancy.

The disease-matched group included 78 women with RRMS reporting on 95 pregnancy outcomes. There were 11 women who reported on two pregnancies, two women who reported on three pregnancies and once twin pregnancy. Of the 78 women, 68 were on disease-modifying drugs: 53

were on interferon β -1a/1b, 11 on glatiramer acetate, three on natalizumab, one on fingolimod, and 22 untreated. Twenty five women were exposed to disease-modifying drugs during the first trimester and seven throughout pregnancy.

The healthy control group included 97 women of whom most had called the MotherRisk lines about mild to severe nausea and vomiting management and had no significant medical history.

The rate of live births was significantly higher in the healthy control group compared to both the exposed and disease-matched groups (Table 8). This corresponded to significantly higher rates of miscarriage in the exposed and disease-matched groups compared to the healthy controls. The authors postulate that this is due to the majority of the healthy control women ringing the MotherRisk lines about to severe nausea and vomiting management and severe nausea and vomiting is associated with a decreased risk of miscarriage.

Table 8: Pregnancy outcomes in each group (23)

Outcomes	Exposed	Disease matched	Healthy controls	<i>p</i> values
Live births	77/98 (78.6%) [∞]	69/95 (72.6%) [‡]	92/98 (93.9%) ^{∞‡}	0.0004
Terminations	4/98 (4.1%)	6/95 (6.3%)	2/98 (2.0%)	0.33
Spontaneous abortions	17/98 (17.3%) [∞]	20/95(21.1%) [‡]	4/98 (4.1%) ^{∞‡}	0.002
Gender	M: 38/76 (50%) F: 38/76 (50%)	M: 17/49 (32%) F: 32/49 (65.3%)	M: 18/36 (50%) F: 18/36 (50%)	0.20
Gestational age at birth (weeks)	38.8±1.6 (38.9)	38.5±2.0 (38.6)	39±1.7 (39.8)	0.17
Birth weight (grams)	3159±478.9 ^c Median (3225)	3198.3±515.3 ^d Median (3247.5)	3436.7±549.5 ^{c,d} Median (3444.5)	0.001
	3247.6±396.4 Median: (3255)	3198.3±515.3 ^d Median (3247.5)	3436.7±549.5 ^d Median: (3444.5)	0.01^a
% Birth weight	44.8	43.6	59.2	0.13 ^b
Median (25%–75%)	(25.1–70.2)	(23–66.5)	(22.9–90.0)	
Head circumference	35.1±2.2	34.2±1.9	34.1±2.2	0.30
Mean±SD (cm)				
Birth length	50.3±2.5 ^c	50.6±3.4 ^d	53.5±2.1 ^{c,d}	0.003
Mean±SD (cm)				

M: male; F: female. ^aExcluding birth weights of babies exposed to steroids (*N* = 21) during relapse treatment(s) in natalizumab exposed pregnancies. ^bKruskal Wallis Test. ^{c‡}Values that match with one of these symbols identify the pairs that differ significantly as per Bonferroni's test. ^{c,d}Matching pairs differ significantly as identified by Tukey's test.

Birth defects were detected in three of 77 (3.9 %) in the exposed, one of 69 (1.4 %) in the disease-matched and two of 92 (2.2 %) in the healthy control group (Table 9). There was no significant difference between the groups.

In the exposed group there was an atrial septal defect in a full-term female newborn, hernia in a premature male, and hexadactyly in one term male newborn. All three of the mothers had discontinued natalizumab in the first week of conception. In addition, one full-term male newborn was diagnosed with neuroblastoma, hepatomegaly, renal and hepatic insufficiency, sepsis and developmental retardation shortly after birth. Among the non-live births, three foetuses with genetic anomalies were reported. One case of Trisomy 16, one case of Heterotaxy syndrome (internal organs are abnormally arranged) with complete atrioventricular septal defect and defected azygos, and one case of Turners Syndrome Mosaicism (Only one X chromosome in some cells). All three women had discontinued natalizumab within the first few weeks of pregnancy.

Table 9: Adverse neonatal outcomes and mode of delivery (23)

Outcomes	Natalizumab exposed	Disease matched	Healthy controls	<i>p</i> values
All anomalies	4/77 (5.2%)	3/69 (4.3%)	5/92 (5.4%)	1.0 ^a
Major birth defects	3/77 (3.9%)	1/69 (1.4%)	2/92 (2.2%)	0.67 ^a
Premature (37 weeks)	6/76 (7.9%)	10/67 (14.9%)	9/92 (9.8%)	0.37
Low birth weight (<2500 g)	6/77 (7.8%)	5/68 (7.4%)	7.0/92 (7.6%)	1.0
Delivery method	36/73 (49.3%) [‡]	43/66 (65.2%)	47/62 (75.8%) [‡]	0.0006
Vaginal	23/73 (31.5%) ^{∞‡}	4/66 (6.1%) [‡]	5/62 (8.1%) [∞]	<0.0001
C/S, planned	8/73 (11.0%) [∞]	19/66 (28.7%) [∞]	10/62 (16.1%)	0.02
C/S, emergency/ repeat				

C/S: cesarean section. ^aFisher's exact test 2 × 3. ^{∞‡}pairs that match on the same symbol in the same row a differ significantly as per Bonferonni's test.

In the disease-matched group there was one case of clubfoot in a premature female baby. The mother had reported a family history of clubfoot. One case of cryptorchidism (undescended testicle), one case of double hernia, and one hypospadias (penis opening is on the underside rather than the tip) were also reported. These three cases were not included in the birth defects as they were medically unconfirmed.

In the healthy control group, there was one case of ureter pelvic junction obstruction in a premature newborn, and one case of ventricular septal defect (hole in the heart) in a premature male.

The authors conclude that natalizumab does not appear to increase the baseline risk for malformations, preterm birth and low birth weight babies when compared to disease-matched controls. However, the authors note the study's sample size had a limited power to discern small differences in malformation rates. The authors also note that while the risk for miscarriage is similar in the exposed and disease-matched groups it may still be of concern and requires further investigation.

Medsafe comment

This is the same pregnancy registry as Haghikia *et al.* 2014 and could contain the 12 mothers described in this case series.

3.1.3.7 Fagius *et al.* 2014 (24)

This is a case report of a 32-year-old woman who had been on natalizumab since January 2008 following unsuccessful MS control with interferon β-1a. Treatment was stopped in April 2011 as the patient wanted to get pregnant. However before becoming pregnant, the patient a mild but bifocal relapse. The patient was restarted on natalizumab. In October 2012, the patient revealed she was 15 weeks pregnant and although being informed she should avoid pregnancy on natalizumab had researched the risks and decided to ahead with a pregnancy without stopping natalizumab. Treatment was continued throughout the pregnancy and the pregnancy course was normal. Ultrasound examination at gestational week 19 was normal. A baby girl was delivered by Caesarean section without complications for mother or daughter. The baby girl was normal according to routine neonatal examination. Development was normal during the eight month follow-up period.

3.1.3.9 Verhaeghe *et al.* 2014 (10)

This is a case report of a 24-year-old woman who was diagnosed with RRMS and being treated with natalizumab. After one year of treatment, the woman had been free of disease activity. Natalizumab treatment was interrupted after 15 infusions due to the women's desire to have children. Four months after stopping treatment and while nine weeks pregnant she relapsed. The relapse was treated with intravenous methylprednisolone. One month later she developed a new large periventricular lesion of the left hemisphere. After two consecutive treatments of intravenous methylprednisolone for three days, five courses of plasmapheresis and maintenance treatment with oral prednisone her condition and MRI lesion slowly improved. Treatment of natalizumab was started one month before delivery after which her condition steadily further improved. She delivered a healthy baby boy with no major obstetrical complications.

3.1.3.10 Ciron *et al.* 2016 (25)

This is a case report of a 28-year-old women who while pregnant with her first child was diagnosed with MS after suffering a relapse in each trimester. She received no treatment throughout this pregnancy following the diagnosis. She gave birth to a healthy baby boy who was born at 39 weeks and two days. She experienced another severe relapse during the early postpartum period and was started on natalizumab.

The patient wished to become pregnant again and was advised to switch treatments. The patient decided against this due to the severity of her disease and with the agreement of her neurologist continued monthly natalizumab infusions. She became pregnant and experienced no complications or relapses during the pregnancy. She gave birth to a healthy boy at 40 weeks and four days without any malformations. The newborn had a low platelet count at birth ($124 \times 10^9/L$; normal range is 150 to 400) without any other haematological abnormality. Ten days after birth the newborn's blood count was normal. The patient did not have any haematological disorder during pregnancy or in the postpartum period.

Medsafe comment

This is the 12th literature report identified of haematological abnormalities (low platelet count) observed in a newborn whose mother was treated with natalizumab during pregnancy. IN this case the patient continued treatment throughout the entire pregnancy.

3.1.3.11 Friend *et al.* 2016 (26)

This article is the evaluation of the global, observational, exposure registration and follow-up study of pregnancy outcomes from the natalizumab pregnancy exposure registry. A total of 369 patients with MS and seven patients with Crohn's disease were enrolled prospectively, of whom 355 patients had known pregnancy outcomes (including eight twin sets) resulting in a total of 363 known outcomes.

The spontaneous abortion rate was 9.0 % (n = 32; 95 % confidence interval [CI] 6.3–12.5 %), which is consistent with that of the general population. The major birth defect rate was determined by an independent advisory committee to be 5.05 % (16 of 316 live births plus one elective abortion; 95 % CI 2.9–8.1 %). The authors note that the although the overall rate of birth defects was higher than that observed by the Metropolitan Atlanta Congenital Defects Program (2.67 %), there was no specific pattern of malformations that would suggest a drug effect.

3.1.3.13 Guilloton *et al.* 2017 (27)

This is a case report of a 27-year-old woman who was exposed to natalizumab throughout pregnancy. The patient had RRMS for seven years with an active form of the disease, marked by medullary relapses. After the birth of her second child she presented with a vestibular relapse with an aggravation of MRI parameters. Following this she was started on natalizumab. The patient began a third pregnancy after three infusions of natalizumab and decided to continue treatment, fearing a relapse.

The pregnancy proceeded without medical events and the patient gave birth to a baby girl at 38 weeks with a weight of 3,140 g and an APGAR score of 10/10. A discreet pancytopenia, with leukopenia, thrombocytopenia and normocytic normochromic anaemia was discovered on the blood count (Table 10). At three months the red blood count had returned to within the normal range.

Table 10: Results of newborn’s blood count (27)

Values	06 06 15	06 15 15	08 28 15
Red blood cell count (4–6T/L)	3.04	2.55	4.1
Hemoglobin (136–195 g/L)	11	9.3	11.9
Hematocrit (0.28–0.42)	34.2	26	34
Mean corpuscular volume (98–120 fl)	113	103	84.1
CCMH (300–600 g/L)	322	351	345
Mean corpuscular hemoglobin (31–37 pg)	36.2	36.5	29
White blood cell count (10–26 G/L)	12.67	14.3	7.4
Neutrophil leukocyte (6–26 G/L)	4.4	2.3	1.1
Eosinophilic leukocyte (0.02–0.85 G/L)	0.32	0.26	16
Basophilic PB (<0.64 G/L)	0.11	0.09	0.02
Lymphocytes (2–11 G/L)	5.92	9.47	5.58
Monocytes (0.4–3.1 G/L)	1.93	2.19	0.53
Blood platelets	116,000	162,000	227,000

The authors note that to date the haematologic disorders remained asymptomatic and have seen spontaneous regression. However, biological and clinical monitoring of the newborn was necessary and more severe complications cannot be excluded.

Medsafe comment

This is the 13th literature report identified of haematological abnormalities (leukopenia, thrombocytopenia and anaemia) observed in a newborn whose mother was treated with natalizumab during pregnancy. This patient continued natalizumab treatment throughout the entire pregnancy.

3.2 Company Review

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3.3 CARM Data

As 30 September 2017, there have been 11 cases regarding natalizumab reported in New Zealand and none include haematological abnormalities in newborns whose mothers were treated with natalizumab during pregnancy.

4.0 DISCUSSION

More and more women with MS want to have children due to the effectiveness of disease-modifying therapy in reducing relapse rate and increasing periods of stable disease. Currently, it is recommended that female patients on natalizumab should only use natalizumab during pregnancy if clearly needed and if a woman becomes pregnant while taking natalizumab, discontinuation of natalizumab should be considered.

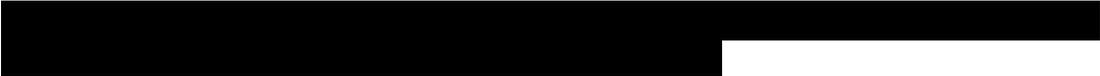
Although pregnancy has been shown to reduce relapse rate, there appears to be a sub population of women with MS whose disease relapses during pregnancy. The majority of women who continued or restarted natalizumab during pregnancy in the case reports did so following relapses or due to prior relapses.

In MS and Crohn's patients treated with natalizumab during clinical trials, natalizumab was associated with increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. This was reversible following cessation of treatment. However, natalizumab remains in the blood, and may have pharmacodynamic effects that include increased lymphocyte counts for approximately 12 weeks following the last dose. In addition, reductions in haemoglobin, haematocrit and red blood cell counts have been observed. Therefore, even if a pregnant patient stops treatment at 28 gestational weeks there may still be pharmacodynamic effects of natalizumab in the pregnant woman. In addition, maternal IgG antibodies transfer across the placenta to the foetus starting in the second trimester and continue to increase.

In animal studies, infant Cynomolgus monkeys in the term treatment group had elevated lymphocytes, nucleated red blood cells and reduction in platelets that were all reversible.

Medsafe identified 13 literature reports of haematological abnormalities in newborns to mothers who were treated with natalizumab during pregnancy. These abnormalities included increases in white blood cell counts, anaemia, and thrombocyte abnormalities with some of the newborns having more than one of these. In addition, there were two reports of newborn who had impaired T cell chemotaxis *in vitro*. In one study, the cord blood was tested from five newborns whose mothers had been treated with natalizumab during pregnancy and natalizumab was detected in all five newborns.

In the company review of this signal, [REDACTED]



Both the Canadian Product Information and the United Kingdom SPC contain an identical statement regarding haematological abnormalities in infants born to women exposed to natalizumab (in their third trimester). However, they are located in different locations with the United Kingdom's statement in Section 4.6: Fertility, pregnancy and lactation and the Canadian statement in the Post-market adverse drug reaction section.

In addition, the UK SPC contains different information regarding pregnancy including the results from the Tysabri prospective pregnancy registry and that a benefit-risk evaluation of the use of natalizumab during pregnancy should also take into account the patient's clinical condition and the possible return of disease after stopping treatment.

From the few cases identified from the literature and from the company's post-market data, the haematologic disorders appear to be asymptomatic and reversible. However, this does not exclude the possibility of more severe complications. Healthcare professionals should be aware that the newborns born to mothers who were treated with natalizumab during the third trimester may have haematological abnormalities and follow up may be required.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- is there a potential for blood abnormalities to occur in newborns whose mothers were treated with natalizumab during pregnancy
- a statement regarding haematological abnormalities in newborns whose mothers were treated with natalizumab during pregnancy is required
 - if required, should the statement be in Section 4.6: Fertility, pregnancy and lactation or Section 4.8: Undesirable effects (or both)
- any of the additional information in the United Kingdom's Summary of Product Characteristics section on pregnancy should be included in the New Zealand data sheet
- is any communication to healthcare professionals warranted?

6.0 ANNEXES

1. Haghikia A, Langer-Gould A, Rellensmann G, et al. 2014. Natalizumab use during the third trimester of pregnancy. *JAMA Neurology* 71: 891-5.
2. Biogen Inc. response to Medsafe's request

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