7.12 CLADRIBINE
Tablet, 10 mg,
Mavenclad®, Merck Serono Australia

1 Purpose of Application

1.1 The minor resubmission requested a general schedule listing for cladribine tablets for the treatment of patients with relapsing remitting multiple sclerosis (RRMS).

2 Requested listing

2.1 The minor resubmission did not propose a revised listing. The sponsor had previously accepted the additions and deletions proposed by the secretariat to the proposed listing presented in the March 2018 minor resubmission.

2.2 The proposed listing from the March 2018 minor resubmission with Secretariat suggested additions (in italics) and deletions (in strikethrough) are presented below.

2.3 The dispensed price for maximum quantity (DPMQ) proposed in the minor resubmission for each pack is also included below.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
CLADRIBINE				
Tablet 10 mg, 1	*1*	*1*	$3,982.56[a]	MAVENCLAD® Merck
Tablet 10 mg, 4	*2*	*1*	$30,813.84[b]	
Tablet 10 mg, 6	*1*	*1*	$23,147.76[c]	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Relapsing remitting multiple sclerosis
PBS Indication:	Relapsing remitting multiple sclerosis
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required – Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be ~~initiated~~ diagnosed by *a* neurologist~~.~~
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord;

	OR 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, AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND 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, AND Patient must be ambulatory (without assistance or support).
Prescriber Instructions	Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records. The prescriber should request authority approval for the appropriate combination of packs (1, 4 or 6 tablets) to provide sufficient drug for a treatment week based on the weight of the patient in accordance with the TGA approved Product Information. Separate authority prescriptions may be required where the dose for treatment week 5 is different to the dose for treatment week 1.
Administrative Advice:	No increase in the maximum quantity may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Relapsing remitting multiple sclerosis
PBS Indication:	Relapsing remitting multiple sclerosis
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be ~~supervised~~ treated by *a* neurologist~~.~~
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis, AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition,

	AND Patient must not show continuing progression of disability while on treatment with this drug, AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Prescriber Instructions	The prescriber should request authority approval for the appropriate combination of packs (1, 4 or 6 tablets) to provide sufficient drug for a treatment week based on the weight of the patient in accordance with the TGA approved Product Information. Separate authority prescriptions may be required where the dose for treatment week 5 is different to the dose for treatment week 1.
Administrative Advice	No increase in the maximum quantity may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Category / Program	*GENERAL – General Schedule (Code GE)*
Prescriber type:	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *Midwives*
Condition:	Relapsing remitting multiple sclerosis
PBS Indication:	Relapsing remitting multiple sclerosis
Treatment phase:	Grandfather treatment
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR 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; AND Patient must have received treatment with this drug for this condition prior to (listing date); AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition; AND Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the 2 years preceding when this drug was initiated for this condition; AND Patient must be ambulatory (without assistance or support); AND Patient must not show continuing progression of disability while on treatment with this drug; AND

	Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Prescriber Instructions	The prescriber should request authority approval for the appropriate combination of packs (1, 4 or 6 tablets) to provide sufficient drug for a treatment week based on the weight of the patient in accordance with the TGA approved Product Information. Separate authority prescriptions may be required where the dose for treatment week 5 is different to the dose for treatment week 1.

[a] Effective price = $[redacted]; [b] Effective price = $[redacted]; [c] Effective price = $[redacted]

2.4 The March 2018 minor resubmission proposed a DMPQ of $[redacted] for seven tablets of cladribine, based on a cost-minimisation analysis versus the published price of fingolimod, and the application of two rebates ([redacted]% and [redacted]%). However the March 2018 minor resubmission did not propose a DPMQ for each of the three different pack sizes for cladribine.

2.5 The minor resubmission proposed a DPMQ of $[redacted] for a pack containing one tablet, a DPMQ of $[redacted] for two packs containing four tablets and a DPMQ of $[redacted] for a pack containing six tablets based on a revised cost-minimisation analysis versus the published price of fingolimod and application of a [redacted]% rebate. The proposed DPMQs equate to an ex- manufacturer price of $[redacted] per tablet.

3 Background

Registration status

3.1 Cladribine is TGA registered for the treatment of RRMS for the following indication:

- The treatment of relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical relapses and to delay the progression of physical disability. Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4. Re-initiation of therapy after year 4 has not been studied.

Previous PBAC consideration

3.2 Cladribine was first considered by the PBAC at the March 2011 meeting. The PBAC did not recommend listing cladribine for the treatment of RRMS on the grounds of several concerns including inappropriate comparator (natalizumab) choice, uncertain claim of the superiority over interferon beta 1a and non-inferiority to natalizumab and uncertainty of usefulness of cladribine given treatment is limited to two years due to safety concerns.

3.3 A major resubmission for cladribine was considered at the November 2017 PBAC meeting. The PBAC did not recommend the listing of cladribine, on the basis of uncertainty in the non-inferior efficacy claim of cladribine versus the comparator, fingolimod, over two and four years. The PBAC considered there was insufficient clinical evidence to support the time horizon of four years for estimating the equi-effective doses of cladribine and fingolimod. The PBAC also considered that it was unrealistic to assume that patients who receive cladribine and experience disease

relapse would not be prescribed another medicine for RRMS before the four-year period or that patients would [redacted]% persistent to fingolimod. Therefore, the PBAC did not accept two years of cladribine treatment versus four years of fingolimod treatment as the basis for the cost-minimisation analysis. The PBAC noted that there were significant uncertainties in the financial analysis, including the persistence rates assumed by the resubmission. The PBAC further noted that the financial analysis estimated a significant net cost to the PBS, which undermined the first principles of a cost minimisation analysis.

3.4 A minor resubmission for cladribine was considered by the PBAC at the March 2018 meeting where the sponsor proposed two rebates ([redacted]% and [redacted]%) to address concerns regarding the compliance and the persistence rates. The PBAC did not recommend the listing of cladribine on the basis that no additional clinical evidence was provided to address its remaining concern around the time horizon of four years for estimating the equi-effective doses of cladribine and fingolimod. The PBAC noted that the reduced DPMQ was predominantly due to a lower number of tablets (from ten to seven) for the maximum quantity requested, rather than a reduction in the price per tablet of cladribine. Further, the PBAC noted there remained significant uncertainties in the financial analysis, including the persistence rates assumed by the resubmission.

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

4 Comparator

4.1 The comparator, fingolimod, remained unchanged from the November 2017 PBAC and March 2018 submissions. At the November 2017 meeting, the PBAC accepted fingolimod as the appropriate main comparator, however, considered that cladribine may replace or displace all PBS listed RRMS treatments to some extent. The PBAC noted that if treatment with cladribine is substantially more costly than an alternative therapy or alternative therapies, the Committee could only recommend listing of cladribine if it is satisfied that cladribine provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The alternative therapies in this case may include interferon beta, dimethyl fumarate and teriflunomide. The PBAC recalled it was uncertain whether cladribine was superior over interferon beta 1a in terms of efficacy, however, the Committee recalled that cladribine was superior over interferon beta 1a in terms of safety. At the November 2017 meeting the PBAC recalled that non-inferior efficacy of cladribine to natalizumab, as noted at the March 2011 meeting, remained (paragraph 7.5, November 2017 PSD).

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 as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from individuals (8), health care professionals (6) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with cladribine including the short duration of dosing, slowing of disease progression, low monitoring burden, tolerable safety profile and relief of symptoms associated with MS (fatigue, pain and loss of mobility).

5.3 The PBAC noted input received from MS Research Australia, Carers Australia and the MS Neurology subspecialty group of the Australian and New Zealand Association of Neurologists (ANZAN) in support of subsidising cladribine through the PBS. The organisations described the impact of MS on the patient's lives and their families. MS Research Australia and the MS Neurology subspecialty group emphasised the significance of a new effective treatment option, with the benefit of oral administration and a short treatment course.

Clinical trials

5.4 As a minor submission, no new clinical trials were presented in the resubmission.

Clinical claim

5.5 The minor resubmission acknowledged the uncertainties associated with the naive indirect comparison of efficacy endpoints in the CLARITY and fingolimod extension studies, which formed the basis of the claim of non-inferior efficacy of cladribine tablets versus fingolimod over two and four years in the November 2017 and March 2018 submissions. However, the minor resubmission noted that formal indirect comparisons of cladribine tablets and fingolimod over two years using placebo as a common reference, have also been presented in previous submissions. The minor resubmission presented results of all indirect comparisons previously presented in the November 2017 major resubmission (see below). The Pre-PBAC response reiterated that indirect comparison of cladribine and fingolimod versus placebo demonstrated no indication that cladribine reduce relapse rates more effectively than fingolimod, thus the conclusion drawn that is reasonable to assume two year treatment of cladribine is non inferior to two year treatment with fingolimod.

Table 1. Results of the indirect comparison of cladribine versus fingolimod

Endpoint	Active treatment	Placebo	Relative risk (95% CI)	Risk difference (95% CI)
Annualised relapse rate (95% CI)				
CLARITY	0.14 (0.12, 0.17)	0.33 (0.29, 0.38)	**0.43 (0.34, 0.54)**	NR
FREEDOMS	0.18 (0.15, 0.22)	0.40 (0.34, 0.47)	**0.46 (0.37, 0.57)**	
FREEDOMS II	0.21 (0.17, 0.25)	0.40 (0.34, 0.48)	**0.52 (0.40, 0.66)**	
		Fingolimod pooled	0.48 (0.41, 0.57)	
Indirect comparison CLARITY vs FREEDOMS			[redacted]	
Indirect comparison CLARITY vs FREEDOMS II			[redacted]	
Indirect comparison CLARITY vs pooled fingolimod trials			[redacted]	
Proportion of patients remaining relapse free				
CLARITY, n/N (%)	345/433 (79.7%)	226/437 (60.9%)	**1.31 (1.2, 1.43)**	**18.8 (12.9, 24.7)**
FREEDOMS, n/N (%)	229/425 (70.4%)	191/418 (45.7%)	**1.54 (1.36,1.74)**	**24.7 (18.2, 31.1)**
FREEDOMS II, n/N (%)	256/358 (71.5%)	187/355 (52.7%)	**1.36 (1.21, 1.53)**	**18.8 (11.8, 25.8)**
		Fingolimod pooled	1.45 (1.28, 1.64)	21.9 (16.2, 27.6)
Indirect comparison CLARITY vs FREEDOMS			[redacted]	[redacted]
Indirect comparison CLARITY vs FREEDOMS II			[redacted]	[redacted]
Indirect comparison CLARITY vs pooled fingolimod trials			[redacted]	[redacted]
Proportion of patients free from 3 month confirmed progression of disability				
CLARITY (post-hoc), n/N (%)	349/407 (85.7%)	306/388 (78.9%)	**1.09 (1.02, 1.16)**	**6.9 (1.6, 12.2)**
CLARITY (ITT) n/N (%)	375/433 (86.6)	355/437 (81.2)	**1.07 (1.01, 1.13)**	**5.4 (0.5, 10.3)**
FREEDOMS, n/N (%)	350/425 (82.4%)	317/418 (75.8%)	**1.09 (1.01, 1.16)**	**6.5 (1.0, 12.0)**
FREEDOMS II, n/N (%)	267/358 (74.6%)	252/355 (71%)	1.05 (0.96, 1.15)	3.6 (-2.9, 10.1)
		Fingolimod pooled	1.07 (1.02, 1.13)	5.3 (1.1, 9.5)
Indirect comparison CLARITY (post-hoc) vs FREEDOMS			[redacted]	[redacted]
Indirect comparison CLARITY (post-hoc) vs FREEDOMS II			[redacted]	[redacted]
Indirect comparison CLARITY (post-hoc) vs pooled fingolimod trials			[redacted]	[redacted]
Indirect comparison CLARITY (ITT) vs FREEDOMS			[redacted]	[redacted]
Indirect comparison CLARITY (ITT) vs FREEDOMS II			[redacted]	[redacted]
Indirect comparison CLARITY (ITT) vs pooled fingolimod trials			[redacted]	[redacted]
Proportion of patients free from 6 month confirmed progression of disability				
CLARITY, n/N (%)	358/393 (91.1%)	310/366 (84.7%)	**1.08 (1.02, 1.13)**	**6.4 (1.8, 11)**
FREEDOMS, n/N (%)	372/425 (87.5%)	339/418 (81.1%)	**1.08 (1.02, 1.14)**	**6.4 (1.5, 11.3)**
FREEDOMS II, n/N (%)	309/358 (86.3%)	292/355 (82.3%)	1.05 (0.98, 1.12)	4.1 (-1.3, 9.4)
		Fingolimod pooled	1.07 (1.02, 1.11)	5.3 (1.7, 9.0)
Indirect comparison CLARITY vs FREEDOMS			[redacted]	[redacted]
Indirect comparison CLARITY vs FREEDOMS II			[redacted]	[redacted]
Indirect comparison CLARITY vs pooled fingolimod trials			[redacted]	[redacted]

Source: Table 1 p5 of the minor resubmission

CI = confidence interval; n = number of participants with event; N = total number of participants in group; NR = not reported; RR = relative risk

Bold typography indicates statistically significant differences

5.6 The minor resubmission claimed that based on the minimal clinically important difference (MCID) of 1.46 nominated in the November 2017 submission and 1.23 nominated in the July 2017 ocrelizumab submission for the annualised relapse rate,

it can be concluded that cladribine tablets are non-inferior to fingolimod at 96 weeks. The minor resubmission acknowledged the PBAC previously considered that the method of calculating the MCID of 1.46 was not adequately justified, and that the PBAC did not explicitly accept the MCID of 1.23 as a criterion to determine non-inferiority between ocrelizumab and fingolimod. However, the minor resubmission argued that given the consistent non-statistically significant difference between cladribine tablets and fingolimod for the outcomes (i) annualised relapse rate, (ii) proportion of patients remaining relapse free, and (iii) proportion of patients free from confirmed disability progression at 3 and 6 months, a claim that a 2-year treatment course with cladribine tablets is non-inferior to two years of treatment with fingolimod in terms of efficacy is reasonable. The clinical claim in the minor resubmission was therefore that [redacted] course of cladribine is non-inferior in terms of efficacy and safety compare to [redacted] treatment with fingolimod.

5.7 At the March 2018 meeting, the PBAC noted that the minor resubmission did not address its concerns regarding the uncertainty in the non-inferior efficacy between cladribine and fingolimod over four years (paragraph 6.3, March 2018 Public Summary Document (PSD)). [redacted]

5.8 At the November 2017 meeting, the PBAC considered that there was uncertainty in the claim that cladribine is non-inferior to fingolimod in terms of efficacy over two years. The PBAC noted that the basis of the claim over two years was an indirect comparison of one cladribine (CLARITY) and two fingolimod (FREEDOMS and FREEDOMS II) trials. Although no statistically significant differences between cladribine and fingolimod were observed in the indirect comparison for the annualised relapse rate, proportion of patients remaining relapse-free; and proportion of patients free from confirmed disability progression at 3 and 6 months; this was based on a minimal clinically important difference (MCID) nominated by the resubmission of 1.46 for the relapse ratio. The PBAC considered that the method of calculating this MCID was not adequately justified. The PBAC therefore considered that the possibility that cladribine was inferior to fingolimod over two years could not be excluded (paragraph 7.6, November 2017 PSD).

5.9 At the March 2018 meeting, the PBAC noted the resubmission's arguments for the use of the MCID (1.23) used in the July 2017 ocrelizumab submission for RRMS in assessing the efficacy of cladribine, however it recalled that the Committee recommended ocrelizumab based on the totality of the evidence presented in that submission, and not on the basis of the proposed MCID (paragraph 5.8, March 2018 PSD).

5.10 The PBAC previously also considered that there was insufficient data to accurately assess the claim of non-inferior safety of cladribine versus fingolimod. The PBAC considered that while it had previously noted cladribine to be generally well

tolerated, cladribine was associated with important adverse events (paragraphs 7.7 – 7.8, November 2017 PSD). The minor resubmission did not address these concerns.

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

Economic analysis

5.11 At the November 2017 and March 2018 PBAC meetings, the PBAC considered there was insufficient clinical evidence to support the time horizon of four years for estimating the equi-effective doses of cladribine and fingolimod.

5.12 The comparison of the equi-effective doses proposed by previous resubmissions and the current minor resubmission is presented below.

Table 2: Comparison of the equi-effective doses proposed for cladribine vs fingolimod in the Nov 2017, March 2018 and July 2018 submissions

Cladribine dose	Fingolimod dose		
	November 2017 major resubmission	March 2018 minor resubmission	July 2018 minor resubmission
280 mg (28 tablets; assuming average weight of 76.6kg)	730 mg (365 days x four years x 0.5mg/day)	697 mg (365 days x four years x 0.5mg/day x 95.48%)	348 mg (365 days x two years x 0.5 mg/day x [redacted]%)

5.13 The minor resubmission proposed a new equi-effective dose for fingolimod, based on two years of treatment rather than four years. As per the March 2018 submission, the equi-effective dose was adjusted to account for compliance ([redacted]%) with fingolimod. This compliance rate was based on calculating the mean duration of exposure of 1394 days out of 1460 days for fingolimod in the FREEDOMS extension trial. The minor resubmission claimed the FREEDOMS trial does not report relevant data from which a two-year compliance rate can be estimated. The minor resubmission claimed it was likely that the compliance rate over two years is greater than that over four years however and therefore indicated that application of this compliance rate is a conservative approach.

5.14 In the March 2018 and November 2017 submissions (unchanged in the current minor resubmission) the base case financial analysis assumed cladribine and fingolimod persistence rates of [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% in Years 1 to 6. This was based on a Prospection analysis of the fingolimod Medicare prescription data for the persistence rates of fingolimod. The cost-minimisation analysis does not include persistence.

5.15 The March 2018 minor resubmission proposed a second rebate of [redacted]% to account for any treatment switching that may occur for patients who experience disease relapse prior to the four-year period with cladribine treatment. The proposed price for cladribine tablets in the current minor resubmission does not incorporate a rebate to account for treatment switching.

5.16 The minor resubmission [redacted]

[redacted] requested, if recommended, the Department of Health to consider using the following wording:

- 'Cladribine tablets were recommended for listing for the treatment of RRMS, on the basis of non-inferiority to fingolimod. The equi-effective doses are 280 mg cladribine = 348.5 mg fingolimod. Special pricing arrangements apply.'

Drug cost/patient/course: $[redacted]

5.17 The drug cost per patient was calculated based on a two year course of fingolimod treatment, assuming an average requirement of seven tablets per patient, based on the average weight (76.6kg) of patients in an Australian MS longitudinal study receiving cladribine and a DPMQ per maximum quantity of 7 tablets for cladribine of $[redacted]. This also includes the proposed [redacted]% rebate for the cost of cladribine tablets. This compares to a cost of $[redacted] for two years treatment with fingolimod, based on the published price of fingolimod, and [redacted]% compliance with fingolimod.

Estimated PBS usage & financial implications

5.18 The estimated utilisation and financial implication were revised from the March 2018 submission by updating the cost of cladribine only, which is informed based on the revised cost-minimisation analysis.

5.19 The minor resubmission estimated a net save to the PBS of $30 - $60 million in Year 6 of listing, with a total net save to the PBS of more than $100 million over the first 6 years of listing. The savings were derived due to the cost of cladribine being calculated over a two year period whereas the financial analyses assume patients treated with cladribine require no further treatment in year 3 and 4. Due to fewer scripts required for patients per two years of treatment with cladribine compared to fingolimod the total patient co-payments decrease. The table below presents a summary of the estimated financial impact in the current minor resubmission compared to previous resubmissions.

5.20 The minor resubmission claimed that due to the cost of a course of cladribine treatment being estimated based on two years of fingolimod treatment, different assumptions of persistence do not change the overall conclusion that listing cladribine tablets on the PBS is associated with cost savings in all years of the financial analysis.

5.21 The cladribine price was based on a cost-minimisation analysis versus the published price for fingolimod, and the cost offsets for fingolimod were estimated based on the published fingolimod DPMQ. A Special Pricing Arrangement applies to fingolimod.

Table 3: Summary of the estimated use and financial implications presented in the previous submissions and the March 2018 minor resubmission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of cladribine (unchanged between November 2017 and July 2018 resubmissions)						
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated cost of cladribine to the PBS (less copayments)						
November 2017	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
March 2018	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
July 2018	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated PBS cost offsets for fingolimod (published price, less copayments)						
November 2017	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
March 2018	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
July 2018	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net cost to the PBS						
November 2017	$[redacted]	$[redacted]	$[redacted]	–$[redacted]	$[redacted]	$[redacted]
March 2018	$[redacted]	$[redacted]	$[redacted]	-$[redacted]	-$[redacted]	$[redacted]
July 2018	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

[a] Assuming 2 scripts per year of treatment as estimated by the resubmissions.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

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

6 PBAC Outcome

6.1 The PBAC recommended the Authority Required listing of cladribine for the treatment of relapsing-remitting multiple sclerosis (RRMS) The PBAC's recommendation for listing was based on, amongst other matters, its assessment than the cost-effectiveness of cladribine would be acceptable if it were cost-minimised against fingolimod based on a claim that two years of cladribine treatment is non-inferior in efficacy to two years' of fingolimod treatment.

6.2 The PBAC noted and welcomed the consumer comments received, including those from MS Research Australia, Carers Australia and the MS Neurology subspecialty group of the Australian and New Zealand Association of Neurologists (ANZAN) in support of subsidy of cladribine. The PBAC noted that the comments indicated patients and clinicians value additional treatment options for multiple sclerosis. Further, the PBAC acknowledged that consumers' perceived cladribine as a drug with a good safety profile, low monitoring burden and favourable dosing regimen.

6.3 The PBAC noted that minor resubmission presented a revised claim of non-inferior efficacy between cladribine and fingolimod over [redacted] years. The PBAC recalled it

previously considered that there was uncertainty in the claim that cladribine is non-inferior to fingolimod in terms of efficacy over two years as this was based on a minimal clinically important difference (1.46) with a calculation methodology that the Committee considered was not adequately justified (paragraph 7.6, November 2017 Public Summary Document). However, the PBAC considered that the [redacted] reduction in the proposed price for cladribine was adequate to address the remaining uncertainty in cost-effectiveness.

6.4 The PBAC recalled that cladribine is associated with important adverse events including lymphopenia and malignancy, however the PBAC accepted that cladribine overall is well tolerated and as such, considered that cost-minimisation to fingolimod over two years without offsets for adverse events was reasonable

6.5 The PBAC considered the equi-effective doses for the treatment of RRMS were:

- Cladribine 3.5 mg/kg over 2 years administered as 1 treatment course of 1.75 mg/kg per year (consisting of 2 treatment weeks) and
- Fingolimod 500 mcg once daily over 2 years.

6.6 The PBAC noted that the proposed DPMQ for seven tablets was reduced by approximately [redacted]% from $[redacted] in the March 2018 resubmission to $[redacted] in the current minor resubmission. The PBAC further noted that the proposed cost-minimised price for cladribine included a [redacted]% rebate to account for a lower compliance rate of fingolimod ([redacted]%). This was derived from calculating the mean duration of exposure of 1,394 days out of 1,460 days in the FREEDOMS extension trial which the sponsor contended was likely to be conservative when applied to a treatment period over two years.

6.7 The PBAC noted that the estimated total financial impact was reduced substantially from a net cost of $30 - $60 million over six years to a net save of more than $100 million over six years. The PBAC considered the estimated magnitude of cost savings to be uncertain as:

- The financial estimates assumed the listing of cladribine tablets would only displace fingolimod. The PBAC considered that cladribine may replace or displace all PBS listed RRMS treatments (many of which are lower cost) to some extent;
- The financial estimates did not account for costs in Years 3 and 4 from patients who do not persist on therapy due to relapse and switch to other treatments; and
- The assumed cladribine persistence rates were based on a Prospection analysis of Medicare prescription data to determine the persistence rates of fingolimod.

6.8 Further, the PBAC considered that the [redacted] difference in estimated financial impact between the current, March 2018 and November 2017 resubmissions was also indicative of the uncertainty in the estimates.

6.9 The PBAC noted that the sponsor has requested a Special Pricing Arrangement (SPA) and that there was currently a SPA in place for fingolimod. The PBAC noted that SPAs are given effect through a deed made under Section 85E of the *National Health Act 1953* (the Act) between the Minister (or his delegate) and the responsible person. The PBAC further noted that the Minister (or his delegate) has requested advice under section 101(3) of the Act as to whether cladribine meets criteria 1 and 2(a) of the SPA criteria when used for the treatment of RRMS. The PBAC advised in relation to the SPA criteria that:

- Criterion 1, that the medicine treats a significant medical condition was met. The PBAC advised it considered that cladribine generates substantial incremental benefit for patients with RRMS.
- Criterion 2, that the medicine has unique characteristics compared to any alternative therapies was met given the unique dosing regimen of cladribine.

6.10 The PBAC reiterated that a General Schedule (Section 85) listing is appropriate for cladribine.

6.11 The Committee reiterated its previous advice that the pack of one tablet should be listed with a maximum quantity of one pack and one repeat; the pack of four tablets with a maximum quantity of two packs and one repeat; and the pack of six tablets with a maximum quantity of one pack and one repeat. The PBAC also reiterated its previous advice that a statement be included in the proposed PBS restriction to indicate that the prescriber should prescribe the appropriate combination of packs to achieve a dose in accordance with the Product Information.

6.12 The PBAC advised that, under subsection 101(3BA) of the *National Health Act, 1953* cladribine should not be treated as interchangeable on an individual patient basis with any other drugs.

6.13 The PBAC advised that cladribine tablet is not suitable for prescribing by nurse practitioners.

6.14 The PBAC recommended that the Early Supply Rule should not apply.

6.15 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:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
CLADRIBINE				
Tablet 10 mg, 1	*1*	*1*	MAVENCLAD®	Merck
Tablet 10 mg, 4	*2*	*1*		
Tablet 10 mg, 6	*1*	*1*		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Relapsing remitting multiple sclerosis
PBS Indication:	Relapsing remitting multiple sclerosis
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required – Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be diagnosed by *a* neurologist.
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR 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, AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND 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, AND Patient must be ambulatory (without assistance or support).
Prescriber Instructions	Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records. The prescriber should request authority approval for the appropriate combination of packs (1, 4 or 6 tablets) to provide sufficient drug for a treatment week based on the weight of the patient in accordance with the TGA approved Product Information. Separate authority prescriptions may be required where the dose for treatment week 5 is different to the dose for treatment week 1.
Administrative	No increase in the maximum quantity may be authorised. No increase in the maximum number of repeats may be authorised.

Advice:	Special Pricing Arrangements apply.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Relapsing remitting multiple sclerosis
PBS Indication:	Relapsing remitting multiple sclerosis
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required - Emergency ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by *a* neurologist.
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis, AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not show continuing progression of disability while on treatment with this drug, AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Prescriber Instructions	The prescriber should request authority approval for the appropriate combination of packs (1, 4 or 6 tablets) to provide sufficient drug for a treatment week based on the weight of the patient in accordance with the TGA approved Product Information. Separate authority prescriptions may be required where the dose for treatment week 5 is different to the dose for treatment week 1.
Administrative Advice	No increase in the maximum quantity may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Category / Program	*GENERAL – General Schedule (Code GE)*
Prescriber type:	☐*Dental* ☒*Medical Practitioners* ☐*Nurse practitioners* ☐*Optometrists* ☐*Midwives*
Condition:	Relapsing remitting multiple sclerosis
PBS Indication:	Relapsing remitting multiple sclerosis
Treatment phase:	Grandfather treatment
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR

	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; AND Patient must have received treatment with this drug for this condition prior to (listing date); AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition; AND Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the 2 years preceding when this drug was initiated for this condition; AND Patient must be ambulatory (without assistance or support); AND Patient must not show continuing progression of disability while on treatment with this drug; AND Patient must have demonstrated compliance with, and an ability to tolerate this therapy.
Prescriber Instructions	The prescriber should request authority approval for the appropriate combination of packs (1, 4 or 6 tablets) to provide sufficient drug for a treatment week based on the weight of the patient in accordance with the TGA approved Product Information. Separate authority prescriptions may be required where the dose for treatment week 5 is different to the dose for treatment week 1.

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

Merck is delighted that reimbursed access to the unique benefits of Mavenclad (2 courses of oral treatment over 4 years) will now be available for people with RRMS. Merck would like to thank the MS Community for their ongoing support.