

**5.05 DACLIZUMAB,  
150 MG PRE-FILLED INJECTION PEN OR SYRINGE,  
ZINBRYTA®, BIOGEN.**

**1 Purpose of Application**

1.1 The submission requested a Section 85 Authority Required PBS listing for daclizumab for the treatment of relapsing-remitting multiple sclerosis (MS).

**2 Requested listing**

2.1 The requested restriction is provided below, including initial and continuing treatment criteria. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DACLIZUMAB Injection 150 mg per 1.0 mL injection in pre-filled pen or syringe	1	5	\$ [REDACTED]	Zinbryta Biogen Australia Pty Ltd
<b>Category / Program</b>	GENERAL – General Schedule (Code GE)			
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
<b>Condition:</b>	Multiple sclerosis			
<b>PBS Indication:</b>	Multiple sclerosis			
<b>Treatment phase:</b>	Initial			
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			

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<b>Clinical criteria:</b>	<p>The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR</p> <p>The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient.</p> <p>AND</p> <p>Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the preceding 2 years</p> <p>AND</p> <p>The treatment must be as monotherapy</p> <p>AND</p> <p>Patient must be ambulatory (without assistance or support)</p>
<b>Prescriber Instructions</b>	Where applicable, the date of the <del>MRI</del> <i>magnetic resonance imaging</i> scan must be provided with the authority application.
<b>Prescriber Instructions</b>	<i>Patient must undergo monthly liver function testing as described in item 66512 of the Medicare Benefits Schedule while being treated with this drug.</i>
<b>Administrative Advice</b>	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p><i>Special Pricing Arrangements apply.</i></p>

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<b>Clinical criteria:</b>	<p><del>The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR</del></p> <p><del>The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient;</del></p> <p>AND</p> <p>Patient must have previously been issued with an authority prescription for this drug <i>for this condition</i></p> <p>AND</p> <p>Patient must not show continuing progression of disability while on treatment with this drug</p> <p>AND</p> <p>The treatment must be as monotherapy</p> <p>AND</p> <p>Patient must have demonstrated compliance with, and an ability to tolerate, this therapy</p>
<b>Prescriber Instructions</b>	<p><i>Patient must undergo monthly liver function testing as described in item 66512 of the Medicare Benefits Schedule while being treated with this drug.</i></p>
<b>Administrative Advice</b>	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p><i>Special Pricing Arrangements apply.</i></p>

- 2.2 Listing was requested on a cost minimisation basis compared to fingolimod.
- 2.3 The Secretariat noted that it may be reasonable to consider a Streamlined Authority listing for daclizumab as it does not have complex administration requirements and appears unlikely to be used outside the requested restriction.
- 2.4 The PBAC noted the restriction may need to be revised based on the outcome of the ACPM meeting and ultimately the indication approved for registration (see below).

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### 3. Background

- 3.1 The submission was made under TGA/PBAC Parallel Process. The TGA Delegate's Overview was provided as a late paper for the July 2016 PBAC meeting. The Overview stated that there was no reason the application should not be approved for registration subject to successful negotiation of indications and access restrictions

which should apply to prescribers and patients.

3.2 The following issues were noted in the TGA Delegate's Overview for daclizumab:

1. 'Delay in progression of disability has not been demonstrated. More recent treatments for MS have demonstrated a delay in progression of disability in clinical trials.
2. The place in therapy of daclizumab is not clear due to the lack of demonstration of superiority over interferon beta-1a (IFN  $\beta$ -1a) for the endpoint of progression of disability. Daclizumab presents more risk of serious adverse effects than IFN  $\beta$ -1a. Given these factors it is not clear whether use of this product should be permitted at all or whether restricting its use to patients who have failed initial treatment would be appropriate.'

3.3 The Delegate requested advice from the ACPM on the following specific issues:

1. Whether use of daclizumab should be allowed in secondary progressive MS (SPMS).
2. If there are any concerns about a specific claim for reduction in disability progression not being proposed for any subgroup of patients with MS.
3. Restricting the indication to third line treatment and limiting initial prescribing to neurologists, and if further restrictions on access should apply to daclizumab.

3.4 The PBAC noted that the clinical place for daclizumab was unclear and that this had implications for the PBS restriction, comparator, relevant clinical evidence, economic analysis and financial forecasts.

3.5 The PBAC had not previously considered daclizumab.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

#### **4. Clinical place for the proposed therapy**

4.1 MS is a progressive, chronic disease of the central nervous system in which the myelin sheath protecting axons is damaged resulting in distorted nerve signals and pathways. Most patients present with relapsing-remitting MS, characterised by acute clinical attacks (relapses) followed by variable recovery and periods of clinical stability. MS is characterised by a complex range of symptoms including visual disturbance, fatigue, pain, reduced mobility and coordination, cognitive impairment and mood changes.

4.2 The submission positioned daclizumab as both a first-line and subsequent-line alternative to all PBS-listed disease modifying therapies. The PBAC noted that the TGA registration was not finalised and the appropriate place in MS therapy for daclizumab was not clear at the time of the July 2016 PBAC meeting.

For more detail on PBAC's view, see section 7 "PBAC outcome"

## 5. Comparator

- 5.1 The submission nominated fingolimod as the comparator. The evaluation noted that as an injectable therapy daclizumab may be more likely to replace existing injectable therapies on the PBS (ABCR therapies - intramuscular interferon beta-1a (IM IFN  $\beta$ -1a), subcutaneous IFN  $\beta$ -1a, IFN  $\beta$ -1a, peginterferon beta-1a, glatiramer acetate).
- 5.2 The Pre-Sub-Committee Response (PSCR) argued the main comparator was fingolimod because daclizumab represents a new therapeutic class, and the PBAC Guidelines (v4.4, p. 65-66) state the main comparator for a medicine in a new class would be the medicine on the PBS currently used to treat the largest number of patients for that indication.
- 5.3 The ESC noted the Drug Utilisation Sub-Committee (DUSC) review of RRMS drugs<sup>1</sup> in October 2015 found that while fingolimod had the largest market share, dimethyl fumarate (DMF) use, which at the time had only been PBS listed for a short time, was growing and it was the most prescribed therapy for new patients and those returning to treatment following a break. The Pre-PBAC response claimed that the DUSC review only captured the first year of listing of DMF and that after an initial spike in initiations on DMF the market share did not markedly grow with an overall market share at May 2016 of approximately 14% for DMF compared to 35% for fingolimod.
- 5.4 The ESC noted that medicines for relapsing-remitting MS are generally categorised into groups based on a similar relative risk reduction (RRR) for relapse and similar level of toxicity or adverse effects (AEs), and medicines were often selected in practice by these outcomes (Broadley et al., 2015) <sup>2</sup>. On the basis of these groupings, the ESC noted that daclizumab would most likely substitute for both fingolimod and DMF in practice, and given the increasing use of DMF noted in the DUSC report, considered that both fingolimod and DMF were appropriate comparators.
- 5.5 The ESC noted that previous PBAC recommendations differed from the groupings published in Broadley et al., in that DMF was recommended on a cost minimisation basis with ABCR therapies. Thus DMF is less expensive than fingolimod and the proposed price for daclizumab.
- 5.6 The PBAC noted the clinical place of daclizumab was unclear and this had implications for the comparator however, considered that other injectable treatments are also likely to be relevant comparators.

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<sup>1</sup> PBAC Drug Utilisation Sub-Committee (2015). *Multiple sclerosis: predicted versus actual analysis*. Available at <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/multiple-sclerosis-dusc-prd-2015-10-abstract>

<sup>2</sup> Broadly, Simon A, Barnett, Michael H et al. A new era in the treatment of multiple sclerosis. *Medical Journal of Australia* 2015; 203: 139-141. Open access available at: <https://www.mja.com.au/journal/2015/203/3/new-era-treatment-multiple-sclerosis>.  
Appendix at: [https://www.mja.com.au/sites/default/files/issues/203\\_03/10.5694mja14.01218\\_Appendix%201.pdf](https://www.mja.com.au/sites/default/files/issues/203_03/10.5694mja14.01218_Appendix%201.pdf)

For more detail on PBAC's view, see section 7 "PBAC outcome"

## **6. Consideration of the evidence**

### **Sponsor hearing**

6.1 There was no hearing for this item.

### **Consumer comments**

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the value of an additional treatment option, and noted that in clinical trials, daclizumab had demonstrated efficacy, tolerability and safety against an active comparator and that the monthly administration would be advantageous for some patients on more frequently dosed treatments.

### **Clinical trials**

6.3 No head-to-head trials comparing daclizumab to fingolimod were available. The submission was based on a series of comparisons between daclizumab, fingolimod and IM IFN  $\beta$ -1a:

- Indirect comparison of daclizumab (SELECT) versus fingolimod (FREEDOMS, FREEDOMS II) using a placebo common comparator.
- Indirect comparison of daclizumab (DECIDE) versus fingolimod (TRANSFORMS) using IM IFN  $\beta$ -1a as the common comparator.
- Supportive direct comparison of daclizumab versus IM IFN  $\beta$ -1a (DECIDE).

6.4 Details of the trials presented in the submission are provided in the table below.

**Table 1: Trials and associated reports included in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Daclizumab trials</b>		
SELECT	Biogen Idec Clinical Study Report (2013). Multicenter, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Safety and Efficacy of Daclizumab HYP (DAC HYP) as a Monotherapy Treatment in Subjects with Relapsing-Remitting Multiple Sclerosis	Internal study report
	Gold R et al (2013). Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): A randomised, double-blind, placebo-controlled trial	The Lancet 381: 2167-2175
	Giovannoni G et al (2014). Effect of daclizumab high-yield process in patients with highly active relapsing-remitting multiple sclerosis	Journal of Neurology 261: 316-323
	Havrdova E et al (2014). Disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with daclizumab high-yield process in the SELECT study	Multiple Sclerosis Journal 20: 464-470
DECIDE	Biogen Idec Clinical Study Report (2015). Multicenter, Double-blind, Randomized, Parallel-group, Monotherapy, Active-control Study to Determine the Efficacy and Safety of Daclizumab High Yield Process (DAC HYP) versus Avonex® (Interferon $\beta$ -1a) in Patients with Relapsing-Remitting Multiple Sclerosis	Internal study report
	Kappos L et al (2015). Daclizumab HYP versus IFN $\beta$ -1ain relapsing multiple sclerosis	New England Journal of Medicine 373: 1418-1428
<b>Fingolimod trials</b>		
FREEDOMS	Kappos L et al (2010). A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis	New England Journal of Medicine 362: 387-401
	Devonshire V et al (2012). Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study	The Lancet Neurology 11: 420-428
	Kremenchtzky M (2014). Impact of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod: Subgroup analyses of the Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study	Multiple Sclerosis & Related Disorders 3: 341-349
	Radue EW et al (2012). Impact of fingolimod therapy on magnetic resonance imaging outcomes in patients with multiple sclerosis	Archives of Neurology 69: 1259-1269
FREEDOMS II	Calabresi P et al (2014). Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): A double-blind, randomised, placebo-controlled, phase 3 trial	The Lancet Neurology 13: 545-556
TRANSFORMS	Cohen JA et al (2010). Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis	New England Journal of Medicine 362: 402-415
	Barkhof F et al (2014). The influence of patient demographics, disease characteristics and treatment on brain volume loss in Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis	Multiple Sclerosis Journal 20: 1704-1713

Trial ID	Protocol title/ Publication title	Publication citation
	(TRANSFORMS), a phase 3 study of fingolimod in multiple sclerosis	
	Khatri BO et al (2014). Effect of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod vs. IFN $\beta$ -1a intramuscular: Subgroup analyses of the Trial Assessing Injectable Interferon vs. Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS)	Multiple Sclerosis & Related Disorders 3: 355-363
	Cohen JA et al (2013). Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS	Journal of Neurology 260: 2023-2032

Note: Abstracts of studies with full publications are not presented

6.5 The key features of the included trials are summarised in the table below.

**Table 2: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Daclizumab vs. placebo</b>					
SELECT	621	MC, R, DB 1 year	Low	Active RRMS	Relapse rates, disability progression
<b>Daclizumab vs. IM interferon beta-1a</b>					
DECIDE	1,841	MC, R, DB 2-3 years	Low	Active RRMS	Relapse rates, disability progression
<b>Fingolimod vs placebo</b>					
FREEDOMS	1,272	MC, R, DB 2 years	Low	Active RRMS	Relapse rates, disability progression
FREEDOMS II	1,083	MC, R, DB 2 years	Low	Active RRMS	Relapse rates, disability progression
Meta-analysis	2,355	Included FREEDOMS and FREEDOMS II results			Relapse rates, disability progression
<b>Fingolimod vs. IM interferon beta-1a</b>					
TRANSFORMS	1,292	MC, R, DB 1 year	Low	Active RRMS	Relapse rates, disability progression

Abbreviations: DB, double blind; IM, intramuscular; MC, multi-centre; R, randomised; RRMS, relapsing-remitting multiple sclerosis

Source: Constructed during the evaluation

6.6 There were differences across the trials in treatment durations; with the SELECT and TRANSFORMS studies having a one year duration; the FREEDOMS and FREEDOMS II studies having a two year duration; and the DECIDE study having a 2-3 year duration. The submission attempted to address this issue by limiting analyses to matched time points as well as using outcome measures that incorporate a time component (annualised relapse rates, time-to-event analyses).

6.7 There were differences across the trials in the enrolled patient populations; with the daclizumab trials (SELECT, DECIDE) generally including patients with higher baseline disability and magnetic resonance imaging (MRI) disease activity and the fingolimod trials (FREEDOMS, FREEDOMS II, TRANSFORMS) generally including more treatment-experienced patients with longer durations of the disease.

## Comparative effectiveness

6.8 The results of the indirect comparison of daclizumab versus fingolimod using placebo as the common comparator is presented in the table below.

**Table 3: Indirect comparison daclizumab vs. fingolimod using a placebo common comparator**

Trial	Daclizumab 150 mg	Placebo	Fingolimod 0.5 mg	Treatment difference (95% CI)
<b>Annualised relapse rate (95% CI)</b>				
SELECT, 1 year (N = 397)	0.21 (0.16, 0.29)	0.46 (0.37, 0.57)	-	<b>Rate ratio: 0.46 (0.32, 0.67)</b>
FREEDOMS, 2 year (N = 843)	-	0.40 (0.34, 0.47)	0.18 (0.15, 0.22)	<b>Rate ratio: 0.45 (0.34, 0.59)</b>
FREEDOMS II, 2 year (N = 713)	-	0.40 (0.34, 0.48)	0.21 (0.17, 0.25)	<b>Rate ratio: 0.52 (0.40, 0.66)</b>
Meta-analysis of fingolimod trials ( $I^2 = 0\%$ )				<b>Rate ratio: 0.49 (0.40, 0.58)</b>
Indirect estimate of effect (results < 1 favour daclizumab)				Rate ratio: 0.95 (0.63, 1.43)
<b>Time to 3-month sustained disability progression, n/N (%)</b>				
SELECT, 1 year (N = 397)	12/201 (6.0%)	26/196 (13.3%)	-	<b>Hazard ratio: 0.43 (0.21, 0.88)</b>
FREEDOMS, 2 year (N = 843)	-	101/418 (24.1%)	75/425 (17.7%)	<b>Hazard ratio: 0.70 (0.52, 0.96)</b>
FREEDOMS II, 2 year (N = 713)	-	103/355 (29.0%)	91/358 (25.3%)	Hazard ratio: 0.83 (0.61, 1.12)
Meta-analysis of fingolimod trials ( $I^2 = 0\%$ )				<b>Hazard ratio: 0.76 (0.61, 0.95)</b>
Indirect estimate of effect (results < 1 favour daclizumab)				Hazard ratio: 0.56 (0.27, 1.19)
<b>Time to 6-month sustained disability progression, n/N (%)</b>				
SELECT, 1 year (N = 397)	5/201 (2.6%)	22/196 (11.1%)	-	<b>Hazard ratio: 0.24 (0.09, 0.63)</b>
FREEDOMS, 2 year (N = 843)	-	79/418 (19.0%)	53/425 (12.5%)	<b>Hazard ratio: 0.63 (0.44, 0.90)</b>
FREEDOMS II, 2 year (N = 713)	-	63/355 (17.8%)	49/358 (13.8%)	Hazard ratio: 0.72 (0.48, 1.07)
Meta-analysis of fingolimod trials ( $I^2 = 0\%$ )				<b>Hazard ratio: 0.67 (0.51, 0.87)</b>
Indirect estimate of effect (results < 1 favour daclizumab)				<b>Hazard ratio: 0.36 (0.13, 0.99)</b>

Abbreviations: CI, confidence interval

Source: Table B.6-2 (p 80), Table B.6-3 (p 81), Table B.6-11 (p 89), Table B.6-13 (p 92), Table B.6-15 (p 96) of the submission;

6.9 There was no statistically significant difference in relapse outcomes between daclizumab and fingolimod. The indirect analysis of disability progression outcomes appeared to favour daclizumab over fingolimod, however, the evaluation noted the indirect analyses should be interpreted with caution given the concerns regarding the exchangeability of the included trials and the robustness of outcome measures to account for differences in study duration. The PBAC noted differences across the daclizumab and fingolimod trials in the results for the placebo treatment groups and that this indicated that there may be exchangeability issues. The PBAC further noted that a non-inferiority margin was not proposed in the submission and that non-inferiority was claimed based on lack of a statistically significant difference. The

PBAC considered this approach was not robust, especially given the wide 95% confidence limits for the indirect comparisons.

- 6.10 The results of the indirect comparison of daclizumab versus fingolimod using IM IFN  $\beta$ -1a as the common comparator is summarised in Table 4.

**Table 4: Indirect comparison of daclizumab vs. fingolimod using IM interferon beta-1a as the common comparator**

Trial	Daclizumab 150 mg	IM IFN $\beta$ -1a	Fingolimod 0.5 mg	Treatment difference (95% CI)
<b>Annualised relapse rate at one year (95% CI)</b>				
DECIDE, 1 year (N = 1,841)	0.25 (0.22, 0.30)	0.43 (0.38, 0.49)	-	<b>Rate ratio: 0.59 (0.49, 0.72)</b>
TRANSFORMS, 1 year (N = 843)	-	0.33 (0.26, 0.42)	0.16 (0.12, 0.21)	<b>Rate ratio: 0.48 (0.36, 0.64)</b>
Indirect estimate of effect (results < 1 favour daclizumab)				Rate ratio: 1.23 (0.87, 1.74)
<b>Proportion of patients with 3-month sustained disability at one year, n/N (%)</b>				
DECIDE, 1 year (N = 1,841)	59/919 (6.4%)	75/922 (8.1%)	-	Relative risk: 0.79 (0.57, 1.10)
TRANSFORMS, 1 year (N = 843)	-	34/431 (7.9%)	25/429 (5.8%)	Relative risk: 0.74 (0.45, 1.22)
Indirect estimate of effect (results < 1 favour daclizumab)				Relative risk: 1.07 (0.59, 1.94)

Abbreviations: CI, confidence interval

Source: Table B.6-2 (p 80), Table B.6-4 (p 84), Table B.6-12 (p 90), Table B.6-14 (p 94-95) of the submission

- 6.11 There were no statistically significant differences in relapse or disability outcomes between daclizumab and fingolimod. As for the indirect comparison using placebo, there were concerns noted during the evaluation regarding the exchangeability of the included trials and the robustness of outcome measures to account for differences in study duration. The PBAC noted the indirect comparison using IM IFN  $\beta$ -1a as the common comparator did not support a difference in disability outcomes.
- 6.12 A direct comparison of daclizumab versus IM IFN  $\beta$ -1a was presented in the submission as supportive evidence. Daclizumab was associated with statistically significant improvements in both relapse outcomes and MRI measures compared to IM IFN  $\beta$ -1a. There was no difference in confirmed disability progression events between treatments although additional analyses suggested that results favour daclizumab when disability progression was relaxed to include tentative cases. The PBAC noted the lack of demonstration of superiority over IFN  $\beta$ -1a for the endpoint of progression of disability was an issue raised in the TGA Delegate's Overview.
- 6.13 The ESC recalled the previous PBAC consideration of DMF in July 2013, in which the submission requested listing on a cost minimisation basis with fingolimod. The PBAC did not accept the superiority claim for DMF over pooled ABCR therapies as the level of heterogeneity between the various trial populations made the indirect comparison difficult to interpret. DMF was recommended on a cost-minimisation basis with ABCR therapies based on a comparison of DMF and glatiramer acetate presented in that submission.

- 6.14 The PBAC considered that other injectable treatments are likely to be relevant comparators noting that the clinical place of daclizumab in the treatment of MS was currently unknown.

### **Comparative harms**

- 6.15 A series of indirect comparisons of safety outcomes between daclizumab and fingolimod were presented in the submission (any adverse event, serious adverse events, adverse events leading to discontinuation, infections, and liver enzyme abnormalities). These analyses did not identify any statistically significant difference in adverse events between treatments.
- 6.16 The PBAC considered the analyses largely non-informative given that there were substantial differences in the incidence of adverse events (particularly serious events) between common comparator arms, the lack of statistical power to detect a meaningful difference in adverse event rates, the analyses were confounded by events of MS relapse being classified as adverse events and differences in study duration across the daclizumab and fingolimod trials.
- 6.17 Based on data from the included clinical trials, the most frequent treatment-related adverse events associated with daclizumab were general disorders (pyrexia, injection-site pain, influenza-like illness, fatigue, injection site erythema, injection site bruising), cutaneous events (rash, eczema), infections and infestations (nasopharyngitis, upper respiratory tract infection, pharyngitis), investigations (ALT increased, AST increased, LFT abnormal, GGT increased), nervous system disorders (headache), gastrointestinal disorders (nausea), blood and lymphatic system disorders (lymphadenopathy, lymphopenia). Treatment with daclizumab was associated with an increased incidence of serious infections and serious cutaneous events. The PBAC noted that steroids may be used more frequently to manage skin reactions associated with daclizumab. The most frequent adverse event leading to treatment discontinuation was liver enzyme abnormalities.
- 6.18 Based on the Development Safety Update Report, important identified risks associated with daclizumab treatment included transaminase elevations and serious hepatic injury; cutaneous and serious cutaneous events; infections and serious infections; and colitis. Important potential risks associated with biological therapies included anaphylaxis, opportunistic infection and malignancy.
- 6.19 Two treatment-related deaths were reported with daclizumab therapy in the clinical trial program (serious rash with subsequent psoas abscess resulting in local thrombosis and acute ischaemic colitis; and autoimmune hepatitis). The occurrence of autoimmune hepatitis resulted in the requirement for monthly liver function testing with daclizumab therapy.
- 6.20 There are limited long-term data on the safety of daclizumab for the treatment of multiple sclerosis. The PBAC also noted that a potential risk of depression associated with daclizumab treatment was identified in the TGA Delegate's Overview.

### Clinical claim

- 6.21 The submission described daclizumab as non-inferior in terms of efficacy and non-inferior in terms of safety compared to fingolimod. The PBAC considered the efficacy claim may be reasonable but the safety claim was inadequately supported by the available data.
- 6.22 The submission described daclizumab as superior in terms of efficacy and similar in terms of safety compared to IM IFN  $\beta$ -1a. The PBAC considered the efficacy claim may be reasonable for the relapse outcomes and MRI measures, but not for the progression of disability. The PBAC considered daclizumab to have a worse safety profile compared to IM IFN  $\beta$ -1a.

### Economic analysis

- 6.23 The submission presented a cost minimisation analysis of daclizumab versus fingolimod for the treatment of relapsing-remitting multiple sclerosis. The PBAC noted the unclear clinical place for daclizumab and therefore that a comparison versus fingolimod may not be appropriate. The PBAC further noted that a cost minimisation analysis may not be appropriate given the claim of non-inferior safety was not adequately supported.
- 6.24 The equi-effective doses were based on the recommended dosing regimens outlined in the relevant product information documents:

Daclizumab 150 mg once monthly = Fingolimod 0.5 mg once daily

The submission acknowledged that the daclizumab clinical trials used a dosage regimen of 150 mg every four weeks rather than monthly dosing. However, the submission argued that the dosing window of 28 days  $\pm$  3 days in the SELECT trial and 28 days  $\pm$  4 days in the DECIDE trial was broadly equivalent to monthly dosing. The evaluation considered the argument was not adequately supported for the purpose of calculating dose equivalence as the majority of patients in the clinical trials appeared to have been administered 13 packs per year which is consistent with a four week dosage regimen rather than a monthly regimen.

- 6.25 The PSCR argued the unconstrained environment of clinical practice (compared with the controlled environment of a clinical trial) would most likely result in monthly administrations of daclizumab. The ESC noted the clinical trial protocols were one injection every 28 days plus or minus 4 days, and that the vast majority of participants received 13 doses per year, and therefore considered that one injection every four weeks was the appropriate dosing regimen, resulting in equi-effective doses of daclizumab 150 mg once every 4 weeks and fingolimod 0.5 mg once daily.

6.26 The cost minimisation analysis is summarised in the table below.

**Table 5: Cost minimisation analysis**

	Cost
<b>Fingolimod 0.5 mg tablets</b>	
Drug acquisition costs (DPMQ)	\$2,313.49
Drug acquisition costs (AEMP)	\$2,166.62
Scripts per year	13.04
Annual cost of therapy (AEMP)	\$28,252.72
<b>Daclizumab 150 mg injection</b>	
Annual cost of monthly liver function testing (12 x MBS 66512, \$17.70)	\$212.40
Annual cost of therapy (AEMP)	\$ [REDACTED]
Scripts per year	[REDACTED]
Drug acquisition costs (AEMP)	\$ [REDACTED]
Drug acquisition costs (DPMQ) <sup>a</sup>	\$ [REDACTED]
<b>Daclizumab 150 mg injection (sensitivity analyses assuming no difference in script duration)</b>	
Annual cost of monthly liver function testing (12 x MBS 66512, \$17.70)	\$212.40
Annual cost of therapy (AEMP)	\$ [REDACTED]
Scripts per year	[REDACTED]
Drug acquisition costs (AEMP)	\$ [REDACTED]
Drug acquisition costs (DPMQ) <sup>a</sup>	\$ [REDACTED]

Abbreviations: AEMP, approved ex-manufacturer price; DPMQ, dispensed price per maximum quantity

Source: Table D.2-3 (p 134) of the submission

<sup>a</sup> Wholesaler mark-up \$69.94, AHI fee \$70.00 and dispensing fee \$6.93

- 6.27 Based on the cost minimisation analysis assuming monthly dosing of daclizumab, the published DPMQ for daclizumab was \$ [REDACTED] (the DPMQ calculated in the submission was \$ [REDACTED] but this did not appropriately account for ex-manufacturer prices).
- 6.28 The claim of monthly versus once every four weeks dosing with daclizumab had a substantial impact on pricing calculations as the submission assumed a difference in script duration between daclizumab ([REDACTED] scripts per year) and fingolimod (28 days per pack, [REDACTED] scripts per year). Assuming no difference in script duration between treatments resulted in a published DPMQ of \$ [REDACTED] for daclizumab. The PBAC accepted that based on the clinical trial the most appropriate dosing regimen for daclizumab was 4 weekly.
- 6.29 The submission noted that the PBS listing of fingolimod is subject to a special pricing arrangement and that published prices do not reflect the effective price subsidised by the government. The submission requested that daclizumab have a similar special pricing arrangement to fingolimod (i.e. cost minimised effective price adjusted for differences in monitoring costs).
- 6.30 The ESC noted that fingolimod is not the least expensive alternative therapy. The ESC further noted that the PBAC could only recommend a higher price for daclizumab 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 PBAC noted the ESC advice and considered that the alternative therapies include ABCR therapies.

**Drug cost/patient/year: \$ [REDACTED] (proposed published price)**

- 6.31 The estimated annual cost of daclizumab using the proposed published DPMQ is DPMQ was \$ [REDACTED] ([REDACTED] scripts per year; \$ [REDACTED] per script).
- 6.32 The estimated annual cost of fingolimod using the current published DPMQ was \$ [REDACTED] ([REDACTED] scripts per year; \$2,313.49 per script).

**Estimated PBS usage & financial implications**

- 6.33 This submission was not considered by DUSC.
- 6.34 The submission used a market share approach to estimate the utilisation/financial implications associated with the PBS listing of daclizumab.

**Table 6: Estimated utilisation and cost to the PBS in the first five years of listing**

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
Projected PBS scripts for MS therapies	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Fingolimod market share	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Projected fingolimod scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Daclizumab uptake rate <sup>a</sup>	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Substituted scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Equivalent daclizumab scripts (script duration adjustment; 30.4 vs 28 days)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost of daclizumab (published DPMQ)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patient co-payments (\$23.51 per script)	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Total cost of daclizumab	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost of substituted fingolimod scripts (published DPMQ less co-pay)	-\$ [REDACTED]	-\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Net cost to the PBS/RPBS</b>	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Cost of liver function testing (\$17.70 per script)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Net cost to government<sup>b</sup></b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Abbreviations: DPMQ, dispensed price for maximum quantity; MS, multiple sclerosis; PBS, Pharmaceutical Benefits Scheme; RPBS Repatriation Pharmaceutical Benefits Scheme

Source: Table E.1-3 (p 138), Table E.1-4 (p 139), Table E.1-5 (p 140), Table E.2-1 (p 142), Table E.2-2 (p 142), Table E.4-1 (p 143), Table E.5-2 (p 144), Table E.5-3 (p 144) of the submission

<sup>a</sup> Uptake rates are the equivalent of 2%, 5%, 7%, 9% and 10% of the overall PBS market for MS therapies

<sup>b</sup> Corrected estimate accounting for patient co-payments

The redacted table shows that at year 5, the estimated number of daclizumab scripts would be 10,000 – 50,000, and the net saving to the PBS would be less than \$10 million per year. The net cost to government after the cost of liver function testing would be less than \$10 million per year.

- 6.35 The evaluation considered the budget impact estimate uncertain due to the rapidly changing dynamics of the PBS MS market, the poorly justified assumption for the expected uptake of daclizumab, the unrealistic assumption that daclizumab will only replace fingolimod in practice and costs that are based on published rather than effective prices. The PBAC noted that the uptake rate in first year was based on the peg-interferon beta-1a market share, and arbitrary assumptions were used in subsequent years.
- 6.36 The PSCR (p1) contended that daclizumab was unlikely to replace other injectable therapies for RRMS because it has superior efficacy compared to interferon beta-1a, and therefore it and other injectable therapies would not substitute for daclizumab. The ESC agreed with the PSCR, but considered that given the likely clinical place of daclizumab it would substitute both DMF and fingolimod. The PBAC agreed with the ESC and considered that the other injectable may also be substituted by daclizumab.
- 6.37 The PBAC indicated that the assumption that daclizumab would only replace fingolimod likely substantially underestimated the net cost to government based on a cost minimisation to fingolimod.

#### **Quality Use of Medicines**

- 6.38 The submission proposed a Risk Management Plan for daclizumab which includes routine pharmacovigilance with periodic safety update reports to monitor safety concerns.

#### **Financial Management – Risk Sharing Arrangements**

- 6.39 The submission noted that fingolimod is subject to a special pricing arrangement. The submission stated that the sponsor is willing to negotiate a similar special pricing arrangement for daclizumab based on the cost minimisation analysis once the actual effective price of fingolimod can be made known to the sponsor.

The submission stated that the sponsor was willing to discuss other appropriate risk management arrangements.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **7. PBAC Outcome**

- 7.1 The PBAC deferred the listing of daclizumab, on the basis that the clinical place for which TGA registration may be approved was unclear and that this would have a significant impact on the choice of comparator for any cost minimisation analysis and the wording of any possible restriction. The TGA Delegate's Overview was provided as a late paper for the July 2016 PBAC meeting. The Overview noted that the place in therapy of daclizumab is not clear due to the lack of demonstration of superiority

over interferon beta-1a (IFN  $\beta$ -1a) for the endpoint of progression of disability and that daclizumab presents more risk of serious adverse effects than IFN  $\beta$ -1a. Given these factors it was considered not clear by the Delegate as to whether use of daclizumab should be permitted at all or whether restricting its use to patients who have failed initial treatment would be appropriate.

- 7.2 The PBAC did not consider that fingolimod was the only comparator for daclizumab and that DMF and possibly other injectable therapies for MS were appropriate comparators as they would likely be replaced by daclizumab.
- 7.3 The PBAC noted that no head to head trials comparing daclizumab to fingolimod were available and that the comparison was based on indirect comparisons using either placebo or IM IFN  $\beta$ -1a as the common comparator. The PBAC considered that there were significant exchangeability issues between the studies including, the durations which limited the analyses to matched time points and patient characteristics such as baseline disability, differences in MRI disease activity, past treatment experience and duration of the disease, all of which reduced the reliability of the conclusions. The differences across the daclizumab and fingolimod trials in the results for the placebo treatment groups further suggested that there may be exchangeability issues. The PBAC noted that a non-inferiority margin was not proposed in the submission and that non-inferiority was claimed based on lack of a statistically significant difference. The PBAC considered this approach was not robust, especially given the wide 95% confidence limits for the indirect comparisons.
- 7.4 While the comparison using placebo as the common comparator indicated that there was an apparent improvement in disability progression outcomes with daclizumab treatment versus fingolimod this was not demonstrated for the indirect comparison using IM IFN  $\beta$ -1a as the common comparator. The PBAC noted the lack of demonstration of superiority over IFN  $\beta$ -1a for the endpoint of progression of disability.
- 7.5 The PBAC considered that the comparison of the safety data between daclizumab and fingolimod was largely non-informative. The PBAC noted that there are limited long-term data on the safety of daclizumab for the treatment of MS, and that the TGA Delegates Overview also identified a potential risk of depression associated with daclizumab treatment.
- 7.6 The PBAC considered that the claim of non-inferior efficacy compared to fingolimod may be reasonable but the claim of non-inferior safety compared to was fingolimod inadequately supported by the available data.
- 7.7 The PBAC considered the claim of superior efficacy compared to IM IFN  $\beta$ -1a may be reasonable for the relapse outcomes and MRI measures, but not for the progression of disability. The PBAC considered daclizumab to have a worse safety profile compared to IM IFN  $\beta$ -1a.
- 7.8 The PBAC considered that the equi-effective doses should be based on the trial data and the therefore the equi-effective doses are daclizumab 150 mg once every 4 weeks and fingolimod 0.5 mg once daily.

- 7.9 The PBAC considered that the financial estimates in the submission were not reliable based on the initial uptake rate being based on the peginterferon beta-1a market share, then arbitrary assumptions thereafter and the assumption that daclizumab would only replace fingolimod.
- 7.10 The PBAC considered that the any reconsideration or resubmission would need to include a comparison with a comparator appropriate to the clinical place of daclizumab as defined in the TGA registration.

**Outcome:**

Deferred

**8. Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9. Sponsor's Comment**

The sponsor acknowledges the deferred decision for daclizumab based on the issues raised in the TGA Delegate's Overview and the lack of clarity around the clinical place for daclizumab at that time. The concerns highlighted by the Delegate in paragraphs 3.2 and 3.3 have been addressed and the TGA registration is now finalised.

The clinical place of therapy has been confirmed by the following indication: "ZINBRYTA is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to delay the progression of physical disability and to reduce the frequency of relapse." This indication is aligned with that included in the July 2016 PBAC submission. Biogen look forward to working with the PBAC towards reimbursement for patients with MS.