

4.03 DACLIZUMAB

Injection 150 mg per 1.0 mL injection in pre-filled pen or syringe, Zinbryta[®], Biogen Australia Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested a General Schedule Authority Required listing for daclizumab for the treatment of relapsing-remitting multiple sclerosis (RRMS). The PBAC deferred consideration of daclizumab to the November 2016 meeting, pending the finalisation of TGA registration.

2 Requested listing

- 2.1 The submission did not request changes to the requested restriction considered by the PBAC in July 2016. The requested listings are reproduced below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough. These include the addition of a treatment criterion, to reflect the final conditions of TGA registration, that treatment must be initiated by a neurologist.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
DACLIZUMAB Injection 150 mg per 1.0 mL injection in pre-filled pen or syringe	1	5	Zinbryta [®]	Biogen Australia Pty Ltd
Category / Program	GENERAL – General Schedule (Code GE)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Condition:	Multiple sclerosis			
PBS Indication:	Multiple sclerosis			
Treatment phase:	Initial			
Restriction Level / Method:	<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			
Treatment criteria:	<i>Must be treated by a neurologist</i>			

Public Summary Document – November 2016 PBAC Meeting

Clinical criteria:	<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>
Prescriber Instructions	Where applicable, the date of the MRI magnetic resonance imaging scan must be provided with the authority application.
Prescriber Instructions	<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>
Administrative Advice	<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>

Public Summary Document – November 2016 PBAC Meeting

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Multiple sclerosis
PBS Indication:	Multiple sclerosis
Treatment phase:	Continuing
Restriction Level / Method:	<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
Clinical criteria:	<p><i>The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR</i></p> <p><i>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,</i></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>
Prescriber Instructions	<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>
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. <i>Special Pricing Arrangements apply.</i>

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

3 Background

- 3.1 The PBAC deferred its decision on whether to recommend a submission for daclizumab in July 2016 on the basis of an unclear clinical place based on concerns raised by the TGA Delegate in the Request for ACPM Advice.

- 3.2 Daclizumab was considered at the ACPM meeting held 4-5 August 2016.
- 3.3 The ACPM recommended the registration of daclizumab for the treatment of relapsing forms of multiple sclerosis under condition of restriction initiation of treatment to neurologists and enhanced risk management procedures (RMPs). The recommended enhanced RMPs included boxed warnings regarding the risk of hepatic disease/impairment, inclusion of advice on the risk of opportunistic infections and a requirement for monthly liver function testing.
- 3.4 The ACPM did not recommend that daclizumab be restricted to third line treatment for RRMS.
- 3.5 Daclizumab was TGA registered for RRMS on 22 September 2016.
- 3.6 Other PBS listed drugs for the treatment of RRMS include subcutaneous and intramuscular forms of interferon (IFN) β -1a, IFN β -1b, glatiramer acetate, pegylated IFN β -1a (Peg-IFN β -1a), dimethyl fumarate (DMF), teriflunomide, fingolimod, natalizumab and alemtuzumab. Older treatments for RRMS, including both forms of IFN β -1a, IFN β -1b and glatiramer acetate are often termed 'ABCR therapies', a reference to the trade names of these products (Avonex, Betaferon, Copaxone and Rebif).

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

4 Clinical place for the proposed therapy

- 4.1 Daclizumab would represent an additional treatment option for RRMS amongst a diverse range of RRMS treatments that are currently PBS listed. In practice, treatments for RRMS are broadly categorised into groups based on their efficacy and safety profiles. Daclizumab would broadly align to the clinical settings in which the oral and injectable therapies are used, but is unlikely to be used in a clinical setting similar to that of the infusible therapies (natalizumab and alemtuzumab) as these treatments have poor safety profiles.

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

5 Comparator

- 5.1 The Sponsor reiterated its position that fingolimod was the appropriate comparator.
- 5.2 The PBAC previously considered that other PBS listed treatments for RRMS, including DMF and other injectable therapies (including ABCR therapies) were also appropriate comparators as they would likely be replaced by daclizumab. The PBAC noted that of the ABCR therapies, IFN β -1b has the lowest cost (as the result of a statutory price reduction), whilst the remaining ABCR therapies, DMF and teriflunomide were all listed on a cost-minimisation basis with IFN β 1a.

- 5.3 The Sponsor argued in the Pre-PBAC response that daclizumab was most likely to replace treatments of moderate efficacy such as fingolimod, rather than ABCR therapies. Further, the Sponsor argued that DMF was not considered an appropriate comparator as it had a substantially smaller market share than fingolimod and the PBAC previously considered that DMF was of similar efficacy to ABCR therapies.
- 5.4 The Pre-PBAC response stated that natalizumab and alemtuzumab were not appropriate comparators, as there were differences in their efficacy and safety profiles and ongoing treatment is limited to neurologists, whereas the ACPM recommended that daclizumab be restricted to initiation by a neurologist only.

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 as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 No new clinical trials were presented in this minor submission. However, the Clinical Trials, Comparative Effectiveness and Comparative Harms sections were reproduced from the July 2016 PBAC Public Summary Document (PSD), with additional data on the direct comparison of daclizumab and IM IFN β -1a added for clarity. The Clinical Claim section reflects consideration by the PBAC at the November 2016 meeting.
- 6.4 No head-to-head trials comparing daclizumab to fingolimod were available. The submission was based on a series of comparisons between daclizumab, fingolimod and either placebo or IM IFN β -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 β -1a as the common comparator.
 - Supportive direct comparison of daclizumab versus IM IFN β -1a (DECIDE).
- 6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports included in the original July 2016 submission

Trial ID	Protocol title/ Publication title	Publication citation
Daclizumab trials		
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 β -1a) in Patients with Relapsing-Remitting Multiple Sclerosis	Internal study report
	Kappos L et al (2015). Daclizumab HYP versus IFN β -1ain relapsing multiple sclerosis	New England Journal of Medicine 373: 1418-1428
Fingolimod trials		
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
	Kremenchutzky 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 (TRANSFORMS), a phase 3 study of fingolimod in multiple sclerosis	Multiple Sclerosis Journal 20: 1704-1713
	Khatri BO et al (2014). Effect of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod vs. IFN β -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

6.6 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
Daclizumab vs. placebo					
SELECT	621	MC, R, DB 1 year	Low	Active RRMS	Relapse rates, disability progression
Daclizumab vs. IM interferon beta-1a					
DECIDE	1,841	MC, R, DB 2-3 years	Low	Active RRMS	Relapse rates, disability progression
Fingolimod vs placebo					
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
Fingolimod vs. IM interferon beta-1a					
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

6.7 The evaluation noted 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).

6.8 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

6.9 The results of the indirect comparison of daclizumab versus fingolimod using placebo as the common comparator are 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)
Annualised relapse rate (95% CI)				
SELECT, 1 year (N = 397)	0.21 (0.16, 0.29)	0.46 (0.37, 0.57)	-	Rate ratio: 0.46 (0.32, 0.67)
FREEDOMS, 2 year (N = 843)	-	0.40 (0.34, 0.47)	0.18 (0.15, 0.22)	Rate ratio: 0.45 (0.34, 0.59)
FREEDOMS II, 2 year (N = 713)	-	0.40 (0.34, 0.48)	0.21 (0.17, 0.25)	Rate ratio: 0.52 (0.40, 0.66)
Meta-analysis of fingolimod trials ($I^2 = 0\%$)				Rate ratio: 0.49 (0.40, 0.58)
Indirect estimate of effect (results < 1 favour daclizumab)				Rate ratio: 0.95 (0.63, 1.43)
Time to 3-month sustained disability progression, n/N (%)				
SELECT, 1 year (N = 397)	12/201 (6.0%)	26/196 (13.3%)	-	Hazard ratio: 0.43 (0.21, 0.88)
FREEDOMS, 2 year (N = 843)	-	101/418 (24.1%)	75/425 (17.7%)	Hazard ratio: 0.70 (0.52, 0.96)
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 ($I^2 = 0\%$)				Hazard ratio: 0.76 (0.61, 0.95)
Indirect estimate of effect (results < 1 favour daclizumab)				Hazard ratio: 0.56 (0.27, 1.19)
Time to 6-month sustained disability progression, n/N (%)				
SELECT, 1 year (N = 397)	5/201 (2.6%)	22/196 (11.1%)	-	Hazard ratio: 0.24 (0.09, 0.63)
FREEDOMS, 2 year (N = 843)	-	79/418 (19.0%)	53/425 (12.5%)	Hazard ratio: 0.63 (0.44, 0.90)
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 ($I^2 = 0\%$)				Hazard ratio: 0.67 (0.51, 0.87)
Indirect estimate of effect (results < 1 favour daclizumab)				Hazard ratio: 0.36 (0.13, 0.99)

Abbreviations: CI, confidence interval

Source: Original July 2016 submission.

- 6.10 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. When considered in July 2016, 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.
- 6.11 The results of the indirect comparison of daclizumab versus fingolimod using IM IFN β -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 β -1a	Fingolimod 0.5 mg	Treatment difference (95% CI)
Annualised relapse rate at one year (95% CI)				
DECIDE, 1 year (N = 1,841)	0.25 (0.22, 0.30)	0.43 (0.38, 0.49)	-	Rate ratio: 0.59 (0.49, 0.72)
TRANSFORMS, 1 year (N = 843)	-	0.33 (0.26, 0.42)	0.16 (0.12, 0.21)	Rate ratio: 0.48 (0.36, 0.64)
Indirect estimate of effect (results < 1 favour daclizumab)				Rate ratio: 1.23 (0.87, 1.74)
Proportion of patients with 3-month sustained disability at one year, n/N (%)				
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: Original July 2016 submission

- 6.12 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 β -1a as the common comparator did not support a difference in disability outcomes.
- 6.13 A direct comparison of daclizumab versus IM IFN β -1a was presented in the submission as supportive evidence. The results of the direct comparison of daclizumab and IM IFN β -1a are presented in Table 5.

Table 5: Direct comparison of key outcomes between daclizumab and IM interferon beta-1a (DECIDE trial)

Outcome	Daclizumab N = 919	IM interferon beta-1a N = 922	Treatment difference (95% CI)
Primary endpoint			
Annualised relapse rate (95% CI) at end of study (2-3 years)	0.22 (0.19, 0.24)	0.39 (0.35, 0.44)	Rate ratio: 0.55 (0.47, 0.65)
Secondary endpoints			
Average number of new/enlarged T2 lesions (95% CI) at Week 96	4.31 (3.85, 4.81)	9.44 (8.46, 10.54)	Mean difference: -54.4% (-60.8, -46.9)
Time to 3-month sustained disability progression (n/N, %) at end of study (2-3 years)	121/919 (13.2%)	140/922 (15.2%)	Hazard ratio: 0.84 (0.66, 1.07)
Proportion of relapse-free patients (n/N, %) at end of study (2-3 years)	659/919 (71.7%)	530/922 (57.5%)	Hazard ratio: 0.59 (0.50, 0.69) ^a
Clinically meaningful worsening on MSIS-29 physical subscale (n/N, %) at Week 96 ^b	171/906 (18.9%)	213/912 (23.4%)	Odds ratio: 0.76 (0.60, 0.95) ^a

Abbreviations: CI, confidence interval

Source: Original July 2016 submission

^a The DECIDE trial used a hierarchical statistical testing approach to adjust for multiple comparisons with daclizumab failing to demonstrate a difference with a higher order comparison (3-month sustained disability progression) and therefore lower order comparisons (such as relapse-free patients and clinical worsening on MSIS-29 subscale) were not statistically significant.

^b MSIS-29 assessed the impact of multiple sclerosis on physical (20 items) and psychological domains (9 items). Clinically meaningful worsening was defined as an increase of at least 7.5 points from baseline in the MSIS-29 physical subscale score (potential scores range from 1 to 100).

- 6.14 Daclizumab was associated with statistically significant improvements in both relapse outcomes and MRI measures compared to IM IFN β -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 β -1a for the endpoint of progression of disability, and that this was an issue that was also raised in the TGA Delegate's Overview.
- 6.15 The PBAC recalled its previous 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.

Comparative harms

- 6.16 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.

- 6.17 In July 2016, 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, and 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.
- 6.18 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.
- 6.19 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.
- 6.20 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 in the TGA registration for monthly liver function testing with daclizumab therapy.
- 6.21 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

- 6.22 The submission described daclizumab as non-inferior in terms of comparative efficacy and safety compared to fingolimod. It also described daclizumab as superior in terms of efficacy and similar in terms of safety compared to IM IFN β -1a.
- 6.23 The PBAC considered there was substantial uncertainty with the indirect comparisons with fingolimod using either placebo or IM IFN β -1a as the common comparator. Given the wide confidence intervals and exchangeability issues with the indirect comparison, the PBAC did not consider the claim of non-inferior efficacy with fingolimod to be adequately supported. The PBAC considered that daclizumab is likely superior to IFN β -1a with regards to comparative efficacy, but noted that only two of the three efficacy outcomes measured supported this conclusion.

6.24 The PBAC considered that the indirect comparison of safety with daclizumab and fingolimod was largely non-informative, and therefore the claim of non-inferior safety was not adequately supported.

Economic Analysis

6.25 The July 2016 submission presented a cost-minimisation analysis versus fingolimod.

6.26 The PBAC considered that daclizumab 150 mg is likely to be administered at 28 day intervals, rather than monthly intervals for any pricing considerations.

Estimated PBS usage & financial implications

6.27 The Sponsor did not provide updated or amended estimates of utilisation or financial implications. The utilisation estimates are reproduced from the July 2016 PSD.

6.28 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					
Fingolimod market share	%	%	%	%	%
Projected fingolimod scripts					
Daclizumab uptake rate ^a	%	%	%	%	%
Substituted scripts					
Equivalent daclizumab scripts (script duration adjustment; 30.4 vs 28 days)					
Cost of daclizumab (published DPMQ)	\$	\$	\$	\$	\$
Patient co-payments (\$23.51 per script)	-\$	-\$	-\$	-\$	-\$
Total cost of daclizumab	\$	\$	\$	\$	\$
Cost of substituted fingolimod scripts (published DPMQ less co-pay)	\$	\$	\$	-\$	\$
Net cost to the PBS/RPBS					
Cost of liver function testing (\$17.70 per script)	\$	\$	\$	\$	\$
Net cost to government^b					

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

Source: Original July 2016 submission

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

^b Corrected estimate accounting for patient co-payments

The redacted table above shows that at year 5, the net cost to the PBS would be less than \$10 million per year.

- 6.29 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 considered the financial estimates in the original submission were not reliable based on the initial uptake rate being based on the Peg-IFN β -1a market share, then arbitrary assumptions thereafter, including the assumption that daclizumab would only replace fingolimod.
- 6.30 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 for both DMF and fingolimod. The PBAC agreed with the ESC but considered that the other injectables may also be substituted by daclizumab.
- 6.31 The PBAC considered in July 2016 that the assumption that daclizumab would only replace fingolimod was likely to substantially underestimate the net cost to government.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of daclizumab on the basis that the presented direct comparison of IM IFN β -1a and indirect comparisons of daclizumab and fingolimod supported a conclusion that daclizumab is likely to be superior to IFN β -1a and may be non-inferior to fingolimod, with regards to comparative efficacy, but may be inferior to IFN β -1a with regards to comparative safety.
- 7.2 The PBAC considered there was substantial uncertainty about the indirect comparisons with fingolimod using placebo and IM IFN β -1a as common comparators (paragraphs 6.10, 6.14, 6.17 and 6.23 refer). The PBAC also again considered it was unable to draw meaningful conclusions with regards to comparative safety from the indirect comparisons with fingolimod, and further considered that daclizumab may have a worse safety profile than IFN β -1a. As such, the PBAC recommended that the superior comparative efficacy over IFN β -1a justified the cost of daclizumab per patient per course being higher than IFN β -1a, however there was insufficient grounds for the cost per patient per course to be as high as fingolimod.
- 7.3 The PBAC additionally noted that a TGA condition of registration would require that monthly liver function testing be conducted on patients, and requested that the cost of this testing be accounted for in determining a price for daclizumab.
- 7.4 The PBAC agreed that consistent with the TGA registration, initiation of daclizumab should be restricted to neurologists.

- 7.5 The PBAC recommended that daclizumab should not be treated as interchangeable with any other drugs.
- 7.6 The PBAC advised that daclizumab is not suitable for prescribing by nurse practitioners.
- 7.7 The PBAC recommended that the Early Supply Rule should apply.
- 7.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
DACLIZUMAB Injection 150 mg per 1.0 mL injection in pre-filled pen or syringe	1	5	Zinbryta®	Biogen Australia Pty Ltd
Category / Program	GENERAL – General Schedule (Code GE)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Condition:	Multiple sclerosis			
PBS Indication:	Multiple sclerosis			
Treatment phase:	Initial			
Restriction Level / Method:	<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			
Treatment criteria:	Must be treated by a neurologist			

Public Summary Document – November 2016 PBAC Meeting

Clinical criteria:	<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>
Prescriber Instructions	Where applicable, the date of the magnetic resonance imaging scan must be provided with the authority application.
Prescriber Instructions	Patient must undergo monthly liver function testing as described in item 66512 of the Medicare Benefits Schedule while being treated with this drug.
Administrative Advice	<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>Special Pricing Arrangements apply.</p>

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Multiple sclerosis
PBS Indication:	Multiple sclerosis
Treatment phase:	Continuing
Restriction Level / Method:	<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

Clinical criteria:	<p>Patient must have previously been issued with an authority prescription for this drug for this condition,</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>
Prescriber Instructions	<p>Patient must undergo monthly liver function testing as described in item 66512 of the Medicare Benefits Schedule while being treated with this drug.</p>
Administrative Advice	<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>Special Pricing Arrangements apply.</p>

9 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.

10 Sponsor's Comment

The sponsor had no comment.