7.02 CLADRIBINE, Tablet 10 mg, Mavenclad®, Merck

1 Purpose of application

1.1 General schedule listing for cladribine tablets for the treatment of relapsing remitting multiple sclerosis (RRMS).

1.2 This is the second submission considered by the PBAC, the first was considered in March 2011.

1.3 The resubmission sought listing based on a cost-minimisation analysis versus fingolimod.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Relapsing remitting multiple sclerosis (RRMS)
Intervention	Cladribine tablets are taken over 4-5 days in Weeks 1 and 5 in each of the first two years of therapy to give a cumulative dose of 3.5mg/kg, followed by observation only for two further years.
Comparator	The main comparator for cladribine is fingolimod 0.5mg administered daily (over four years to match duration of therapeutic effect for cladribine). Fingolimod is a relevant comparator, but not the only comparator.
Outcomes	Annualised relapse rate, proportion of subjects remaining free from relapses, proportion of subjects remaining free from sustained progression of disability (as measured by an Expanded Disability Status Scale [EDSS]).
Clinical claim	Cladribine is non-inferior in terms of effectiveness compared with fingolimod. Cladribine is non-inferior in terms of safety compared with fingolimod. The two agents have different but comparable safety profiles. Whether cladribine is non-inferior in terms of safety and efficacy may require consideration.

Source: Table 1.1.1, p 19 of the resubmission. EDSS = Expanded Disability Status Scale

2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
CLADRIBINE, Tablet 10mg	10	0	$[redacted]	MAVENCLAD®, Merck

Category / Program	Section 85
Condition:	Relapsing remitting multiple sclerosis
PBS Indication:	Multiple sclerosis
Treatment phase:	Initial
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing X Authority Required - Telephone X Authority Required – Emergency X Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be initiated and supervised by neurologists
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 treatment 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.
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	Section 85
Condition:	Relapsing remitting multiple sclerosis
PBS Indication:	Multiple sclerosis
Treatment phase:	Continuing
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing X Authority Required - Telephone X Authority Required – Emergency X Authority Required - Electronic ☐ Streamlined

Treatment criteria:	Must be initiated and supervised by neurologists
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

2.1 The resubmission based the cladribine requested price on a cost-minimisation analysis versus the published price of fingolimod. The resubmission noted that it is expected that the effective price of fingolimod is lower than its published price.

2.2 In the March 2011 submission, the requested ex-manufacturer price for ten 10mg tablets (consistent with current maximum quantity) was $[redacted] compared to $[redacted] in the resubmission.

2.3 Although ten tablets constituted the maximum quantity requested per script, the price derived from the cost-minimisation analysis and applied in the financial estimates was based on an average of seven tablets per script based on the estimated average weight (76.6kg) of patients in an Australian MS longitudinal study receiving cladribine.

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

3 Background

Registration status

3.1 Cladribine was approved for the treatment of RRMS by the TGA in September 2010 for the following indication:

- the treatment of relapsing-remitting multiple sclerosis (RRMS) for a maximum duration of two years.

3.2 The PBAC noted that an application to the European Medicines Agency (EMA) was made for approval of oral cladribine tablets for the treatment of RRMS in 2009, which was rejected in 2010, and an appeal was denied in 2011. The FDA rejected a similar application in 2011. The concerns of the European Committee for Medicinal Products for Human Use (CHMP) leading to rejection were:

- The disproportionate numbers of patients developing malignancies in the cladribine treatment arms of clinical studies, compared with placebo;
- The risk of developing Grade 3 or 4 lymphopenia, which was thought to be associated with an increased risk of infection. The prolonged recovery time from lymphopenia in some patients was thought to expose these patients to risks

- The subsequently proposed patient population (patients with high disease activity) consisted of what the committee considered to be too small a proportion of the patients who had been studied in the clinical development programme;
- In the above context, it was considered that the optimal dose and the revised treatment regimen had not been adequately investigated in the target patient population.

3.3 Cladribine was voluntarily withdrawn from the Australian Market in December 2011.

3.4 In 2015 and 2016, new analyses of the clinical and safety data for cladribine from the ongoing CLARITY extension, ORACLE-MS and ONWARD trials were performed. The PBAC noted that in June 2017, the CHMP recommended the approval of cladribine in the European Union, however, for the indication of, "Treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features", which is narrower than the TGA indication and PBS population sought by the resubmission.

3.5 In Australia, a minor Category 1 (C) (Product Information update) was submitted to the TGA in January 2017. Final approval is anticipated in January 2018. The PBAC noted the TGA Delegate's Overview (17 October 2017) to recommend amendment of cladribine's indication to, "(cladribine) is indicated for the treatment of relapsing-remitting multiple sclerosis 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."

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

Previous PBAC consideration

3.6 In its consideration of the previous submission in March 2011, the PBAC noted several matters of concern. However, most related to a comparison versus natalizumab and the cost-effectiveness model presented at the time. Since the PBAC's first consideration of cladribine in 2011, the RRMS landscape has evolved substantially. Table 2 summarises the remaining relevant, key matters of concerns and how they were addressed by the resubmission.

Table 2: Summary of matters of concern from the cladribine March 2011 Public Summary Document (PSD)

Matter of concern	How the resubmission addresses it
Uncertainty of usefulness of cladribine given treatment is limited to two years due to safety concerns (p6).	The resubmission presented several years of follow-up safety data and requested an amendment to the TGA PI to remove the two year restriction for treatment.
The PBAC did not accept natalizumab as the main comparator.	The resubmission nominated fingolimod as the main comparator.
The PBAC did not accept the claim that cladribine was of superior efficacy over interferon beta 1a and was non-inferior to natalizumab.	Not addressed by the resubmission.

4 Population and disease

4.1 Multiple sclerosis (MS) is a central nervous system disease associated with the loss of the myelin sheath, a fatty material that insulates nerves. MS disrupts the ability to conduct electrical impulses to and from the brain. Once MS presents, the condition is permanent and degenerative. Relapsing remitting MS (RRMS) is characterised by unpredictable relapses during which new symptoms appear or existing symptoms become more severe, followed by periods of relative clinical stability. Approximately 85% of MS patients are initially diagnosed with RRMS. Over time, there is less recovery from relapses and patients accumulate underlying disability. Most RRMS patients progress to secondary progressive MS (SPMS), characterised by ongoing deterioration in function with interspersed relapses.

4.2 In Australia, cladribine (tablet) is indicated for RRMS regardless of line of treatment.

5 Comparator

5.1 The resubmission nominated fingolimod as the main comparator. The PBAC accepted fingolimod as the appropriate main comparator, however, considered that cladribine was likely to replace or displace all PBS listed RRMS treatments.

5.2 The resubmission included informal comparisons of key trial evidence versus dimethyl fumarate, daclizumab, alemtuzumab and ocrelizumab. No conclusions regarding comparative efficacy or safety could be made from these comparisons.

5.3 Interferon beta-1b has the lowest cost (as the result of a statutory price reduction), whilst the remaining ABCR/BRACE therapies, dimethyl fumarate and teriflunomide were all listed on a cost-minimisation basis with interferon beta. Fingolimod and natalizumab were listed on a cost-effectiveness basis against interferon beta. Alemtuzumab was listed on a cost-minimisation basis with fingolimod and natalizumab. Fingolimod and alemtuzumab have Special Pricing Arrangements. Ocrelizumab received a positive recommendation for the treatment of RRMS at the July 2017 PBAC meeting on a cost-minimisation basis with fingolimod.

5.4 Daclizumab was recommended for listing in November 2016 on the basis that the presented direct comparison of IM interferon β-1a and indirect comparisons of daclizumab and fingolimod supported a conclusion that daclizumab is likely to be superior to interferon beta-1a and may be non-inferior to fingolimod with regard to comparative efficacy, but may be inferior to interferon beta-1a with regard to comparative safety. The PBAC recommended that although the superior comparative

efficacy over IFN β-1a justified the cost of daclizumab per patient per course being higher than IFN β-1a, there were insufficient grounds for the cost per patient per course to be as high as fingolimod because of the substantial uncertainty about the indirect comparisons with fingolimod. Daclizumab has a Special Pricing Arrangement.

5.5 If treatment with cladribine is substantially more costly than an alternative therapy or alternative therapies, the PBAC 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 *(National Health Act 1953,* Section 101(3B)). The alternative therapies in this case may include interferon beta, dimethyl fumarate, teriflunomide and daclizumab.

5.6 At the March 2011 PBAC meeting, in its consideration of the indirect comparison of cladribine versus interferon beta, the lowest cost comparator, presented in the previous submission, the PBAC noted that cladribine may be more effective than interferon beta in terms of reducing the annualised relapse rate, but given the differences in the annualised relapse rates reported for the placebo arms in the trials, it was uncertain whether these trials and their populations were sufficiently comparable to inform a meaningful indirect comparison. The PBAC therefore considered that there was uncertainty about a claim of superiority of cladribine over interferon beta 1a (Cladribine, March 2011 PSD, p6).

5.7 The PBAC also recalled that the March 2011 submission claimed cladribine was non-inferior in terms of comparative effectiveness and with a different safety profile to natalizumab , based on an indirect comparison of cladribine versus natalizumab, with placebo as the common reference. The PBAC recalled that, "Concerning the comparison with natalizumab, the PBAC did not accept the claim of non-inferiority based on the non-significant differences for the indirect comparison. The reported annualised relapse rates amongst the placebo arms in each of the trials differ, which suggests that the populations in the trials are not exchangeable and therefore could indicate that the conduct of such an indirect comparison is not appropriate. Based on the entry criteria for the trials, the likelihood of relapse may be higher in the natalizumab trial (AFFIRM) and (in conjunction with the definition of relapse being more stringent in CLARITY) natalizumab may be likely to show a greater improvement in the primary outcome of annualised relapse rate, than is cladribine." (March 2011 Cladribine PSD).

5.8 The Pre-Sub-Committee Response (PSCR) (p1) acknowledged that there is the potential for therapies other than fingolimod to also be replaced by cladribine. However, the PSCR argued that due to the dominance of fingolimod's market share, and the non-inferior efficacy and different but non-inferior safety of cladribine compared to fingolimod, that substitution of fingolimod will predominate. The PSCR further argued that, "The non-inferiority of cladribine to fingolimod, which has already been deemed by the PBAC to be more effective than IFNB, means that it is entirely appropriate for the cost of cladribine to be higher than that of the cheapest alternatives on the PBS". The ESC noted however, that the PBAC considered there was uncertainty regarding whether cladribine was superior over interferon beta 1a at the March 2011 PBAC meeting (refer to paragraph 5.6). The ESC further noted that dimethyl fumarate may be considered by clinicians to be an alternative therapy to

fingolimod, and it is therefore also likely to be replaced in practice. The ESC also considered that due to the convenience of the cladribine treatment regimen, it is possible that some patients on other RRMS therapies may switch to cladribine for increased compliance.

5.9 The pre-PBAC response (p2-3) maintained that fingolimod was the appropriate main clinical and economic comparator for cladribine.

5.10 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 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.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the CLARITY and CLARITY EXT trial design and endpoints; how cladribine will be used in practice; safety data regarding the risk of malignancy; and other matters in response to the Committee's questions. The PBAC noted the clinician's view that cladribine was not associated with a higher risk of malignancy; that treatment switching is common in clinical practice; and that cladribine is viewed as a higher efficacy medicine among medicines available to treat RRMS. The clinician explained that in Europe the clinical algorithm for medicines for RRMS are based on lines of therapy, whereas this is not the case in Australia. The clinician expressed the view that cladribine should therefore not be restricted to patient subgroups with highly active disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from health professionals (4), individuals (5), and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with cladribine, including its efficacy, safety profile, and ease of administration as an oral medicine with infrequent dosing and long duration of effect.

6.3 The PBAC noted input received from MS Australia and MS Research Australia in support of subsidising cladribine through the PBS. The organisations described the impact of MS on patients' lives and that of their families, and highlighted the significance of a new effective treatment option, which will allow increased choice for patients and clinicians. MS Australia also provided various testimonials from patients who have been prescribed cladribine.

Clinical trials

6.4 The indirect comparison between cladribine and fingolimod was based on one trial comparing cladribine to placebo (CLARITY; N=1,326), and two trials comparing

fingolimod to placebo (FREEDOMS; N=1,272 and FREEDOMS II; N=1,083) and their respective extension studies.

6.5 Details of the trials presented in the submission are provided in Table 3. The reported citations relate to the primary publications of the trials and citations relating to conference abstracts (except for the two abstracts describing the FREEDOMS II extension) have been excluded.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
CLARITY	CLARITY CSR report.	18 May 2010
	Cook S et al. (2009) "Safety of Cladribine Tablets in the Treatment of Relapsing-Remitting Multiple Sclerosis (RRMS): Results from the CLARITY Study, a 96-week, Phase III, Double-blind, Placebo-Controlled Trial."	Journal of Neurology 2009; 259(Suppl. 2):S128 ;360
	De Stefano, N., et al. "Cladribine effect on brain volume loss and its correlation with disability progression in patients with relapsing multiple sclerosis."	Multiple Sclerosis 2016; 22: 216-217.
	Giovannoni, G., et al. "A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis."	N Eng J Med 2010; 362(5): 416-426
CLARITY extension	CLARITY EXT CSR report	22 April 2016
	Giovannoni, G., et al. (2016). "Benefits of cladribine tablets on the proportion of patients with multiple sclerosis free from clinical and radiological indicators of disease activity in the CLARITY EXTENSION study."	Multiple Sclerosis 22: 300-301
Pooled data for Cladribine	Giovannoni, G., et al. "Benefits of cladribine tablets on magnetic resonance imaging (MRI) outcomes in patients with multiple sclerosis: Analysis of pooled double-blind data from the CLARITY and ONWARD studies."	Multiple Sclerosis 2016; 22: 304
	Giovannoni, G., et al. "Durable efficacy of cladribine tablets in patients with multiple sclerosis: Analysis of relapse rates and relapse-free patients in the CLARITY and CLARITY Extension studies."	Multiple Sclerosis 2016; 22: 48-49.
	Soelberg-Sorensen, P., et al. "Absolute lymphocyte count recovery in patients with relapsing-remitting multiple sclerosis (RRMS) treated with cladribine tablets 3.5 mg/kg in CLARITY and CLARITY Extension."	Neurology 2017; 88(16)
FREEDOMS	Calabresi, P. A., et al. "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 2014; 13(6): 545-556.
	Kappos, L., et al. "A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis."	New England Journal of Medicine 2010; 362(5): 387-401.
FREEDOMS II	Calabresi P et al., "Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis (RRMS): Results from an additional 24-month double-blind, placebo-controlled study (freedoms II study)."	Neurology 2012; 79(11): e90-e91
	Calabresi PA et al., "Efficacy and safety of fingolimod versus placebo: Primary outcomes from the phase 3 FREEDOMS II study in patients with relapsing-remitting multiple sclerosis."	Multiple sclerosis: 2012; 18 (4) Suppl. 1; 205-6
	Calabresi, P. A., et al. "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 2014 13(6): 545-556
FREEDOMS extension	Kappos, L., et al. Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial.	Neurology 2015; 84(15): 1582-1591
FREEDOMS II extension	Vollmer T et al., (2013) "Long-term safety of fingolimod in patients with relapsing-remitting multiple sclerosis: Results from phase 3 freedoms II extension study" YR: 2013 VL: 80	Unidentified congress 2013 (abstract)

Trial ID	Protocol title/ Publication title	Publication citation
	Cree BAC et al,. Long-term effects of fingolimod on no evidence of disease activity (NEDA) by year of treatment".	MENACTRIMS Congress 2016; 22 (6) (abstract)
Meta-analyses of direct randomised trials		
Pooled FREEDOMS and FREEDOMS II	Agius M et al., "Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom."	CNS neuroscience & therapeutics 2014; 20(5)
	Bergvall N et al., "Effects of fingolimod on disability progression in patients with disability as measured by edss at baseline: Post-HOC analyses of freedoms I and II."	Neurology 2013; 80
	Sfikas et al. ": Effect of fingolimod in patients with no disability as measured by EDSS at baseline: Post-Hoc analyses of freedoms I and II."	Neurology 2013; 80(1)

Source: Table 2.2.2 p59-68 of the resubmission

6.6 The CLARITY and FREEDOMS trials have been previously considered by the PBAC (Cladribine, March 2011) and (Fingolimod, March 2011), respectively. The FREEDOMS II trial has been considered by the PBAC in the context of comparisons versus fingolimod (alemtuzumab July 2014, daclizumab November 2016). In contrast to the March 2011 submission, the resubmission presented data from the CLARITY extension trial as well as the extension trials for fingolimod.

6.7 The key features of the direct randomised trials and their extension studies are summarised in Table 4.

Table 4: Key features of the included evidence cladribine versus fingolimod – indirect comparison

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes
Cladribine versus placebo					
CLARITY	870*	R, DB 96 weeks	Low	RRMS	ARR, % remaining relapse free, 3-month disability progression
Fingolimod versus placebo					
FREEDOMS	843*	R, DB 96 weeks	Low	RRMS	ARR, % remaining relapse free, 3-month disability progression, 6 month disability progression
FREEDOMS II	713*	R, DB 96 weeks	Low		
Meta-analysis	NA	Pooled analysis of FREEDOMS and FREEDOMS II			
Trial extensions					
CLARITY ext	284**	R, DB	Unclear	RRMS	ARR, % remaining relapse free, 3-month disability progression, 6 month disability progression
FREEDOMS ext	486	R, DB	Unclear		
FREEDOMS II ext	632	Trial design not reported,	Unclear		

ARR=annualised relapse rate; DB=double blind; MC=multi-centre; NA = not applicable OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.

Source: compiled during the evaluation

* N based on total randomised to the relevant active treatment arm (3.5mg/kg cladribine and 0.5mg fingolimod) plus placebo only

** based only on relevant arms of extension study (cladribine 3.5mg/kg to placebo arm and cladribine 3.5mg/kg continued arm)

6.8 The resubmission stated that CLARITY was powered to detect a meaningful 25% relative reduction in the annualised relapse rate (ARR) when comparing each of the cladribine dose groups to the placebo group, but no minimal clinically important

difference (MCID) was reported for CLARITY or for any of the trials included in the resubmission.

6.9 The resubmission further noted that there was no universally accepted MCID in the treatment of RRMS, and stated that a review of Public Summary Documents for treatments used in RRMS revealed no MCID either proposed or validated by the PBAC. An independent review of previous PBAC considerations similarly did not identify an accepted MCID. However, in its consideration of daclizumab, the PBAC noted 'that a non-inferiority margin was not proposed in the submission and that non-inferiority was claimed based on lack of a statistically significant difference. The PBAC considered this approach was not robust, especially given the wide 95% confidence limits [RR=0.95 (95% CI: 0.63, 1.43)) for the indirect comparisons' (Daclizumab PSD, November 2016).

6.10 The resubmission adopted a statistical approach to selecting an MCID (Massacessi, 2013, 2014). This method defined the MCID as 50% of the excess to 1.0 of the relapse ratio for fingolimod compared to placebo. For example, the ARR in FREEDOMS was 0.40 for placebo and 0.18 for fingolimod. The rate ratio was 2.17 (1/0.46), the excess to 1.0 was 1.17 and 50% of this difference gave the MCID of 1.59. The resubmission noted that the more strict MCID for fingolimod was 1.46, (the MCID derived from the FREEDOMS II trial), and provided a narrower margin within which a product could be said to demonstrate non-inferiority.

6.11 The resubmission did not provide any explanation about how the Massacessi (2013, 2014) approach was validated. There was no statistical or clinical explanation for why the MCID was defined as 50% of the excess of 1.0 of the relapse ratio. The resubmission cited a presentation and a publication, which did not adequately justify this approach.

6.12 The PSCR (p1) stated that in order to confirm the MCID of 1.46 the sponsor attempted to define the MCID by applying distribution based methods to data from CLARITY as described by Copay 2007. Of these methods, the one found suitable on effect size, defined as the mean change between placebo and treatment relative to the placebo standard deviation. The ARR in CLARITY was 0.33 for placebo and 0.14 for cladribine 3.5mg/kg. The estimated effect size was 0.33-0.13 /√(0.33) equal to 0.33. The PSCR stated that this surpasses the small effect size, which by convention is considered to be 0.2, leading to a threshold on the treatment effect of ARR of 0.2151. This corresponds to an effect of 1.53 (0.33 / 0.2151) when expressed as an ARR ratio. The PSCR considered that the consistency of this estimate with that presented in the resubmission confirms 1.46 as a reasonable MCID. The PBAC considered that the method of calculating the MCID was not adequately justified, nor could it replicate the calculations.

Comparative effectiveness

6.13 The results of the direct (cladribine and fingolimod versus placebo) and indirect (cladribine versus fingolimod) comparisons are presented in Table 5.

Table 5: Results of the indirect comparison

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 2.6.8, p185 of the 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

6.14 A statistically significant difference favouring cladribine was observed in the direct comparison of cladribine 3.5mg/kg taken over 4-5 days in Weeks 1 and 5 of Years 1 and 2 versus placebo over 96 weeks with respect to the:

- annualised relapse rate;
- proportion remaining relapse-free; and
- proportion of patients free from confirmed disability progression at 3 months (by the post-hoc analysis presented by the resubmission and by the ITT analyses conducted during the evaluation) and at 6 months.

6.15 A statistically significant difference favouring fingolimod was observed in the direct comparison of fingolimod 0.5mg/day versus placebo over 96 weeks with respect to the:

- annualised relapse rate,
- proportion remaining relapse-free and;
- proportion of patients free from confirmed disability progression at 3 months (in FREEDOMS but not FREEDOMS II) and 6 months (in FREEDOMS but not FREEDOMS II).

6.16 No statistically significant differences were observed in the indirect comparison of cladribine 3.5mg/kg taken over 4-5 days in Weeks 1 and 5 of Years 1 and 2 versus fingolimod 0.5mg/day over 96 weeks with respect to the:

- annualised relapse rate;
- proportion remaining relapse-free; and
- proportion of patients free from confirmed disability progression at 3 months (by the post-hoc analysis presented by the resubmission and by the ITT analyses conducted during the evaluation) and 6 months.

6.17 There was a non-significant trend for cladribine to have fewer patients remaining relapse free.

6.18 The resubmission considered that the lack of statistical significance in the indirect comparisons across annualised relapse rate, proportion of patients remaining free from relapse, and proportion of patients remaining free of 3 or 6 month disability progression, as well as meeting the non-inferiority threshold for ARR of 1.46 (as described by Massacessi 2013, 2014) supported a claim of non-inferiority.

6.19 In addition to concerns regarding the MCID, several differences existed between CLARITY and the fingolimod trials, which may have affected the results of the indirect comparison:

- Baseline prior use of disease modifying drugs (DMDs) across the trials (lower in CLARITY compared with the fingolimod trials). CLARITY also had lower discontinuation rates than the fingolimod trials (this may have reflected the difference in dosing regimens).
- Definitions for relapse and progression across the trials. This may explain the differences in the rates of relapse and progression reported in the placebo arms of the cladribine and fingolimod trials.

  It was unclear whether this biased results, and if so, in what direction this bias would have occurred.

6.20 Although cladribine satisfied non-inferiority to fingolimod according to a MCID of 1.46 for the relapse ratio nominated by the resubmission, as noted above, the PBAC considered that the method of calculating the MCID was not adequately justified. The PBAC noted that the confidence intervals were narrower than those reported for the comparison of daclizumab versus fingolimod (RR=0.95; 95% CI: 0.63, 1.43), however, and consistent with the PBAC's findings for daclizumab, the Committee considered the possibility that cladribine is inferior to fingolimod could not be excluded.

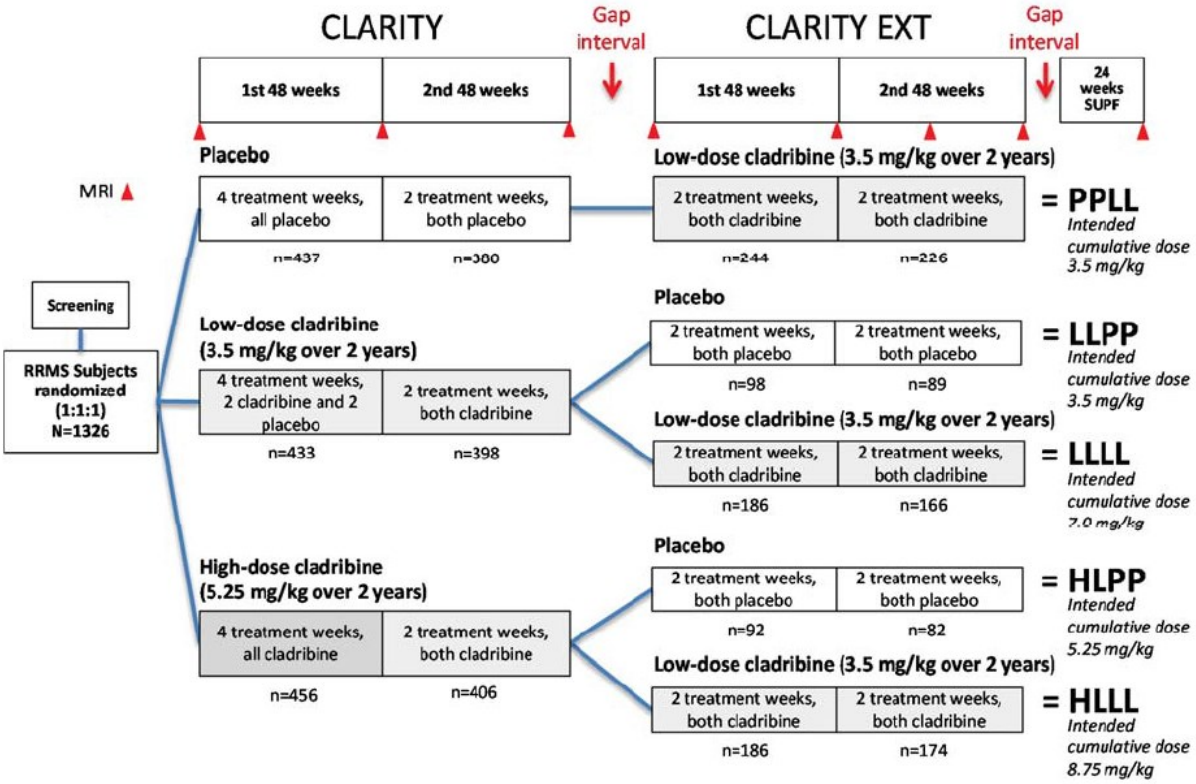
6.21 The resubmission presented results of the CLARITY extension study to support a claim that the therapeutic effect of two years of cladribine treatment was maintained with no treatment over the subsequent two years (patients originally randomised to cladribine 3.5mg/kg in the CLARITY trial who were re-randomised to placebo during the extension) compared with continued treatment (patients originally randomised to cladribine 3.5mg/kg who were re-randomised to continue this treatment during the extension). The claim was based on the lack of statistically significant differences in multiple endpoints (ARR, proportion of patents remaining relapse-free and proportion of patients remaining disability progression-free).

6.22 The proportion of patients remaining relapse-free in the CLARITY extension indicated a sustained improvement in all randomised groups compared to patients initially randomised to placebo and subsequently administered cladribine 3.5mg/kg in the extension. It is also notable that while not statistically significantly different, sustained improvement was greater among those randomised to cladribine in CLARITY continuing cladribine 3.5mg/kg through the CLARITY extension compared with those re-randomised to placebo. This needs to be interpreted with caution considering that the CLARITY extension was not powered to detect differences in efficacy outcomes.

6.23 To support a claim of non-inferior efficacy to fingolimod over a four-year treatment duration the resubmission presented non-statistical comparisons of efficacy endpoints in the CLARITY and fingolimod extension studies. There were some similarities in endpoints, but as a statistical comparison was not possible, inferiority to fingolimod could not be excluded. The PBAC considered that the resubmission provided insufficient evidence to support the claim of durability of effect, to demonstrate that two years of cladribine treatment was comparable to four years of fingolimod treatment.

6.24 The ESC noted the randomisation and patient flow from the CLARITY trial to the CLARITY extension study, as presented below.

Figure 1: Subject randomisation in CLARITY and CLARITY EXT



Source: p7, CLARITY EXT CSR provided with the submission

6.25 The ESC noted that of those randomised to low dose (3.5mg/kg) cladribine in the CLARITY trial, only 71% (284/398) of subjects entered the extension study. Therefore, the ESC was concerned that the trial population for CLARITY and CLARITY EXT are not comparable. For example, the overall annualized relapse rate for the CLARITY treatment arm was 0.14, but the Low-dose CLARITY subgroup that was randomized to the Low dose (LLLL) and placebo (LLPP) arms of CLARITY EXT, had annualized relapse rates of 0.12 and 0.10 respectively in the CLARITY study itself. Thus the population randomized to the LLLL and LLPP arms may represent a disease population which has less severe disease than the original CLARITY population, and the proposed 'sustained improvement' may represent the natural history of a group with less severe disease, instead of 'sustained improvement'. The ESC considered that there was insufficient evidence to support the claim that cladribine administered in the first two years of a four year period, is non-inferior to fingolimod administered throughout a four year period, in terms of efficacy or safety.

6.26 The pre-PBAC response (p1-2) argued that the 'sustained improvement' in CLARITY EXT does not represent a population with less severe disease. It stated that the differences in annualised relapse rates mentioned by the ESC represent a maximum difference of four relapses per 100 patient-years. The pre-PBAC response compared this to the difference seen between patients treated with fingolimod in FREEDOMS (ARR 0.18) and those receiving ongoing treatment with fingolimod in FREEDOMS EXT (0.20) as similar. It argued that these differences reflect re-randomisation and are not clinically meaningful. The pre-PBAC response also argued that cladribine has demonstrated sustained improvement in patients with high disease activity (HDA) as defined by ≥1 relapse in the previous year while on DMD therapy and ≥1 T1Gd+ lesion

or 9 T2 lesions OR ≥2 relapses in the previous year (regardless of previous treatment status). The pre-PBAC response claimed that approximately 70% of cladribine patients and 60% of fingolimod patients remain relapse-free at four years.

6.27 The PBAC agreed with the ESC's concerns that the trial population for CLARITY and CLARITY EXT may not be comparable. The PBAC considered that a naïve comparison of point estimates of the cladribine and fingolimod extension studies did not provide sufficient evidence to demonstrate that two years of cladribine treatment was comparable to four years of fingolimod treatment.

6.28 The pre-PBAC response (p1) maintained that the clinical evidence justifies the four-year treatment regimen for cladribine tablets. The pre-PBAC response argued that the TGA Delegate's Overview (p9) confirms the proposed treatment regimen for cladribine: "The annualised relapse rate in these patients was similar to the annualised relapse rate in the CLARITY study, strongly suggesting continued benefit up to 6 years after commencing treatment with cladribine. The risk of disability progression over the 96 weeks of the CLARITY study for patients given 3.5 mg cladribine was 33%. Disability progression occurred in 27.6% over the course of the extension study, again indicating sustained benefit from cladribine given only in the CLARITY study. These results strongly support continuing benefit from the current dose regimen." (p9, Delegate's Overview).

6.29 The PBAC considered that in clinical practice, patients who complete the two treatment courses of cladribine in Years 1 and 2 but progress in Years 3 and 4 are highly likely to be prescribed other therapies for RRMS. Furthermore, the PBAC considered that in practice, not all patients who commence Year 1 of cladribine treatment may continue in Year 2. As such, the PBAC considered that it was not appropriate to assume that two years of treatment with cladribine was equal to four years of treatment with fingolimod.

Comparative harms

6.30 The PBAC has previously noted that cladribine 3.5mg/kg was generally well tolerated and that only slightly more patients in the cladribine group of the CLARITY trial reported an adverse event (AE) (80.7% v 73.3%) or a serious adverse event (SAE) (8.4% v 6.4%), and demonstrated a low rate of discontinuations due to AEs (3.5% v 2.1%) compared with placebo. Cladribine was associated with more cases of cancer than placebo (6 v 0) (Cladribine March 2011 PSD).

6.31 The resubmission presented results of a meta-analysis of malignancy rates in the cladribine trials and concluded that the increase in cancers in comparison to placebo in the CLARITY trial was a result of uniquely low cancer rates in the placebo arm. The ESC considered that the resubmission's explanation of low placebo cancer rates was inadequate to justify the increase in cancers in patients on cladribine. The ESC considered that given patients were randomised to active and placebo arms, that the low cancer rates in the placebo arm should reflect the underlying population risk in the trial population. The ESC therefore considered that the resubmission's argument would imply that the randomisation was not successful.

6.32 The resubmission presented a comparison of adverse events between cladribine and fingolimod with no statistical analysis (e.g. risk difference, relative risk). There were

substantial variations in the frequency of adverse events in the placebo arms of the cladribine and fingolimod trials, with adverse events being lower in the placebo arm of the CLARITY trial. Therefore, a statistical analysis of safety without adjustments may not be informative.

6.33 The resubmission stated that cladribine has a different but comparable safety profile to fingolimod. While the safety comparison did not demonstrate non-inferiority in terms of safety, there were similarly no strong indicators of inferiority. The evaluation considered that overall, it was difficult to determine comparative safety amongst the two treatments.

Interpretation of clinical evidence

6.34 The resubmission claimed that cladribine was non-inferior in terms of effectiveness compared with fingolimod over both a two year and a four year treatment period. However, due to their different mechanisms of action, cladribine tablets are administered over 4-5 days in Weeks 1 and 5 of the first two years of therapy only, followed by observation only in the following two years, whereas fingolimod must be administered on an ongoing daily basis.

6.35 The PBAC considered there was uncertainty in the claim that cladribine is non-inferior to fingolimod in terms of efficacy over two years, as the Committee considered that the method of calculating the MCID was not adequately justified. The PBAC considered that the claim of non-inferior comparative effectiveness of two years of cladribine treatment versus four years of fingolimod treatment was not adequately supported by the data.

6.36 The resubmission also claimed that cladribine was non-inferior in terms of safety compared with fingolimod, and that the two agents had different but comparable safety profiles. The PBAC considered that the claim of non-inferior comparative safety of two years of cladribine treatment versus four years of fingolimod treatment was not adequately supported by the data.

Economic analysis

6.37 The resubmission presented a cost minimisation analysis based on a claim of non-inferiority to fingolimod over a four-year time horizon. Table 6 summarises the components of the cost-minimisation analysis.

Table 6: Summary of the cost minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Cladribine is assumed to have non-inferior effectiveness to fingolimod over two years based on an indirect comparison. Cladribine treatment for two years followed by two years of observation is assumed to have non-inferior effectiveness to fingolimod based on a non-statistical comparison of trial extensions. .
Therapeutic claim: safety	Cladribine is assumed to have a different but comparable safety profile to fingolimod based on non-statistical comparisons of trial adverse event data.
Evidence base	CLARITY, CLARITY ext, FREEDOMS, FREEDOMS II, FREEDOMS ext, FREEDOMS II ext.
Equi-effective doses	280 mg cladribine ≡ 730 mg fingolimod over a four-year treatment horizon
Direct medicine costs	Equivalent cost of cladribine vs fingolimod over a four-year period. Costs of cladribine are substantially higher than fingolimod over shorter periods.
Other costs or cost offsets	Monitoring costs were included.

Source: Table 3.1.1, p220 of the resubmission
ext = extension.

6.38 The equi-effective doses are estimated over a four-year treatment horizon as:

280mg (28 tablets; assuming average weight of 76.6kg) cladribine ≡
730mg (365 days x four years x 0.5mg/day) fingolimod

These are based on the fingolimod TGA approved dose and the cladribine proposed treatment regimen. The equi-effective doses were generally consistent with the clinical trials. The one main exception was the use of Australian data to derive an average weight of 76.6kg versus the CLARITY average of 69kg. This approach was more conservative and appropriate.

6.39 The resubmission did not test different average weights or distributions of patients requiring different numbers of tablets in the cost-minimisation analysis. The resubmission noted seven tablets would meet the dosing requirements of 80% of patients in each treatment week (consistent with the equi-effective dose).

6.40 The resubmission proposed a maximum quantity (MQ) of ten tablets, rather than a quantity based on the weight of the patient up to a maximum of ten tablets. This MQ creates a large potential for wastage with significant financial implications for government as well as a quality use of medicine (QUM) issue. The evaluation considered that former of these issues could be addressed in one of two ways: (a) by basing the cost-minimised price on the MQ of ten tablets; or (b) by requiring the prescriber to prescribe the appropriate combination of the listed packs (one, four and six tablets) based on the weight of the patient. The second of these methods is preferred by the Secretariat as it also addresses the QUM issue. The PSCR (p3-4) stated that the sponsor welcomed the Secretariat proposed changes to the requested PBS restriction and MQ.

6.41 The resubmission additionally included costs for monitoring for cladribine (full blood count and a consultation) and fingolimod (two consultations, a same day hospital admission for required cardiac monitoring, and overnight hospitalisation for 1.7% of patients who have cardiac abnormalities). Fingolimod was estimated to have a greater monitoring burden than cladribine. Relative to the drug acquisition costs of either treatment over four years, the monitoring burden of both drugs was minor.

6.42 The evaluation considered that the greatest concern regarding the approach to the cost-minimisation analysis was the selection of a four-year treatment horizon. Aside from the clinical concerns on whether an efficacy claim of non-inferiority over four years was adequately supported, it was unreasonable to assume that [redacted]% of patients would remain on cladribine or fingolimod for four years (or more importantly, that no subsequent DMDs would be used in the four year period).

6.43 Data provided from MSBase noted that for Australian patients treated with cladribine, 67% (N=70) reported using a subsequent DMD before four years (and indicated a median time to subsequent DMD use of 1.2 years after the first year of cladribine treatment). Additionally, the financial estimates provided in the resubmission demonstrate that when [redacted]% persistence is not assumed, net financial implications to the PBS are not cost neutral. As such, the price estimated in the cost-minimisation analysis presented in the resubmission was based on inappropriate assumptions.

6.44 The evaluation considered that a time horizon of two years appeared to be more consistent with the MSBase data. The PSCR (p3) disagreed with the evaluation's consideration that a two year time horizon for the cost-minimisation was more consistent with the MSBase Australian utilisation data. The PSCR noted that the patients in the MSBase registry only received cladribine for one year which was not consistent with the TGA approved dosage, and that initiation of another DMD was not necessarily driven by clinical or MRI outcomes.

6.45 The pre-PBAC response (p4) agreed that it is implausible that all patients would persist with either cladribine or fingolimod over four years. It proposed that any uncertainty in this regard could be managed during pricing negotiations and/or the development of a mutually acceptable Risk Share Agreement (RSA). The PBAC considered that it was most appropriate for this issue to be dealt with in the cost-minimisation analysis, particularly in view of the administrative burden of tracking individual patient's treatment histories through an RSA.

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

6.46 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 compares with a cost of $114,806.12for fingolimod (assuming 13 packs per year for four years at a DPMQ of $2,207.81 and 100% compliance), based on published prices.

Estimated PBS usage & financial implications

6.47 This submission was not considered by DUSC.

6.48 The resubmission used a market share approach to estimate the financial impact of listing cladribine, based on utilisation data of oral agents, fingolimod, teriflunomide

[1] The drug cost per patient per course, based on the maximum quantity of ten tablets for the cladribine PBS listing as originally requested in the submission, and a DPMQ of $[redacted], is $[redacted]. The PSCR (p3-4) welcomed the Secretariat's suggestions to amend the proposed PBS listing to minimise issues with wastage and quality use of medicines. Therefore, the drug cost/patient/course in this Public Summary Document has been revised to reflect an average of seven tablets per patient, and to be consistent with the quantity of tablets that was applied in the cost minimisation analysis.

and dimethyl fumarate (DMF). Although a market share approach was considered appropriate, limiting the market to only oral RRMS therapies may not have been appropriate. The PBAC considered that the route of administration would not primarily drive decisions for choice of treatment.

6.49 The resubmission estimated that cladribine would have a total net cost to the PBS/RPBS of $30 - $60 million per year in Year 1 to $30 - $60 million per year in Year 6 for a total of more than $100 million over the first six years of listing, as presented in Table 7.

Table 7: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of cladribine						
Cost to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for fingolimod (published price)						
Cost to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net savings to MBS & hospitals	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Assuming 2 scripts per year of treatment as estimated by the resubmission.
Source: Table 4.2.1, p 232, Table 4.4.1, p237, and Table 4.5.4, p238 of the resubmission

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.

6.50 The financial estimates included in the resubmission were based on an average dose requirement of seven tablets per patient per course. The resubmission considered that estimating financial implications for only six years would not capture the displacement of fingolimod in the years beyond Year 6. Therefore, the resubmission also presented financial estimates over nine years, as shown below.

Table 8: Estimated net financial implications to the PBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
Expected cost of listing cladribine on PBS									
PBS scripts	[redacted]								
PBS costs	[redacted]								
Copay	[redacted]								
Net cost	[redacted]								
Expected cost of fingolimod displaced with cladribine on PBS									
PBS scripts	[redacted]								
PBS costs	[redacted]								
Copay	[redacted]								
Net cost	[redacted]								
Net implications to the PBS – cladribine impact after displacing fingolimod									
Net cost	[redacted]								
Cumul.	[redacted]								

Source: Table 4.4.1, p237 of the resubmission and 'Att_10 Section 4.xlsx'. Cumul = cumulative costs; PBS = Pharmaceutical Benefits Scheme

Note: the resubmission assumed no RPBS use and hence is not included.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.

6.51 The resubmission estimated that the cost to the PBS over the first nine years of listing would be $30 - $60 million. This analysis assumed that no new patients would initiate treatment with cladribine after Year 6 and consequently no patients would receive cladribine treatment in Years 8 and 9. Although this nine-year analysis was presented to show the impact on the PBS of the 'additional therapeutic cover', it was unrealistic to assume that patients would not initiate treatment over those years. The resubmission stated that the persistence rates used to calculate financial impact of listing cladribine were based on fingolimod data, and hence may not be applicable. These rates were a major reason for the absence of cost-neutrality in the PBS financial implications even on a nine-year horizon.

6.52 The resubmission also presented a scenario analysis (Table 9) where cost neutrality is achieved by Year 9, based on the following assumptions:

- 100% persistence of cladribine every year (base case assumes [redacted] in Years 1 to 6, respectively);
- Cladribine is assumed to have the same DPMQ as fingolimod (fingolimod has a higher DPMQ due to differences in mark-ups and due to the 5% statutory price reduction); and
- Patient co-payments are set to zero (fingolimod is associated with more co-payments).

Table 9: Resubmission's scenario analysis of cost-neutrality

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
Expected cost of listing cladribine on PBS									
Total cost	[redacted]								
Expected cost of fingolimod displaced with cladribine on PBS									
Total cost	[redacted]								
Net implications to the PBS – cladribine impact after displacing fingolimod									
Net cost	[redacted]								
Cumul.	[redacted]								

Source: Table 4.6.3, p242 of the resubmission and 'Att_10 Section 4.xlsx'. Cumul = cumulative costs; PBS = Pharmaceutical Benefits Scheme

Note: the resubmission assumed no RPBS use and hence is not included.

6.53 The PSCR (p4) argued that the persistence rates for cladribine should be theoretically higher than for fingolimod due to cladribine's posology. The PSCR considered that since persistence rates are assumed to be identical for cladribine and fingolimod, this does not bias results in favour of either cladribine or fingolimod. The ESC considered that regardless of trial based evidence for tolerability and discontinuation, assuming a high persistence favours cladribine. This is because drug costs of cladribine are weighted towards the first two years of treatment, and so the incremental cost of patients who do not persist on therapy (and switch to another DMD) is much higher for cladribine than for fingolimod, which is dosed daily.

6.54 The PBAC noted that cost-neutrality over nine-years was only achieved in a scenario analysis that assumed no patients initiated treatment with cladribine in Years 7-9 and no patients were re-treated in Years 8 and 9. However, application of treatment persistence rates below [redacted]% in the cost minimisation analysis resulted in net costs to the PBS. The PBAC considered that treatment persistence rates were overestimated for the six- and nine-year time horizons, which significantly underestimated the financial impact to the PBS. The PBAC therefore considered that the cost minimisation analysis presented by the resubmission lacked validity, given the significant net costs to the PBS even on a nine-year time horizon. The PBAC noted that the lack of cost neutrality in the cost minimisation analysis was predominantly due to the assumption of 100% persistence of cladribine and fingolimod over four years in calculating the equi-effective doses, which did not correspond with the application of lower persistence rates in the financial analysis. The PBAC considered that this affirms the Committee's concerns that two years' treatment with cladribine is not equivalent to four years' treatment with fingolimod. Furthermore, the PBAC noted that the scenario analysis over nine years was not consistent with the PBAC Guidelines (v5.0), which requests the estimates of financial impact each year over six years. The PBAC therefore considered that the scenario analysis presented by the resubmission to be uninformative.

Quality use of medicines

6.55 The resubmission noted quality use of medicines activities undertaken by the sponsor including education programs packaging, a patient support program, and post-marketing surveillance.

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

7 PBAC Outcome

7.1 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 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 proposed by the resubmission. 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 undermines the first principles of a cost minimisation analysis.

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

7.3 The PBAC noted the TGA recommendation that following the completion of the two treatment courses in Years 1 and 2, no further cladribine treatment is required in Years 3 and 4. However, in consideration of the wording for a PBS restriction, the PBAC considered that it would be inappropriate to specify that a patient who has received PBS-subsidised treatment with cladribine for RRMS is not eligible to receive any other PBS-subsidised RRMS medicines for a period of four years. The PBAC considered the proposed General Schedule (Section 85) listing is appropriate for cladribine.

7.4 The PBAC noted the number of cladribine tablets to provide for the recommended dosage depends on the body weight. The resubmission proposed a maximum quantity of ten tablets and stated that [redacted] of patients would require a maximum quantity of seven tablets. The resubmission proposed listing three different pack sizes; packs containing one, four and six x 10 mg tablets. Each pack must be differentiated in the Schedule of Pharmaceutical Benefits, and listed with associated maximum quantities and repeats. One listing with a maximum quantity of ten tablets as proposed by the sponsor does not differentiate between the three different pack sizes. The PBAC advised that the proposed PBS restriction be worded to list the pack of one tablet 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. One pack or a combination of these

packs will provide for the first weeks' treatment at any of the doses between 40 mg and 100 mg as recommended in the TGA Product Information (PI). The repeat will provide for the second weeks' treatment, although separate authority prescriptions will be required where the dose for treatment in Week 5 is different to the dose for treatment in Week 1. The PBAC advised 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 PI.

7.5 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, teriflunomide and daclizumab. 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.

7.6 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.

7.7 The PBAC therefore did not accept the claim that cladribine is non-inferior to fingolimod in terms of efficacy over four years. In addition to the issues surrounding the validity of the claim of non-inferiority as 2 years, the PBAC considered that there was inadequate and weak long-term evidence to support the claim of non-inferiority over four years, which the resubmission made, based on a naïve comparison of point estimates of the extension studies to the three trials. The PBAC noted that of those randomised to low dose (3.5mg/kg) cladribine in the CLARITY trial, only 71% (284/398) of subjects entered the extension study. Therefore, the PBAC was concerned that the trial population for CLARITY and CLARITY EXT are not comparable. The PBAC also noted that the CLARITY extension study was primarily a safety study and was not powered for efficacy endpoints. The PBAC considered that in clinical practice, patients who complete the two treatment courses of cladribine in Years 1 and 2 but experience disease relapse in Years 3 and 4 are highly likely to be prescribed other therapies for RRMS before the four-year treatment period for cladribine is reached.

7.8 The PBAC considered that there was insufficient data to accurately assess the claim of non-inferior safety of cladribine versus fingolimod. The PBAC noted comments from the TGA Delegate's Overview (p9-10) that,

- "Cladribine results in prolonged dose-related lymphocyte suppression and there are major safety concerns with over-exposure."
- "Cladribine is potentially very toxic and it would be clearly inappropriate for it to be given to patients who do not have a poor prognosis without aggressive treatment."
- "… careful surveillance for infection and lymphopenia is required for all patients who have received cladribine… (and) … patients with persistent lymphopenia should continue to be monitored until lymphocyte counts return to the normal range"; and
- "Whether surveillance for AEs including malignancy can be reduced over time is not able to be determined from the data presented."

The PBAC therefore considered that while it had previously noted cladribine to be generally well tolerated, cladribine was associated with important adverse events.

7.9 As the PBAC did not accept the claim of non-inferiority of two years of cladribine treatment versus four years of fingolimod treatment, the Committee did not accept this as the basis for estimating the equi-effective doses of cladribine and fingolimod. Additionally, the PBAC considered it was implausible that 100% of patients would remain on cladribine or fingolimod for four years and that no treatment switching or use of subsequent DMDs would occur in the four-year period. Therefore, the PBAC considered that it was inappropriate to conduct the cost-minimisation analysis based on two years of cladribine treatment versus four years of fingolimod treatment.

7.10 The PBAC noted that the resubmission proposed a 'maximum quantity' of ten tablets in the requested listing, however only applied the price of seven tablets (based on the average weight [76.6kg] of patients in an Australian MS longitudinal study receiving cladribine) in the cost minimisation and financial analyses. The PBAC noted that this would have created a large potential for wastage, with significant financial implications for government, and issues with the quality of use of cladribine. The PBAC noted that the PSCR accepted the Secretariat's suggestions to modify the proposed PBS listing (as outlined in paragraph 7.4 above) and considered that this approach was appropriate.

7.11 The PBAC noted that the resubmission's base case financial analyses estimated the net cost to the PBS to be more than $100 million per year and $30 - $60 million, over six and nine years, respectively. The significant net costs to the PBS even on a nine-year time horizon, added to the PBAC's concern that the cost minimisation analysis presented by the resubmission lacked validity.

7.12 The PBAC also noted that the resubmission's scenario analysis projected the listing of cladribine to be cost neutral to the PBS over nine years, however the Committee considered this was substantially underestimated due to unreasonable assumptions that:

- Cladribine dosing in Weeks 1 and 5 of Years 1 and 2, followed by two years of no treatment was equal to four years of continuous fingolimod treatment;
- Persistence with all treatments is 100%;
- All cladribine patients would remain treatment free in Years 3 and 4 (i.e. patients do not commence another DMD).

The PBAC noted that the financial analyses over nine years was not consistent with the PBAC Guidelines (v5.0), which requests the estimates of financial impact each year over six years.

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

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

7.15 The PBAC considered that any resubmission for cladribine for RRMS would require a major submission including new economic and financial analyses that addresses the Committee's concerns.

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

Outcome:

Rejected

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

Cladribine tablets have a unique treatment regimen. Based on the results of CLARITY and CLARITY EXTENSION, the TGA-approved indication for cladribine tablets is now "Cladribine is indicated for the treatment of relapsing-remitting multiple sclerosis 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." As noted in the TGA Delegate's Summary, the annualised relapse rate in patients in CLARITY extension who had received no further cladribine since CLARITY, strongly suggests a continued benefit for up to 6 years after commencing treatment with cladribine. The risk of disability progression over the 96 weeks of the CLARITY study for patients given 3.5 mg cladribine was 33%. Disability progression occurred in 27.6% over the course of the extension study, again indicating sustained benefit from cladribine given only in the CLARITY study. The PBAC noted that consumers perceived cladribine as a medicine with a good safety profile and ease of administration. Merck therefore remains committed to working with the PBAC to make sure that this important treatment option becomes available on the PBS for patients with RRMS.