7.08 CLADRIBINE
Tablet, 10 mg,
Mavenclad®, Merck Serono Australia Pty Ltd

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 requested the following new listing. 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	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
CLADRIBINE				
Tablet 10 mg,1	*1*	*1*	$[redacted] (for 7 tablets) *DPMQ for different pack sizes are to be determined*	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 initiated ~~and supervised~~ by *a* neurologist~~s.~~

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). ~~Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.~~
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. ~~A grandfathering clause applies.~~

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 ~~initiated and~~ supervised by *a* neurologist~~s~~.
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. ~~A grandfathering clause applies.~~

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.*

2.2 The November 2017 major resubmission requested a DPMQ for ten tablets of cladribine ($[redacted]), but applied the price of seven tablets ($[redacted]) in the cost minimisation and financial analysis, based on the average weight (76.6kg) of patients in an Australian multiple sclerosis longitudinal study receiving cladribine. The Secretariat noted that this created a large potential for wastage and proposed changes to the requested restriction, maximum quantity and number of repeats, which were welcomed by the sponsor in its Pre-Sub-Committee Response and accepted by the PBAC at its November 2017 meeting.

2.3 The minor resubmission requested a DPMQ ($[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]%). The revised DPMQ has accounted for updated administration and handling fees, which occurred

between the time of lodgement for the November 2017 major resubmission and the current minor resubmission. However, the minor resubmission did not propose a DPMQ for each of the three different pack sizes for cladribine.

2.4 The March 2011 major submission requested a DPMQ of $[redacted] for ten tablets of cladribine. This is approximately [redacted]% less per tablet of cladribine compared to the requested price in the minor resubmission. The pre-PBAC response agreed with the minor overview that the per tablet price requested for cladribine in 2011 was [redacted]% lower than the currently proposed price, however argued that this does not take into account the evidence base now available. It claimed that, "in 2011, the extended duration of benefit (of cladribine) was not yet known. The cost of treatment over 2 years at the 2011 price of $[redacted] per tablet would be $[redacted], or $[redacted] on an annual basis. The currently proposed 4-year cost of treatment is $[redacted], or $[redacted] on an annual basis. The cost of treatment with cladribine tablets on an annual basis has therefore decreased by [redacted]% since 2011." The pre-PBAC response also highlighted that these prices do not take into account the Special Pricing Arrangement (SPA) in place for fingolimod, which would also apply to cladribine if cladribine was to be PBS-listed.

2.5 The pre-PBAC response accepted the Secretariat's suggested changes to the proposed restriction.

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

3 Background

Registration Status

3.1 Cladribine (tablet) was approved by the TGA in December 2017 for "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 cladribine on the grounds of several concerns, including:

- Natalizumab was not accepted as the main comparator and therefore the associated cost effectiveness model was not accepted;
- The claim that cladribine was of superior efficacy compared to interferon beta 1a and non-inferior to natalizumab was not accepted;
- 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 be 100% 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.

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

4 Comparator

4.1 The minor resubmission did not change the main comparator nominated in the November 2017 major resubmission. 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 considered it was uncertain whether cladribine was superior over interferon beta 1a in terms of efficacy, however, the Committee considered that cladribine was superior over interferon beta 1a in terms of safety. The PBAC recalled that at its March 2011 consideration of cladribine, the Committee did not accept that cladribine was of non-inferior efficacy to natalizumab. The PBAC noted that this matter remains (paragraph 7.5, November 2017 PBAC meeting 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 (26), health care professionals (10) 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 ability to help a patient retain a "normal life" for longer, low monitoring burden, improvement in disability, ease in administration and relief of MS symptoms other than relapses and progression of disability (sensations, fatigue, social engagement, ability to walk unaided).

5.3 The PBAC noted input received from MS Ireland, MS Research Australia and the Trish Multiple Sclerosis Research Foundation in support of subsidising cladribine through the PBS. The organisations described the impact of MS and treatments for MS on patients' lives, and emphasised the significance of a new effective treatment option, which will allow increased choice for patients. MS Ireland described a survey it conducted on the experiences of MS patients in accessing and taking disease modifying therapies. Based on the results of the survey, MS Ireland reported that patients found injections difficult to manage and administer. It highlighted the benefit of oral administration with cladribine and the shorter treatment course compared to existing oral therapies for MS.

Clinical trials

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

Clinical claim

5.5 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 PBAC meeting PSD).

5.6 The minor resubmission (p4) argued that, "application of the MCID of 1.23 noted in the ocrelizumab public summary document (PSD) (paragraph 6.15, July 2017) to the upper confidence interval (CI) of the indirect estimate of annualised relapse rate for cladribine compared to fingolimod (0.89 [0.67, 1.18]; Table 5, p11, cladribine November 2017 PBAC Meeting PSD), confirms that cladribine is non-inferior to fingolimod using a MCID already accepted by the PBAC".

5.7 A comparison of the key elements of the indirect comparison of ocrelizumab versus fingolimod compared to that of cladribine versus fingolimod is presented below.

Table 1: Comparison of key elements of the evidence presented in the ocrelizumab July 2017 and cladribine November 2017 major submissions.

Submission	***Ocrelizumab July 2017 major***	***Cladribine November 2017 major[a]***
Indirect comparison	*Ocrelizumab vs fingolimod*	*Cladribine vs fingolimod*
Common reference	*Interferon beta-1a/placebo[1]*	*Placebo[2]*
Efficacy outcome		
Annualised relapse rate (rate ratio)	[redacted]	*0.89 (95% CI: 0.67, 1.18)*
Confirmed 3-month disability progression (HR)	[redacted]	*0.78 (95% CI: 0.53, 1.14)[b]*
Confirmed 6-month disability progression (HR)	[redacted]	*0.79 (95% CI:0.49, 1.27)[c]*

CI=confidence interval; HR=hazard ratio
a Clinical data was unchanged in the cladribine March 2018 minor resubmission
*b Calculated from HR = **0.59 (0.43, 0.80)** for cladribine vs. placebo and HR = **0.76 (0.61, 0.95)** for fingolimod vs. placebo, from Tables 2.5.1 (p42) and 2.6.1 (p47) of the cladribine November 2017 commentary.*
*c Calculated from HR = **0.53 (0.36, 0.79)** for cladribine vs. placebo and HR = **0.67 (0.51, 0.87)** for fingolimod vs. placebo, from Tables 2.5.1 (p42) and 2.6.1 (p47) of the cladribine November 2017 commentary*
Source: Ocrelizumab July 2017 PBAC Minutes; Cladribine November 2017 commentary and PBAC Minutes

5.8 Although the nominated non-inferiority margin of 1.23 (ocrelizumab July 2017 submission) was not reached for the key relapse and disability outcomes, [redacted]

Additionally, treatment with ocrelizumab was associated with a statistically significant delay in the time to six-month confirmed disability progression compared to fingolimod. Furthermore, whilst the MCID nominated by the ocrelizumab submission was noted in the PBAC Minutes, the Committee did not explicitly accept it as a criterion to determine non-inferiority between ocrelizumab and fingolimod. Rather, the PBAC's acceptance of the non-inferiority claim for ocrelizumab versus fingolimod was based on the totality of the evidence presented.

5.9 The pre-PBAC response reiterated that there were no statistically significant differences in the indirect comparison between cladribine and fingolimod for the annualised relapse rate and the proportion of patients remaining free from disability progression at 3 and 6 months. The pre-PBAC response also noted that the PSD for ocrelizumab stated that "the ESC commented that these comparisons should be interpreted with caution due to the inherent uncertainty of multi-step indirect comparisons as well as substantial transitivity issues between trials"; and "The ESC noted that, for example, the analysis of disability progression at six months between

[1] The indirect comparison of ocrelizumab vs. fingolimod was a multi-step indirect comparison based on:
- Indirect analysis of ocrelizumab vs. IM interferon beta-1a (OPERA-I, OPERA-II; EVIDENCE, Etemadifar 2006) linked to a meta-analysis of direct (TRANSFORMS) and indirect (BRAVO, MSCRG, FREEDOMS-I, FREEDOMS-II) comparisons of IM interferon beta-1a vs. fingolimod; and
- Three step indirect analysis using SC interferon beta-1a/teriflunomide/placebo as bridging comparators (OPERA-I, OPERA-II, TENERE, TEMSO, TOWER, FREEDOMS-I, FREEDOMS-II)

[2] The indirect comparison between cladribine and fingolimod was based on one trial comparing cladribine to placebo (CLARITY), and two trials comparing fingolimod to placebo (FREEDOMS and FREEDOMS II) and their respective extension studies.

ocrelizumab and fingolimod was based on a three step indirect analysis and included trials spanning 21 years." The pre-PBAC response argued that in comparison, "the indirect evaluation of six-month confirmed disability progression for cladribine and fingolimod did not require a multi-step indirect comparison and compared trials which commenced within one year of each other."

5.10 At the November 2017 meeting, the PBAC did not accept the claim that cladribine is non-inferior to fingolimod in terms of efficacy over four years, which was based on a naïve comparison of point estimates of the extension studies to the three trials. The PBAC 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 PBAC Meeting PSD). The minor resubmission did not address these concerns.

Economic analysis

5.11 At the November 2017 meeting, 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 be [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 (paragraph 7.1, November 2017 PBAC Meeting PSD).

5.12 The comparison of the equi-effective doses proposed by the November 2017 major resubmission and the current minor resubmission is presented below.

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

Cladribine dose	Fingolimod dose	
	November 2017 major resubmission	March 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%)

5.13 The minor resubmission proposed a new equi-effective dose, based on adjusting the fingolimod dose to account for a lower compliance rate (95.48%[3]) for fingolimod over four years. This revised 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. In the November 2017 major resubmission (unchanged in the current

[3] Kappos, L., et al. Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial. *Neurology* 2015; 84(15): 1582-1591

minor resubmission), the base case financial analysis assumed cladribine 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. It is therefore inconsistent to apply the trial-based compliance rate for fingolimod of 95.48% in the calculation of equi-effective doses and Medicare prescription data (with lower compliance rates) as the basis for estimating cladribine usage.

5.14 The pre-PBAC response argued that using the trial based compliance rate for fingolimod is consistent with the preferred approach in the PBAC Guidelines. As an alternative, the pre-PBAC response also proposed to apply a compliance rate of 91.20% for fingolimod, based on the MS DUSC Report 2015 and therefore increase Rebate 1 from [redacted]% (see paragraph 5.16 below) to [redacted]%.

5.15 The PBAC noted that the MS DUSC report simply presented what the assumed treatment compliance for fingolimod was in the teriflunomide submission seeking PBS listing for the treatment of MS; and that this figure (91.20%) was not based on any analysis conducted by DUSC to determine fingolimod persistence rates.

Special pricing arrangement

5.16 The minor resubmission proposed a rebate of [redacted]% to the cost of cladribine to account for a lower compliance rate for fingolimod. The PBAC recalled that in November 2017, it did not accept the clinical claim that cladribine is of non-inferior efficacy to fingolimod over four years. Therefore, the Committee considered that the proposed rebate did not sufficiently address its concern on this issue. The PBAC also noted that, as reflected by the Prospection analysis above, compliance to fingolimod in the PBS setting is likely to be lower than that observed in a clinical trial setting.

5.17 The minor resubmission also proposed a second rebate, of [redacted]% to the cost of cladribine, 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 minor resubmission stated that, "the rebate uses time to first relapse in CLARITY and CLARITY EXTENSION as an appropriate proxy for time to treatment switch. The rebate is based on the price of cladribine tablets. It assumes a simple linear increase in the proportion of patients who experience a relapse, so that the total proportion of patients who switch to another therapy by the end of Year 4 ([redacted]%) is divided by four to give the annualised rate. It is assumed that patients relapse, and therefore switch to another therapy, at the mid-point of each year. The analysis takes into account the fact that patients who relapse in Year 1 have only incurred the cost of treatment courses in Year 1. Patients who relapse in subsequent years have already incurred the full cost of cladribine treatment courses in Years 1 and 2". The calculations are presented below.

Table 3: Summary of the derivation for 'Rebate 2'

	Time of switch (years)	Duration with overlapping costs (years)	Rebate as a % of 4-year cost	Proportion of patients switching during year[b]	Weighted % of 4-year cost overpaid
	A	B	C	D	C x D
Relapse in Yr 1 (cost of treatment courses in Year 1 only have been paid)	0.5	1.5	[redacted]	[redacted]	[redacted]
Relapse in Yr 2	1.5	2.5	[redacted]	[redacted]	[redacted]
Relapse in Yr 3	2.5	1.5	[redacted]	[redacted]	[redacted]
Relapse in Yr 4	3.5	0.5	[redacted]	[redacted]	[redacted]
Overall weighted price adjustment for patients switching to another therapy					[redacted]%

[a] For Year 1 only, duration of overlapping costs is limited to a proportion of 2 years of upfront treatment cost (in subsequent years the full 4 year cladribine cost has already been paid upfront).
[b] Calculated from [redacted]% / 4 = [redacted]%, where [redacted]% of patients who relapse in the 4-year treatment period is derived from 100% - [redacted]% (patients relapse free at the end of Year 4 in CLARITY and CLARITY EXT)
Source: "Rebate 2 switch" worksheet of the workbook submitted with the minor resubmission

5.18 Under usual practice, deeds for Special Pricing Arrangements (SPA) specify a single rebate rather than a two-tiered rebate as proposed by the minor resubmission. Therefore, any deed for an SPA may require the sponsor to propose a consolidated, single rebate.

5.19 The pre-PBAC response clarified that the total rebate proposed, including the increased Rebate 1 (from [redacted]% to [redacted]%), is [redacted]%. The pre-PBAC response emphasised that this rebate is in addition to the SPA that is currently in place for fingolimod, which would also apply to cladribine.

Drug cost/patient/course: $[redacted] (based on treatment in years 1 and 2, and no treatment in years 3 and 4)

5.20 The drug cost per patient per course, 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 of $[redacted], is $[redacted]. This estimate includes the [redacted]% and [redacted]% rebates proposed for the cost of cladribine tablets. This compares to a cost of $115,122 for four years treatment with fingolimod (assuming a DPMQ of $2,207.81 and approximately 52 packs of fingolimod), based on the published price of fingolimod, and assuming 100% compliance with fingolimod.

Estimated PBS usage & financial implications

5.21 The minor resubmission presented revised financial analyses, which reduced the estimated six-year cost to the PBS from more than $100 million in the November 2017 resubmission to $30 - $60 million in the minor resubmission. A comparison of the financial implications to the PBS between the two resubmissions is presented below.

Table 4: Summary of the estimated use and financial implications presented in the November 2017 major resubmission and 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 March 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]
Estimated PBS cost offsets for fingolimod[b] (published price, less copayments)						
November 2017	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
March 2018	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net cost to the PBS						
November 2017	$[redacted]	$[redacted]	$[redacted]	–$[redacted]	$2[redacted]	$[redacted]
March 2018	$[redacted]	$[redacted]	$[redacted]	–$[redacted]	–$[redacted]	$[redacted]

a Assuming 2 scripts per year of treatment as estimated by the resubmissions.
b The minor difference in the estimated PBS cost for fingolimod is due to the change in administration and handling fees in between the lodgement of the two resubmissions. Fingolimod DPMQ = $2,206.17 vs $2,207.81 applied in the November 2017 and March 2018 resubmissions, respectively.

The redacted table shows that at Year 6 the estimated number of patients was less than 10,000, and the March 2018 minor resubmission net cost to the PBS would be $10 - $20 million.

5.22 The minor resubmission argued that due to the dosing regimen for cladribine, the upfront cost of cladribine tablets in Years 4, 5 and 6 cannot be offset within the six-year time horizon specified by the PBAC guidelines, therefore the net financial impact of listing cladribine will never be zero in any given year.

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

6 PBAC Outcome

6.1 The PBAC did not recommend the listing of cladribine for the treatment of relapsing remitting multiple sclerosis (RRMS), on the basis of uncertainty in the non-inferior efficacy claim of cladribine versus fingolimod over two and four years. The PBAC recalled that in November 2017 it 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 noted that the minor resubmission did not provide additional clinical evidence to address its concerns. Therefore, the PBAC again did not accept two years of cladribine treatment versus four years of fingolimod treatment as the basis for the cost-minimisation analysis proposed by the minor resubmission. The PBAC noted that there remained 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 undermines the first principles of a cost minimisation analysis.

6.2 The PBAC noted the consumer comments that patients and clinicians value additional treatment options for multiple sclerosis. The PBAC also noted consumers' perceived cladribine as a medicine with a good safety profile and ease of administration.

6.3 The PBAC noted the minor resubmission's arguments for the use of the MCID used in the ocrelizumab submission for RRMS (July 2017) 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. 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, or uncertainty in the non-inferior safety between cladribine and fingolimod. The PBAC therefore considered that the uncertainty in the non-inferior efficacy claim over two and four years, and non-inferior safety claim between cladribine and fingolimod, remained.

6.4 The PBAC noted that the DPMQ proposed by the minor resubmission was substantially reduced from $[redacted] in the November 2017 resubmission to $[redacted] to the current minor resubmission. However, the PBAC noted that this was predominately 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.

6.5 The PBAC noted that the total financial impact was reduced substantially from more than $100 million to $30 – 60 million over six years. The PBAC noted the minor resubmission's arguments that due to the dosing regimen for cladribine, the upfront costs of cladribine in Years 4, 5 and 6 cannot be offset within the six-year time horizon specified by the PBAC Guidelines. However, the PBAC considered that this scenario may only be reasonable if the non-inferior efficacy claim of cladribine versus fingolimod over four years was accepted. Given that the PBAC did not accept the claim that cladribine is non-inferior to fingolimod in terms of efficacy over four years, it did not accept this as the basis for estimating the equi-effective doses of cladribine and fingolimod, or as the basis for the financial analyses.

6.6 The PBAC recalled that it previously advised that cladribine is not suitable for prescribing by nurse practitioners and that the Early Supply Rule should not apply. The PBAC also advised that cladribine should not be treated as interchangeable on an individual patient basis with any other drugs under Section 101(3BA) of the National Health Act, 1953.

6.7 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

7 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.

8 Sponsor's Comment

Cladribine tablets have proven efficacy and safety, and a low monitoring burden. Their unique dosing regimen provides additional patient and carer benefits. Merck therefore remains intent on working with the PBAC to ensure that this important treatment option becomes available on the PBS for patients with RRMS.