

**5.19 NATALIZUMAB,  
Injection 150 mg in 1 mL single dose pre-filled  
syringe,  
Tysabri®,  
Biogen Australia Pty Ltd**

**1 Purpose of Submission**

- 1.1 The Category 4 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) listing of a new form of natalizumab (Tysabri®) for the treatment of clinically definite relapsing-remitting multiple sclerosis (RRMS).
- 1.2 The submission sought to list a 150 mg in 1 mL prefilled syringe (PFS) form of natalizumab for subcutaneous (SC) injection (herein referred to as natalizumab SC) under the same circumstances as the PBS-listed natalizumab 300 mg in 15 mL vial for intravenous infusion (IV) (herein referred to as natalizumab IV).

**2 Background**

***Registration status***

- 2.1 Natalizumab SC was approved by the Therapeutic Goods Administration (TGA) on 7 December 2021 for the same indication as natalizumab IV.

***Previous PBAC consideration***

- 2.2 Natalizumab SC has not been considered by the PBAC previously.

**3 Requested listing**

- 3.1 The submission requested the following new listing, under the same conditions as the currently listed form of natalizumab. The submission did not request making any changes to the restriction. Suggested additions are in italics and deletions are in strikethrough.

Add new medicinal product pack as follows:

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MEDICINAL PRODUCT Medicinal Product Pack		PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
NATALIZUMAB						
natalizumab 150 mg/mL injection, 2 x 1 mL syringes		NEW (Public) NEW (Private)	1	42	5	Tysabri
<b>Restriction Summary / Treatment of Concept:</b>						
Concept ID (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program (Public/Private)					
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]					
Prescribing rule level	<b>Caution:</b> Progressive multifocal leukoencephalopathy has been reported with this drug.					
	<b>Indication:</b> Clinically definite relapsing-remitting multiple sclerosis					
<b>Treatment criteria:</b>						
Must be treated by a neurologist						
<b>Clinical criteria:</b>						
The treatment must be the sole PBS-subsidised disease modifying therapy for this condition						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must be ambulatory (without assistance or support)						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition						
<b>AND</b>						
<b>Clinical criteria:</b>						
The condition must be confirmed by magnetic resonance imaging of the brain and/or spinal cord; or						
Patient must be deemed unsuitable for magnetic resonance imaging due to the risk of physical (not psychological) injury to the patient						
<b>Prescribing Instructions:</b>						
The date of the magnetic resonance imaging scan must be included in the patient's medical notes, unless written certification is provided, in the patient's medical notes, by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient.						
<b>Prescribing Instructions:</b>						
Treatment with this drug must cease if there is continuing progression of disability whilst the patient is being treated with this drug.						
<b>Prescribing Instructions:</b>						
For continued treatment the patient must demonstrate compliance with, and an ability to tolerate, this drug.						

- 3.2 The submission states that natalizumab SC is less invasive, reduces the time required for drug administration, reduces post administration observation time and allows for

administration to occur outside of the hospital setting. The submission suggested that natalizumab SC would be administered by a general practitioner at consulting rooms.

- 3.3 The Product Information states that ‘Tysabri therapy is to be initiated and supervised by neurologists, with timely access to Magnetic Resonance Image. Administration is to be performed by a healthcare professional and patients are to be monitored for early signs and symptoms of progressive multifocal leukoencephalopathy’.
- 3.4 The pre-PBAC response stated that the Product Information permits administration of natalizumab SC ‘to be performed by a healthcare professional’, which includes a neurologist, general practitioner, nurse or pharmacist.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

## **4 Comparator**

- 4.1 The submission nominated natalizumab IV as the main comparator. At its March 2021 meeting, the PBAC recommended the listing of ofatumumab for the treatment of RRMS. Its recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of ofatumumab would be acceptable if it were cost minimised to the least costly therapy of either fingolimod, natalizumab, alemtuzumab, ocrelizumab, cladribine or ozanimod (the higher tier agents).
- 4.2 The pre-PBAC response asserted that natalizumab SC is unlikely to replace fingolimod, ozanimod or cladribine, which are often chosen for their convenience in being oral formulations. The pre-PBAC response considered that patients who are on ocrelizumab or alemtuzumab (IV infusion) are likely to be kept on these therapies because of the reduced frequency of administration, different mode of action and safety profile of these two higher tier agents. Further, the pre-PBAC response noted that the only other high tier agent with a subcutaneous administration (monthly) is ofatumumab, a self-administered therapy.
- 4.3 The PBAC considered that patients who are currently on natalizumab IV would most likely be switched to natalizumab SC.

*For more detail on PBAC’s view, see section 6 PBAC outcome*

## **5 Consideration of the evidence**

### ***Sponsor hearing***

- 5.1 There was no hearing for this item.

### ***Consumer comments***

- 5.2 The PBAC noted and welcomed the input from individuals (8), health care professionals (4) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with natalizumab SC including improved convenience and flexibility, reduced stress, reduced time

required for administration, avoidance of risks associated with intravenous infusion and improved quality of life. The comments from health care professionals noted that a subcutaneous form of natalizumab would improve access for those unable to attend a hospital for treatment, such as those who live in remote or rural areas.

- 5.3 The PBAC noted the view received from Multiple Sclerosis Australia clarifying the likely use of natalizumab SC in clinical practice. The PBAC noted the view that the use of natalizumab SC may expand the clinical settings for treatment and reduce the administration and travel time for patients.

### **Clinical trials**

- 5.4 The submission stated that the pharmacokinetics (PK), pharmacodynamics (PD), clinical effectiveness, and safety of natalizumab SC compared to natalizumab IV in the treatment of patients with RRMS is informed by two pivotal clinical trials (REFINE, DELIVER):
- REFINE (101MS206): a 72-week, randomised, multi-centre, blinded Phase 2 study conducted in five European countries evaluating the safety, tolerability, and efficacy of natalizumab in adult patients (18 to 55 years of age) with RRMS.
  - DELIVER (101MS102): a 32-week, randomised, multi-centre, open-label study conducted in the United States evaluating the PK, PD, and immunogenicity of natalizumab in adult patients (18 to 65 years of age) with RRMS and secondary progressive multiple sclerosis.

### **Clinical claim**

- 5.5 The submission stated that neither trial was specifically designed to confirm non-inferiority.
- 5.6 The submission claimed that natalizumab SC administered once every 4 weeks (Q4W) was demonstrated to have a similar PK, PD, efficacy, and safety profile to natalizumab IV Q4W based on evidence from the DELIVER and REFINE studies.

### **Economic analysis**

- 5.7 The submission did not present a formal cost minimisation approach, but assumed, based on the DELIVER and REFINE studies, that the equi-effective doses for natalizumab are:
- Natalizumab SC: 2 x 150 mg/mL of PFS (300 mg Q4W)
  - Natalizumab IV: 1 x 300 mg/15mL vial (300 mg Q4W).
- 5.8 Under Section 101(3B) of the *National Health Act 1953* (the Act), the PBAC could only recommend listing natalizumab SC at a higher price than the alternative therapy or therapies if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The advice provided by the PBAC applies to each medicine on a case by case basis. In this case,

the PBAC did not consider other available PBS-listed RRMS therapies (fingolimod, alemtuzumab, ocrelizumab, cladribine, ozanimod, or ofatumumab) appropriate alternatives for patients who are already stabilised on natalizumab IV.

### ***Estimated PBS utilisation and financial implications***

- 5.9 The requested price for natalizumab SC (i.e. two 150 mg PFS) was based on the AEMP (\$1268.34) of natalizumab IV (i.e. one 300 mg vial) as of February 2023.
- 5.10 The submission used a market share approach to estimate the financial impact of listing natalizumab SC on the PBS. The submission estimated that the rate at which natalizumab SC would substitute for natalizumab IV in the RRMS market is expected to be █% in year 1, increasing to █% in year 2, █% in year 3, █% in year 4, █% in year 5 and █% in year 6.
- 5.11 The submission estimated that the proposed listing of natalizumab SC would have no net impact on the PBS/RPBS.
- 5.12 The submission stated that the proposed change would result in an overall net saving to Government, driven by the lower MBS costs (administration and monitoring) associated with the SC formulation, compared with the IV formulation, noting that:
- the cost of each administration of natalizumab IV is based on the cost of MBS Item 14245 (\$103.55), which covers the cost of an IV administration over approximately 1 hour followed by a 1-hour period of observation for signs or symptoms consistent with a hypersensitivity-type reaction.
  - the cost of each administration of natalizumab SC is based on the cost of MBS Item 36 (\$76.95), which covers the cost of a general practitioner attendance to administer the first subcutaneous injection, followed by the second subcutaneous injection no later than 30 minutes after the first injection, and for observation up to an hour for signs and symptoms of injection reactions including hypersensitivity.
- 5.13 The submission estimated that the requested listing is expected to result in a net cost saving to the Government in year 1 to year 6.
- 5.14 While not a matter for PBAC, the pre-PBAC response accepted that a first new brand price reduction would be applied to natalizumab SC in accordance with Section 99ACB of the Act.

### ***Quality use of medicines***

- 5.15 The Product Information states that natalizumab IV is not intended for subcutaneous administration and vice versa.
- 5.16 Noting issues raised in paragraphs 3.2, 3.3 and 3.4, the PBAC considered there would not be additional quality use of medicines issues associated with natalizumab SC being administered outside of the hospital outpatient setting.

- 5.17 The PBAC noted the submission considered that administration outside of the hospital outpatient setting is particularly important for patients in rural and remote areas who are currently required to travel for hours to have their treatment administered in a hospital. The submission further claimed that introduction of a SC formulation of natalizumab also has the potential of increasing capacity for IV infusions across the health system for other conditions.

*For more detail on PBAC's view, see section 6 PBAC outcome*

## **6 PBAC Outcome**

- 6.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) listing of natalizumab 150 mg in 1 mL PFS for subcutaneous injection under the same circumstances as the PBS-listed natalizumab 300 mg in 15 mL vial for intravenous infusion.
- 6.2 The PBAC recommended listing natalizumab SC on a cost-minimisation basis against the PBS-listed natalizumab IV for the treatment of RRMS. The PBAC considered that the nomination of natalizumab IV as comparator is appropriate. While there are PBS-listed RRMS therapies which may be less costly, the PBAC considered these are not relevant comparators, as it is unlikely to be appropriate for patients stabilised on another RRMS treatment to switch to natalizumab, or to change prescriber choice of agent in new RRMS patients, because an SC form is available. The PBAC considered the most likely candidates to use natalizumab SC are patients who are already using natalizumab IV. This was also consistent with the financial estimates presented which assumed replacement of natalizumab IV only.
- 6.3 The PBAC advised that the equi-effective doses were natalizumab SC 300 mg Q4W and natalizumab IV: 300 mg Q4W.
- 6.4 The PBAC noted the listing of natalizumab SC is expected to have no net cost to the PBS. The PBAC considered that it was uncertain whether the estimated MBS save would be realised.
- 6.5 The PBAC acknowledged a high demand from patients for a subcutaneous form of natalizumab because it would improve access for those unable to attend a hospital for treatment, such as those who live in remote or rural areas.
- 6.6 The PBAC noted the TGA assessed the bioequivalence between natalizumab SC and natalizumab IV, and did not consider these two forms to be bioequivalent. The PBAC considered that natalizumab SC was therapeutically equivalent to natalizumab IV at the equi-effective doses.
- 6.7 The PBAC noted that the pre-PBAC response requested that natalizumab SC be determined as a pharmaceutical item exempt from statutory price reductions in accordance with Section 84AH of the Act. The PBAC noted that natalizumab SC is suitable therapy for patients with RRMS (in accordance with the circumstance specified under Section 101 (4AB) (a) of the Act). However, the PBAC considered that

patients who have difficult or poor venous access due to the current natalizumab IV regimen or other health conditions do not represent an alternative, demographically based subgroup of patients as set out in S101(4AB) (b) of the Act. Moreover, the PBAC considered that the existing natalizumab IV is a suitable alternative therapy for patients with RRMS and therefore considered that Section 101(4AB) (c) was not met. Overall, the PBAC had no reason to advise the Minister under section 101(4AB) of the Act that the relevant circumstances exist for natalizumab SC to be determined as an item exempt from statutory price reductions.

- 6.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because natalizumab SC is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over currently listed form of natalizumab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 6.9 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 7 Recommended listing

7.1 Add new item as follows:

MEDICINAL PRODUCT Medicinal Product Pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
NATALIZUMAB					
natalizumab 150 mg/mL injection, 2 x 1 mL syringes	NEW (Public) NEW (Private)	1	2	5	Tysabri
<b>Restriction Summary / Treatment of Concept:</b>					
Concept ID (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program (Public/Private)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]				
Prescribing rule level	<b>Caution:</b> Progressive multifocal leukoencephalopathy has been reported with this drug.				
	<b>Indication:</b> Clinically definite relapsing-remitting multiple sclerosis				
	<b>Treatment criteria:</b> Must be treated by a neurologist				
	<b>Clinical criteria:</b> The treatment must be the sole PBS-subsidised disease modifying therapy for this condition				

	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must be ambulatory (without assistance or support)
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must be confirmed by magnetic resonance imaging of the brain and/or spinal cord; or
	Patient must be deemed unsuitable for magnetic resonance imaging due to the risk of physical (not psychological) injury to the patient
	<b>Prescribing Instructions:</b> The date of the magnetic resonance imaging scan must be included in the patient's medical notes, unless written certification is provided, in the patient's medical notes, by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient.
	<b>Prescribing Instructions:</b> Treatment with this drug must cease if there is continuing progression of disability whilst the patient is being treated with this drug.
	<b>Prescribing Instructions:</b> For continued treatment the patient must demonstrate compliance with, and an ability to tolerate, this drug.

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

Biogen welcomes the PBAC decision to recommend a new subcutaneous (SC) formulation of TYSABRI (natalizumab) for relapsing-remitting multiple sclerosis. TYSABRI (natalizumab) adds to the portfolio of multiple sclerosis treatments, to provide further choice to healthcare professionals and those they care for.