

# 11.01 CLADRIBINE, Tablet 10 mg, Mavenclad<sup>®</sup>, Merck Healthcare Pty Ltd

## 1 Purpose of Submission

- 1.1 The submission requested an increase in the effective price of cladribine for relapsing remitting multiple sclerosis (RRMS) based on a revision of equi-effective doses.
- 1.2 The requested basis for the price increase is a cost-minimisation analysis against fingolimod (and ozanimod) over a four year duration (i.e. by re-specifying the equi-effective doses of cladribine to other RRMS therapies). Cladribine was recommended by the PBAC on the basis of a cost-minimisation to fingolimod over a two-year time period in July 2018.
- 1.3 Key components of the clinical issues addressed by the submission are presented in Table 1.

**Table 1: Key components of the clinical issue as stated by the submission**

Component	Description
Population	Patients with 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).
Outcomes	Annualised relapse rate; proportion of patients remaining relapse free; treatment switching.
Clinical claim	Cladribine is non-inferior in terms of effectiveness compared with fingolimod over both a two year and a four-year treatment period. Cladribine is non-inferior in terms of safety compared with fingolimod. The two agents have different but comparable safety profiles.

Source: pp2-64 of the submission

## 2 Background

### **Registration status**

- 2.1 Cladribine was approved by the TGA in December 2017. The current TGA-approved indication for cladribine tablets is as follows:

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 Considerations

2.2 Table 2 gives a brief overview of the history of key PBAC considerations relevant to the current submission.

**Table 2: Overview of key PBAC considerations relevant to the current submission**

Submission /description	Key PBAC considerations
November 2017	
<p>Submission based on CLARITY and CLARITY Extension trials comparing cladribine to fingolimod daily. Listing sought on cost-minimisation over 4 years to fingolimod.</p>	<p>Not recommended. PBAC considered:</p> <ul style="list-style-type: none"> <li>• Uncertainty of non-inferiority claim over both 2 and 4 year periods.</li> <li>• Insufficient clinical evidence to support the time horizon of four years for estimating the equi-effective doses.</li> <li>• 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 persistent to fingolimod.</li> <li>• Significant uncertainties in financial analysis.</li> <li>• Financial analysis estimated a significant net cost to the PBS, which undermines the first principles of a cost-minimisation analysis.</li> </ul>
March 2018	
<p>Minor re-submission, requesting listing for 7 tablets compared to 10 tablets in previous submission.</p> <p>No new clinical trial data presented.</p> <p>Resubmission argued that “application of the MCID of 1.23 noted in the ocrelizumab public summary document (PSD) to the upper confidence interval (CI) of the indirect estimate of annualised relapse rate (ARR) for cladribine compared to fingolimod (0.89 [95%CI 0.67, 1.18]) confirms that cladribine is non-inferior to fingolimod using a MCID already accepted by the PBAC”.</p>	<p>Not recommended. PBAC considered:</p> <ul style="list-style-type: none"> <li>• That it had recommended ocrelizumab based on the totality of the evidence presented in that submission, and not solely on the basis of the proposed MCID.</li> <li>• No new clinical data was presented to address previous concerns regarding the clinical claim of non-inferiority.</li> </ul>
July 2018	
<p>Minor resubmission.</p> <p>No new clinical evidence, elaborated on arguments regarding MCID in previous submissions and requested listing on a two year cost-minimisation rather than four years.</p>	<p>Recommended- based on:</p> <ul style="list-style-type: none"> <li>• “amongst other matters, its assessment than the cost-effectiveness of cladribine would be acceptable if it were cost-minimised against fingolimod based on a claim that two years of cladribine treatment is non-inferior in efficacy to two years of fingolimod treatment.”</li> <li>• PBAC also “previously considered that there was uncertainty in the claim that cladribine is noninferior to fingolimod in terms of efficacy over two years as this was based on a minimal clinically important difference (MCID) of 1.46 with a calculation methodology that the Committee considered was not adequately justified (paragraph 7.6, November 2017 Public Summary Document). However, the PBAC considered that the [redacted] reduction in the proposed price for cladribine was adequate to address the remaining uncertainty in cost-effectiveness”</li> </ul>

Source: March 2011, November 2017, March 2018, July 2018 PBAC Public Summary Documents.

2.3 Additionally, the ratified minutes of the May 2021 intracycle meeting noted the following:

“The Minister’s delegate sought the advice of the PBAC as to whether it considers that there are reasons why the Minister (or delegate) should not delist, by revoking determinations under subsections 85(3), (5) and (6) of the Act, the only listed brands of pharmaceutical items containing cladribine (in tablet form), and if so what those reasons are.”

2.4 At the intracycle meeting the PBAC concluded:

- “that in the absence of a price reduction for cladribine (tablet form) to the equivalent price of ozanimod, cladribine (tablet form) would no longer be considered cost effective for the treatment of RRMS.” (paragraph 3.9)
- “The PBAC noted that the sponsor may make a further submission on whether cladribine (tablet form) is cost effective compared to ozanimod, or other medicines currently listed for the treatment of RRMS, at any time. This includes the sponsor making a submission after the price of cladribine (tablet form) is reduced (in the event the currently requested price reduction is agreed), presenting evidence of superior efficacy and/or safety over ozanimod to justify a price increase request. The PBAC did not consider that it should defer its current consideration of the Minister’s request for advice.” (paragraph 3.10)
- “The PBAC further noted that as there is no cost-effectiveness basis for the current differential between the price of cladribine (tablet form) and ozanimod, as well as a number of other PBS listed medicines for the treatment of RRMS, a full cost-effectiveness submission will be required to demonstrate the basis for any premium over these other therapies in the future.” (paragraph 3.11)
- “the PBAC considered that there were no reasons why the Minister should not, as proposed, delist by revoking determinations under subsections 85(3), (5) and (6) of the National Health Act 1953, the only listed brands of pharmaceutical items containing cladribine (tablet form), if Merck does not agree to the price reduction sought in the Department’s original correspondence to Merck of 10 March 2021.” (paragraph 3.12)

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

### 3 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Cladribine					MAVENCLAD, Merck
Tablet, 10mg	1	1	1	\$ [REDACTED]	
Tablet, 10mg	1	6	1	\$ [REDACTED]	
Tablet, 10mg	2	8	1	\$ [REDACTED]	

Source: Table 5, p14 of the submission, p1 of the Pre-Sub-Committee Response (PSCR).

3.1 The AEMP presented for one tablet of cladribine in the cost-minimisation analysis was \$ [REDACTED] (DPMQ of \$ [REDACTED]) in the submission. The pre-PBAC response requested an AEMP of \$ [REDACTED] for one tablet of cladribine. The current effective AEMP for cladribine is \$ [REDACTED].

3.2 No changes were requested to the PBS restriction.

### 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.

### 5 Comparator

5.1 The submission nominated fingolimod as the main comparator. The main arguments provided in support of this nomination were:

- Fingolimod was accepted as the appropriate main comparator to cladribine at the July 2018 PBAC meeting. The PBAC noted that “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” (Cladribine Public Summary Document (PSD), July 2018, paragraph 4.1). Fingolimod remains the comparator for this resubmission as post-market data shows that fingolimod has been the treatment most commonly displaced since the listing of cladribine.
- Internal data from the sponsor shows that the majority of patients who are switching to cladribine from any other pharmacological treatment are switching

from fingolimod (20%). The largest subset of patients (23%) were treatment naïve. The next two largest groups at 11% are patients switching from dimethyl fumarate and interferon beta 1 b.

- At the May 2021 PBAC Intracycle Meeting, it was suggested that a comparison to ozanimod would be required in this resubmission (Ratified Minutes – May 2021 PBAC Intracycle Meeting). However, in the public summary document for ozanimod (Ozanimod PSD, March 2020, paragraph 5.1), the PBAC accepted fingolimod as ozanimod’s comparator, “based on both drugs being pharmacological analogues that target the S1P receptor pathway, fingolimod having the largest market share of RRMS treatments, and both treatments being oral DMTs [disease modifying therapies].” The PBAC also suggested that “in practice, ozanimod could substitute for all PBS subsidised RRMS medicines” (Ozanimod PSD, March 2020, paragraph 5.1).
- Using the most recent evidence, the sponsor considered that fingolimod remains the appropriate ‘proxy’ comparator based on: (a) market share and (b) similarity in treatment administration (oral capsules unlike ocrelizumab infusions).

5.2 Fingolimod is an appropriate comparator, but cladribine may replace any of the PBS subsidised RRMS treatments.

5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. During its March 2021 consideration of ofatumumab, the PBAC considered fingolimod, natalizumab, alemtuzumab, ocrelizumab, cladribine and ozanimod to be alternative (higher tier) therapies (March 2021 ofatumumab Public Summary Document, Paragraph 7.1).

*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 presented Australian real-world evidence from an unpublished longitudinal analysis of the MSBase registry. Australian patients with RRMS were identified who had initiated cladribine or other oral DMTs (including fingolimod). Outcomes included time-to-discontinuation (for cladribine, time to treatment switch), annualised relapse rate (ARR) and time-to-first relapse, with a data-cut in August 2018. The clinician stated that the data showed there may be a durability of effect of cladribine into the third year (after 2 years' treatment with cladribine) in terms of relapse rates, time to first relapse and rate of treatment discontinuation. However, these data could not be assessed as only limited information was provided. The clinician also outlined her clinical experience of treating patients with cladribine, stating that she has many patients in their third year of treatment and is only considering re-treatment in around 10% of these patients.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (1) and health care professionals (HCPs) (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with cladribine, including the ease of use due to the dosing regimen and oral dosage form. The individual and HCPs also commented that many patients had not required additional treatment (either with cladribine or an alternative DMT) in their third year since commencing cladribine.

### ***Clinical trials***

- 6.3 To support the submission's claim of non-inferiority to fingolimod over a four year time horizon, the submission presented a naïve comparison of the relevant arms of the CLARITY extension (CLARITY EXT; n=284), the FREEDOMS I extension (FREEDOMS EXT; n=486) and the FREEDOMS II extension (FREEDOMS II EXT; n=632). The low dose cladribine (LLPP) arm is the arm most relevant to the submission, and most consistent with the approved cladribine treatment regimen (patients received 3.5 mg/kg cumulative dose of cladribine in CLARITY, then were assigned to placebo in the CLARITY EXT study). Consequently, unless otherwise noted, data from CLARITY EXT refers to the LLPP arm. The submission also presented evidence from supplemental 'Real World Evidence' (RWE) studies.
- 6.4 As cladribine is currently listed on the basis of an indirect comparison of pivotal trial evidence (CLARITY for cladribine and FREEDOMS I & II for fingolimod, and their extension studies), this evidence has already been presented and evaluated by the PBAC.
- 6.5 Details of the trials and supplemental RWE studies presented in the submission are provided in Table 3. The submission did not provide a comparison versus ozanimod.

**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. 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." De Stefano, N., et al. "Cladribine effect on brain volume loss and its correlation with disability progression in patients with relapsing multiple sclerosis." Giovannoni, G., et al. "A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis."	18 May 2010 <i>Journal of Neurology</i> 2009; 259(Suppl. 2):S128 ;360 <i>Multiple Sclerosis</i> 2016; 22: 216-217. <i>N Eng J Med</i> 2010; 362(5): 416-426
CLARITY Extension	CLARITY EXT CSR report 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."	22 April 2016 <i>Multiple Sclerosis</i> 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." 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." 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."	<i>Multiple Sclerosis</i> 2016; 22: 304 <i>Multiple Sclerosis</i> 2016; 22: 48-49. <i>Neurology</i> 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." Kappos, L., et al. "A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis."	<i>The Lancet Neurology</i> 2014; 13(6): 545-556. <i>New England Journal of Medicine</i> 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 (freedom II study)." 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." 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."	<i>Neurology</i> 2012; 79(11): e90-e91 <i>Multiple sclerosis</i> : 2012; 18 (4) Suppl. 1; 205-6 <i>The Lancet Neurology</i> 2014 13(6): 545-556
FREEDOMS Extension	Kappos, L., et al. Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial.	<i>Neurology</i> 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 freedom II extension study" YR: 2013 VL: 80 Cree BAC et al., Long-term effects of fingolimod on no evidence of disease activity (NEDA) by year of treatment".	<i>Unidentified congress</i> 2013 (abstract) <i>MENACTRIMS Congress</i> 2016; 22 (6) (abstract)

Trial ID	Protocol title/ Publication title	Publication citation
Real World Evidence (RWE) supplementary evidence		
Pfeuffer (2021)	Pfeuffer et al. "Effectiveness and safety of cladribine in MS: Real-world experience from two tertiary centres."	<i>Multiple Sclerosis Journal</i> 2021 ; 0 (00): 1-12
De Stefano (2020)	De Stefano et al. "Analysis of frequency and severity of relapses in multiple sclerosis patients treated with cladribine tablets or placebo: The CLARITY and CLARITY Extension studies."	<i>Multiple Sclerosis Journal</i> 2020; 1-10
Patti (2020)	Patti et al. "Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian multiple sclerosis registry (CLARINET-MS)"	<i>Ther Adv Neurol Disord</i> 2020; 13: 1-10
Giovannoni (2021)	Giovannoni et al. "CLASSIC-MS: Long-term Efficacy and Real-World Treatment Patterns for Patients with Relapsing Multiple Sclerosis who Received Cladribine Tablets in Phase III Parent Trials (1919)."	<i>Neurology</i> 2021; 96 (15 Supplement):
Achiron 2021	Achiron et al "Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies"	<i>Ther Adv Neurol Disord</i> 2021; 14: 1-8

Source: Table 2.2.2 p59-68 of the November 2017 resubmission and pp112-115 of the current submission.

6.6 The key features of the direct randomised trials and their extensions are summarised in Table 4.

**Table 4: Key features of the included evidence cladribine versus fingolimod**

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		

Source: compiled during the November 2017 evaluation

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

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

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

6.7 In the November 2017 PBAC ratified PSD for cladribine (Item 7.02), the PBAC noted concerns about the usefulness of CLARITY EXT in supporting a claim of non-inferior efficacy between cladribine and fingolimod over four years. The current submission

presented a summary of the PBAC issues and how these were addressed in the current submission.

- Paragraph 6.25: “The ESC noted that of those randomised to low dose (3.5 mg/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.” The submission stated that using the proportion of patients continuing as “dispositive” of the similarities between the populations would be to ignore the baseline characteristics of populations in each group. Patients in CLARITY and EXT were similar in sex (68.8% vs 68.4%), race (98.2% vs 98.0% white), weight (68.1 vs 67.93 kg), and median EDSS score (2.5 vs 2.5). Additionally, only 77% of patients in the 0.5 mg population of FREEDOMS continued into FREEDOMS EXT, a likely insignificant 6% increase over cladribine. During the evaluation it was considered that, given that a key claim of this submission is that patients continue treatment over a four year time horizon, the fact that nearly 30% of patients are effectively lost to follow-up after 2 years is pertinent, regardless of the baseline characteristics of patients in the extension study. The fact that FREEDOMS EXT also had a high proportion of patients not electing to enter the extension makes a claim of non-inferiority more difficult to demonstrate.
- Paragraph 6.22: “...CLARITY extension was not powered to detect differences in efficacy outcomes.” Real world evidence published since 2017 and presented in this submission supports the efficacy findings of CLARITY EXT. These studies are discussed below but none provide evidence of improved comparative efficacy against fingolimod or any PBS-listed DMT.
- Paragraph 6.27: “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.” The submission also referred to additional real world evidence studies. As stated above, none of these studies provide improved comparative evidence against fingolimod.

6.8 The submission presented supplemental RWE from the following studies:

- Pfeuffer (2021): studying 270 adults with RRMS who had cladribine treatment at two German tertiary centres over 36 months. The authors of the study acknowledged the limitation of the non-controlled real-world setting and unknown existence of confounders in patient subgroups.
- De Stefano (2020): new analysis of frequency and severity of relapses in CLARITY and CLARITY EXT. This may not be considered RWE as it is a post-hoc analysis of CLARITY and CALRITY EXT. Furthermore, as it is based on the same data, it may not be considered confirmatory.

- Patti (2020) – study of 34 patients from Italian MS centres who previously were enrolled in CLARITY and had one full course of treatment in Years 1 and 2.
  - Giovannoni (2020)/ Giovannoni (2021)/ CLASSIC MS ongoing interim data of 147 patients who had initially received 1 dose of either cladribine or placebo in CLARITY, CLARITY EXT or ORACLE MS (a randomized, double-blind, clinical trial to assess the safety and efficacy of two doses of oral cladribine versus placebo in participants who had a first clinical demyelinating event [clinically isolated syndrome]).
- 6.9 The submission also included discussion of Achiron (2021) to inform a cost per successfully vaccinated patient against COVID-19 analysis in a supplementary analysis in the economic section (see below). Achiron (2021) studied the effect of the COVID-19 vaccine (BNT162b2-COVID-19; Pfizer) on patients using cladribine, ocrelizumab, or fingolimod with the aim of analysing the humoral immunity of these patients. The submission presented limited evidence discussing a correlation between humoral response and clinically relevant endpoints, but this was not a validated surrogate measure. The Pre-Sub-Committee Response (PSCR) reiterated the analysis of humoral response to COVID-19 vaccination with an mRNA vaccine was indicative only and was not used to support the primary efficacy claim, nor was a price advantage being sought on the basis of that claim.

### **Comparative effectiveness**

- 6.10 The PBAC reviewed the results of CLARITY EXT in November 2017. However, the current submission provided more detail regarding ‘gaps’ in the CLARITY EXT evidence. Specifically, the submission noted that between the end of the CLARITY trial and the beginning of the extension phase there was a gap in which efficacy was evaluated retrospectively. The submission added annualised relapse rates calculated for relapses that occurred during the ‘gap.’
- 6.11 The ‘gap’ occurred because CLARITY EXT was initiated after 54% of patients enrolled in CLARITY had already completed that trial. This gap included the time required for consent and ethics approval. The median duration of this gap was 40.3 weeks (range 1 day to 118 weeks). The submission stated that, including this gap (along with a second shorter gap between CLARITY EXT and a supplemental period of follow-up), “means that the extended benefit of treatment demonstrated for the LLPP group described as ‘Years 3 and 4’ is in fact a conservative measure of the sustained duration of benefit of treatment with cladribine tablets at the start of Years 1 and 2 because the total duration of the observation period was just over 5 years”.
- 6.12 Table 5 presents the annualised relapse rate during CLARITY EXT of the patients who had received low dose cladribine during the CLARITY trial and were randomised to placebo during the extension (LLPP). The ARR for cladribine 3.5 mg/kg in CLARITY (0.14) was maintained in the LLPP group in CLARITY EXT (0.15). This within-group difference was not significant ( $p=0.4526$ ). The submission stated that in order to explore the potential effect of the duration of the gap between CLARITY and CLARITY

EXT, selected efficacy endpoints were assessed by the duration of the gap (≤4 weeks, >4 to ≤43 weeks, >43 weeks.)

**Table 5: Annualised relapse rate during CLARITY EXT (ITT population)**

	LLPP (n=98)
Number of qualifying relapses, Mean (SD)	0.35 (0.79)
Annualised relapse rate (97.5% CI)	0.15 (0.09, 0.21)
<b>Annualised relapse rate by duration of gap</b>	
≤4 weeks	0.17 (n = 9)
>4 to ≤43 weeks	0.15 (n = 47)
>43 weeks	0.14 (n = 42)

Source: Table 16, p36 of the submission. LLPP = low dose cladribine followed by placebo; SD = standard deviation.

6.13 Table 6 presents the proportion of patients remaining free from relapse for the patients who had received low dose cladribine during the CLARITY trial and were randomised to placebo during CLARITY EXT. The proportion of patients remaining relapse free in CLARITY EXT (75.6%) was similar to that demonstrated for cladribine in CLARITY (79.7%). The difference within the group was not significant (p=0.705).

**Table 6: Proportion of patients remaining free from relapses during CLARITY EXT (ITT population)**

	LLPP (n=98)
Patients relapse free (%)	68 (75.6%)
<b>Proportion of patients remaining free from relapse by duration of gap</b>	
≤4 weeks	6 (75.0%), n = 9
>4 to ≤43 weeks	34 (75.6%), n = 47
>43 weeks	28 (75.7%) n = 42

Source: Table 17, p37 of the submission.

6.14 Table 7 presents the comparison of annualised relapse rates and proportion free of relapses in the CLARITY EXT and FREEDOMS I/II EXT.

**Table 7: Comparison of the duration of benefit over four years (including the extension trials)**

	CLARITY + EXT (LLPP)	FREEDOMS + EXT (Continuous fingolimod 0.5 mg)	FREEDOMS II + EXT (Continuous fingolimod 0.5 mg)
<i>Annualised relapse rate</i>			
Core study ITT (Years 1 and 2)	0.14	0.20	0.21
Extension study ITT (Years 3 and 4)	0.15	0.17	-
Entire trial period (core + extension)(Years 1 to 4)	-	0.19	0.19
<i>Proportion free from relapses, n/N (%)</i>			
Core study ITT (Years 1 and 2)	345/433 (79.7%)	229/425 (70.4%)	256/358 (71.5%)
Extension study ITT (Years 3 and 4)	68/98 (75.6%)	-	-
Entire trial period (core + extension) (Years 1 to 4)	-	59.3% <sup>a</sup>	66.6% <sup>a</sup>

Source: Table 26, p48 of the submission.

<sup>a</sup> patient numbers (n/N) not presented.

6.15 As previously stated, the PBAC has previously reviewed the results of the naïve comparison of the trial extensions and considered that these results did not provide sufficient evidence to demonstrate that two years of cladribine treatment was comparable to four years of fingolimod treatment. The ESC acknowledged the additional information that was provided in the resubmission regarding the annualised relapsed rates (inclusion of relapses that occurred during the ‘gap’

between the end of the CLARITY trial and the beginning of the extension). However, the ESC considered that the additional information, which still relied on a naïve comparison of point estimates of the cladribine and fingolimod extension studies, still did not provide sufficient evidence to demonstrate that two years of cladribine treatment was comparable to four years of fingolimod treatment.

6.16 Table 8 presents a summary of the results of the ‘real world evidence’ (RWE) studies.

**Table 8: Summary of published RWE on duration of treatment effect**

Reference	Relapses	Treatment switch
Pfeuffer (2021) Real-world experience from two tertiary centres	25.6% - 4 years	5.6% - 3 years
De Steffano (2020) Analysis of frequency and severity of relapses in the CLARITY and CLARITY Extension studies	15.3% (qualifying relapses) to 26.5% (all relapses) - 4 years	15.3% (qualifying relapses) to 26.5% (all relapses) - 4 years <sup>a</sup>
Patti (2020) Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian MS registry (CLARINET-MS)	14.6% – 2 years 33.8% – 4 years 41.1% – 6 years	20.6% - 2 years 44.4% - 4 years 67.6% - 6 years
Giovannoni (2021) CLASSIC-MS: Long-term Efficacy and Real-World Treatment Patterns for Patients with Relapsing Multiple Sclerosis who Received Cladribine Tablets in Phase III Parent Trials (1919)	NR	17.2% <sup>a</sup> - 4 years
Lizak (2020) -excluded on the basis that some patients received incorrect dosage of cladribine  MSBase Australian Registry sub study.	NR	62 of 90 patients (69%) received another DMT following cladribine treatment during the reported follow-up period (median 3.5 years). Overall, 45 (73%) patients who switched did so before a relapse and 17 (27%) experienced relapses prior to switching. The median (95% CI) time to next DMT was 1.7 years (1.36–2.28).

Source: Table 30, p57-58 of the submission. NR = not reported

<sup>a</sup> Using proportion of patients who relapse in the study period as a surrogate endpoint for patients who switch treatments if treatment switching is not explicitly recorded.

6.17 The point estimates of relapse in these observational studies overall indicated some preservation of clinical effect beyond two years. However, none of these studies provided comparative effect estimates to fingolimod to inform a non-inferiority claim over four years.

6.18 Furthermore, Giovannoni (2021) and Patti (2020) followed cohorts of patients who had originally been in the cladribine trials, and consequently, may not be appropriate to serve as confirmatory studies. De Steffano (2020) was a re-analysis of CLARITY EXT, and consequently does not necessarily address the limitations of the extension study.

6.19 Estimates of treatment switch rates, which were used in the cost-minimisation analysis were all from foreign jurisdictions except for the excluded Lizak (2020). It was unreasonable to assume that post cladribine treatment switch data from other jurisdictions would be directly applicable to the Australian context.

- 6.20 The PSCR argued the evidence presented, including the RWE, indicated a majority of patients continue to experience a therapeutic effect after 2 years and further argued the current basis upon which cladribine is listed assumes no patients experience any benefit beyond 2 years of treatment. The PSCR also stated the Sponsor surveyed six hospitals that participated in a cladribine patient access program between May and December 2018 (prior to its PBS listing on 1 January 2019), representing 145/273 (53%) of patients in the program and within that cohort, 84% of patients were stated to “continue to benefit from treatment” ... “with no additional treatment for MS”. The methodology and raw data were not provided, so this information could not be assessed.
- 6.21 The ESC noted the RWE evidence presented was based upon the rate of initiation of alternative DMTs which is not a direct measure of the effectiveness of cladribine in years 3 and 4, and it was unclear whether this was a reasonable surrogate measure.
- 6.22 The Pre-PBAC Response argued it was reasonable to suggest that if a patient switches treatment it is likely due to a lack of efficacy on their current treatment and argued that based on the available Australian data to date, the international studies which formed the basis of the cost minimisation approach (see economic analysis section) were conservative, however acknowledged the Australian data on the rate and timing of switching to other DMTs after treatment with cladribine were immature.
- 6.23 The Pre-PBAC Response also argued that the RWE demonstrates many cladribine patients continue without additional DMT treatment for a period beyond 2 years. The PBAC acknowledged that some patients continue for a period without further DMT treatment following 2 years’ treatment with cladribine, however agreed with the ESC that the rate and timing of switching to alternative DMTs was unsupported as a valid surrogate marker of efficacy for informing the clinical claim of non-inferiority over 4 years.
- 6.24 Furthermore, the ESC considered there were additional issues with the RWE studies, including:
- The ESC agreed with the evaluation and considered the data from Patti 2020, an Italian study of 34 patients, was unlikely to be applicable to the Australian population; and additionally given the small size of the study, was unlikely to be reliable for estimating the rates of DMT initiation in the Australian context following 2 years of treatment with cladribine.
  - The ESC considered the Lizak 2020 study, the only Australian RWE evidence presented, was also not applicable to the submission request as it was largely based on the patient familiarisation program implemented around the time of the first rejection for cladribine in March 2011 in which most patients only received one dose of cladribine.
  - The ESC considered the Giovannoni 2021 publication (a combination of 3

studies) was also not applicable to the RRMS population as one of the studies was in clinically isolated syndrome (CIS) and therefore the study population was likely heterogeneous.

### Comparative harms

6.25 Table 9 presents a comparison of safety in the CLARITY trial and in CLARITY EXT. This comparison was previously considered by the PBAC at the November 2017 Meeting.

**Table 9: Summary of safety in CLARITY and CLARITY EXT**

	CLARITY		CLARITY EXT
	Cladribine 3.5 mg/kg (n=430)	Placebo (n=435)	LLPP (n=98)
Any AE	80.7%	73.3%	75.5%
Any SAE	8.4%	6.4%	16.3%
AE resulting in treatment discontinuation	3.5%	2.1%	3.1%
Deaths	0.5%	0.5%	2.0%
Lymphopenia	21.6%	1.8%	9.2%
Grade 3 lymphopenia	24.9%	0.5%	5.1%
Grade 4 lymphopenia	0.7%	0	0
Infections	47.7%	42.5%	49.0%
Infections reported as a SAE	2.3%	1.6%	2.0%
Herpes zoster	1.9%	0	2.0%
Malignancies	0.6%	0	2.0%

Source: Table 23, p43 of the submission.

AE = adverse event; SAE = serious adverse event

6.26 The submission did not explain the high rate of serious adverse events (SAE) in the CLARITY extension (LLPP arm) compared to the arms of the pivotal trial. It is unclear why over an observation period, serious adverse events would increase substantially compared to an active treatment period. This may be a result of longer follow-up.

### Clinical claim

6.27 The submission made the following claims:

- RCT and supporting RWE demonstrates that cladribine is 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 in the following two years, whereas fingolimod must be administered on an ongoing daily basis.
  - The submission's main basis for the claim of non-inferiority over four years was a naïve comparison of the results of CLARITY EXT versus FREEDOMS I and II EXT, which has already been reviewed by the PBAC in November 2017. The PBAC at the time 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 (paragraph 6.27). The ESC considered that the

additional information provided in the resubmission did not adequately justify the efficacy claim that was made.

- The submission presented more recent RWE to serve as confirmatory results. These observational studies did not include any comparative evidence versus fingolimod, and many of these studies were based on patients from the CLARITY or other cladribine trials. Overall, these studies did not provide better evidence of comparative long term non-inferiority.
- Applicability issues of these RWE studies were particularly relevant in consideration of proportion of patients receiving subsequent DMTs in Years 3 or 4 when treated with cladribine. It was unlikely that these studies provided applicable estimates of switching for the Australian population.
- Cladribine is non-inferior in terms of safety compared with fingolimod. The two agents have different but comparable safety profiles. The submission stated it is likely that cladribine is superior to fingolimod in many key aspects, particularly over four years. In lieu of a full analysis, only a non-inferior claim is made. As with the efficacy data, non-inferior safety was not adequately demonstrated on the basis of the trial extensions. The submission did not explain the high rate of serious adverse events (SAE) in the CLARITY extension (LLPP arm) compared to the arms of the pivotal trial.

6.28 The ESC and PBAC considered the clinical claim of non-inferior comparative efficacy and safety of cladribine and fingolimod over four years was not adequately justified, as outlined in the paragraphs above.

### **Economic analysis**

6.29 The submission presented a cost-minimisation analysis of cladribine against fingolimod over four years. This differed from the July 2018 submission, where the PBAC recommended cladribine on the basis of a cost-minimisation analysis versus two years of fingolimod.

6.30 Table 10 presents the key components and assumptions of the cost-minimisation analysis.

**Table 10: Key components and assumptions of the cost-minimisation analysis**

<b>Component</b>	<b>Claim or assumption</b>
Equi-effective doses	Cladribine 3.5 mg/kg over 2 years administered as 1 treatment course of 1.75 mg/kg per year (consisting of 2 treatment weeks per year) = Fingolimod 500 mcg once daily over 4 years/Ozanimod 920 mcg once daily over 4 years.
Direct medicine costs	Two years of cladribine medicine costs is no more expensive than four years of fingolimod or ozanimod treatment costs.
Other costs or cost offsets	For MS outcomes, some cost offsets in healthcare professional (HCP) time as shown by a Time and Motion (T&M) study. Additional medicine costs for cladribine patients who switch to another treatment after 2 years.

Source: Table 36, p67 of the submission. MS = multiple sclerosis

- 6.31 If the clinical claim of non-inferiority over four years is not accepted, a cost-minimisation over four years is not appropriate.
- 6.32 The submission also presented a cost-minimisation against ozanimod. This is not expected to have an impact on any economic considerations because of the same costs for ozanimod and fingolimod.
- 6.33 The proposed equi-effective doses were:
- Cladribine 3.5 mg/kg over 2 years administered as 1 treatment course of 1.75 mg/kg per year (consisting of 2 treatment weeks), with observation (i.e. no active cladribine treatment) in Years 3 and 4.
  - Fingolimod 500 mcg once daily over 4 years.
  - Ozanimod 920 mcg once daily over 4 years.
- 6.34 The submission proposed that two years of cladribine treatment is equivalent to four years of fingolimod and ozanimod treatment in the absence of progression. The submission did not explain the qualification of the 'absence of progression' in its consideration of equi-effective dose.
- 6.35 The submission made a claim that two years of cladribine treatment (plus two years of observation) is equivalent to four years of fingolimod and based equi-effective doses on this claim. Treatment switching was not addressed in the consideration of equi-effective doses but rather included as an offset. This approach may be the simplest way to calculate the effects of treatment switching. However, it is unclear if these doses can be accepted as equi-effective when a large portion of patients are assumed to switch to another DMT before four years of cladribine treatment. Further, the ESC noted that inclusion of any rate of treatment switching would only be appropriate if non-inferiority is demonstrated.
- 6.36 The submission calculated the number of patients who were administered alternative MS treatments in Year 3 and 4 following two years of cladribine using estimates of treatment switch from Patti (2020). (Sensitivity analyses were presented using PBS 10% data and MSBase registry data).
- 6.37 Patti (2020) reported that over 44.4% of CLARITY patients commenced another therapy after cladribine treatment over a period of 36 months after the last dose of cladribine (four years from first dose). The submission stated the reason for the higher rate of treatment switching versus the other RWE publication is unknown, as the study identified low relapse rates and disability progression. Switch estimates from Patti (2020) were not likely to be applicable to the Australian population given it reflected an Italian health care context. It was unclear if these rates would be expected to be higher or lower. Further, the ESC noted that the study was based on 34 patients (the CLARITY extension cohort) and so may not be sufficiently reliable to inform this parameter.

- 6.38 The submission also identified a PBS 10% Sample Dataset as a supplementary data source to calculate the number of patients who switch treatment. The dataset consisted of claims information for a 10% sample of the Australian Medicare population, providing detailed information of medicine utilisation. As cladribine was first listed on the PBS in January 2019, limited data was available on patients treated for more than two years following initiation. The switch rate for cladribine patients in Year 3 of treatment was 30 out of 220 (13.6%). The submission considered that this confirms the Patti (2020) findings and supports the claims in this submission for a re-pricing of cladribine.
- 6.39 In the absence of Year 4 data, the submission applied the relative change in switch rates from Patti (2020) between Year 3 and 4 to Year 4 of cladribine patients when using this dataset. This dataset was used in the sensitivity analysis. Of note was that the PBS 10% sample appeared to be only based on 2 months of the third year. Consequently, this can neither serve to confirm the validity of the Patti (2020) estimates, nor as an informative sensitivity analysis. It should however be noted that data for Year 3 and Year 4 switch rates may eventually be available from the PBS 10% data, and this could provide Australian PBS-specific estimates of treatment switching should non-inferiority be accepted.
- 6.40 The submission used Patti (2020) to derive the basket of post-cladribine treatments. As previously stated, Patti (2020) was likely not applicable to the Australian setting.
- 6.41 The submission's base case estimated that a proportion of patients who switch from cladribine would switch to treatments that are not considered equivalent to (and likely to be less effective than) cladribine according to the PBS, and thus are less expensive (teriflunomide, cyclophosphamide, dimethyl fumarate, glatiramer acetate, interferon, azathioprine). Consequently, this further underestimated the costs associated with cladribine. The PBS sample which estimated that patients only switched to high efficacy DMTs (ocrelizumab and natalizumab) was probably more realistic, acknowledging that patients may also switch to other high efficacy DMTs.
- 6.42 The submission used a time and motion study conducted by the sponsor to estimate the difference in medical costs for nurse and neurologist consultations between cladribine and fingolimod. The study compared the time burden associated with the treatment regimens of three MS treatments (cladribine, fingolimod and ocrelizumab).
- 6.43 The study estimated the difference in time for a number of health services associated with:
- The workup, education and administration of RRMS therapies (cladribine, fingolimod, ocrelizumab).
  - The follow-up and monitoring requirements for that medicine.
  - The time burden associated with the management of treatment complications.

- 6.44 The submission applied a price for each hour for neurologist and nurse time, sourced from the MBS schedule. The submission considered the MBS item that would be used for one hour of neurologist time (MBS Item 116) is likely to be only a 30-45 minute consultation (based on a “personal communication”). The submission claimed that using this MBS item is conservative as the cost of one hour of neurologist time is likely to be much higher than the item number used, and using this item does not favour cladribine.
- 6.45 The submission claimed that the MBS item used for one hour of nurse time was a reasonable approximation of an hour of nurse time as the code specifies at least 40 minutes (which could be an hour or well over an hour).
- 6.46 Though the time and motion study presented in the submission was informative, MBS costs are not typically accrued in this manner. Consequently, specifically estimating the number of visits per patient for each treatment is likely more consistent with other approaches to cost-minimisation analysis in MS and more consistent with how costs to the MBS may be accrued. It is, for example, not necessarily reasonable that nurse and neurologist hours, as recalled in a specific survey, translate minute per minute to approved MBS items.
- 6.47 Additionally, given the claim of non-inferior efficacy, fewer scripts does not necessarily translate to a lesser frequency of neurologist follow-up visits, as frequency of visits to manage clinical relapse would be expected to be equivalent between treatments.
- 6.48 The November 2017 cladribine submission based its MBS cost offsets on MBS items and expected frequency of appointments and tests. Total offsets estimated over four years were \$585.54 compared to \$1,722 in the current submission.
- 6.49 The PSCR noted the time and motion studies between the 2017 submission and current application were different in terms of survey types, sample size and interview method. The PSCR stated it showed a greater time burden for cladribine in years 1 and 2 versus years 3 and 4 and supported a claim that there would be lower MBS costs in years 3 and 4 for patients treated with cladribine, however also noted the inclusion of these offsets (or not) does not have a substantial impact on the proposed price. The ESC considered the results of the time and motion study may not reflect clinical practice overall as neurologists would continue to see patients at regular intervals irrespective of whether patients were actively receiving treatment at that point in time.
- 6.50 The submission stated there were three stages in the stepped analysis, as follows:
- Step 1: the total medicine cost for fingolimod and ozanimod over two years.
  - Step 2: the total medicine cost for fingolimod and ozanimod over four years.
  - Step 3: the base case model which calculated the cost-minimised price of a one tablet pack of cladribine based on an equivalent total healthcare cost for fingolimod

and ozanimod over four years, including the cost offsets and cost for switch patients.

6.51 Table 11 presents a summary of the cost-minimisation approach (CMA).

**Table 11: CMA of cladribine versus fingolimod and ozanimod**

<b>Step 1: equi-effective price over two years</b>			
	<b>Cladribine</b>	<b>Fingolimod</b>	<b>Ozanimod</b>
Number of years	2	2	Not presented
Total mg	280	348.5	
Prescriptions over 2 years	28	24.89	
Total medicine cost over two years (at proposed price)	\$ [REDACTED]	\$ [REDACTED]	
Difference in treatment cost over two years	\$ [REDACTED]		
<b>Effective AEMP (maximum quantity; 1 tablet of cladribine)</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>	
<b>Step 2: equi-effective price over 4 years</b>			
	<b>Cladribine</b>	<b>Fingolimod</b>	<b>Ozanimod</b>
Number of years of treatment	2	4	4
Total mg	280	697.50	1283.39
Equi-effective dosage vs fingolimod	0.40	1	1.84
Equi-effective dosage vs ozanimod	0.22	1.84	1
Effective Price per mg	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Mg per max quantity	10	14	25.76
Max quants overs 4 years	28	49.82	49.82
Effective AEMP	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Total medicine cost over four years</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>
<b>Difference in treatment cost over four years</b>	<b>-\$ [REDACTED]</b>		
<b>Step 3: including offsets over 4 years</b>			
	<b>Value</b>	<b>Source/Note</b>	
Total cost of cladribine treatment for 4 years from Step 2	\$ [REDACTED]	See above	
Cladribine patients who switch in year 3	30%	Patti (2020)	
Cladribine patients who do not switch in year 3	70%	Patti (2020)	
Cladribine patients who switch in year 4	44.4%	Patti (2020)	
Cladribine patients who do not switch in year 4	55.6%	Patti (2020)	
Maximum quantity of cladribine packs over 4 years (1 tablet per pack at average patient weight)	28	Cladribine PI	
Weighted average drug cost per year for switch patients	\$ [REDACTED]	Calculated	
Total cost offsets from HCPs resource use over 4 years	\$1,722	Calculated	
Effective price per mg	\$ [REDACTED]	-	
Mg per maximum quantity	10	Max quantity of 1 tablet	
% of fingolimod and ozanimod patients who discontinue treatment in years 3 and 4	8.28%	Calculated	
Total cost of fingolimod and ozanimod treatment per patient including patient discontinuation	\$ [REDACTED]	-	
<b>Cladribine effective AEMP</b>	<b>\$ [REDACTED]</b>	<b>-</b>	
<b>Recalculated cost of cladribine treatment for 4 years</b>	<b>\$ [REDACTED]</b>	<b>-</b>	

Source: Tables 47-49, pp79-81 of the submission. AEMP = approved ex-manufacturer price

6.52 Overall, even if non-inferiority over four years were accepted, the submission's CMA likely substantially overestimated the cladribine cost-minimised price, this was due primarily to uncertain treatment switching based on switch rates from a non-Australian jurisdiction (Patti 2020) and likely overestimated cost-offsets for MBS costs.

- 6.53 The ESC considered that the results from the Patti 2020 study were likely not applicable to the Australian context and therefore the DMT switch/utilisation rate assumptions in years 3 and 4 were not reliable. The ESC considered that clinical non-inferiority would first need to be demonstrated, and then treatment switching rates should ideally be based on Australian data reflective of the PBS population.
- 6.54 The Pre-PBAC Response stated that ‘the PBS 10% sample data has been updated and now contains data from patients of 6 months of their third year. Cladribine treatment reported in the PBS 10% sample data shows that most cladribine patients do not require another treatment (as only 10.3% (7 out of 68) switched to another treatment). The PBS 10% sample data at this stage does not include any Year 4 patients. As Australian Year 4 data is not yet available, a revised price proposal was provided. Using a conservative switch rate of 30% from Patti et al (2020) in Year 3 and 100% in Year 4 and the switch to Australian PBS sample data treatments, the effective AEMP would be \$ [REDACTED] for one 10mg tablet of cladribine’. This revised approach was not evaluated.

Supplementary analysis: Cost per successfully vaccinated RRMS patient analysis

- 6.55 Based on data presented in Achiron (2021), the submission conducted a cost per successfully vaccinated MS patient analysis. This analysis was supplementary and was not included in the cost-minimisation analysis.

**Drug cost/patient/course: \$ [REDACTED] (based on price proposed in submission)**

- 6.56 The drug cost per patient per course of cladribine is \$ [REDACTED] based on the price proposed in the submission, which was an effective AEMP of \$ [REDACTED] per tablet and a dosage of 28 tablets over two years of treatment.
- 6.57 This compares to \$ [REDACTED] for four years of fingolimod based on an effective AEMP of \$ [REDACTED] and a 679 mg dispensed over four years (3.5 mg/week x 52.18 weeks on treatment x 95.48% compliance x 4 years of treatment).
- 6.58 Table 12 presents the drug cost per patient for cladribine and fingolimod.

**Table 12: Drug cost per patient for cladribine and fingolimod**

	Cladribine Trial dose and duration	Cladribine Model	Cladribine Financial estimates	Fingolimod Trial dose and duration	Fingolimod Model	Fingolimod Financial estimates
Mean dose	280 mg over two years of treatment followed by two years of observation <sup>a</sup>			0.5mg/day	0.5mg/day	0.5mg/day
Mean duration				24 months	4 years	4 years
Cost/patient/course (\$)	[REDACTED]			[REDACTED]	[REDACTED]	[REDACTED]

Source: compiled during the evaluation

<sup>a</sup> 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.

**Estimated PBS usage & financial implications**

- 6.59 This submission was not considered by Drug Utilisation Sub Committee (DUSC).

- 6.60 The submission estimated the cost of cladribine to the PBS with the proposed higher effective price (based on the proposed equi-effective doses), assuming not all patients in Years 3 and 4 switch to fingolimod. The submission compared this to the cost to the PBS that was previously accepted by PBAC, where pricing was based on two years of cladribine treatment and all patients on cladribine switching to fingolimod after two years. The financial estimates also included offsets for reductions in fingolimod use (as a proxy for all higher efficacy DMTs), with DMT initiation rates in Years 3 and 4 informed by the results of the Patti (2020) study, consistent with the economic analysis presented in the submission.
- 6.61 The submission stated that under the current cladribine listing, all patients were expected to switch to fingolimod (as a proxy for higher efficacy tier DMTs) after two years of cladribine treatment. On the other hand, the proposed effective price change in the submission assumed only a proportion of patients would initiate an alternative DMT in Years 3 and 4. The submission calculated the fingolimod offsets based on an assumption that 70% of patients would not require fingolimod in year 3 and 55.6% of these patients would not require fingolimod in year 4 (based on Patti (2020)).
- 6.62 The ESC considered the estimates were unreliable as Patti (2020) was not applicable to the Australian RRMS population and the likely rates of DMT initiation in Australia were unknown as insufficient time since listing had passed to make such an assessment.
- 6.63 To clarify, the financial estimates compared the cost of listing cladribine at the proposed higher price including offsets for: (a) fingolimod replaced over a four year time period; and (b) cladribine at the currently reimbursed price. Consequently, the submission's estimates of financial implications are costs in addition to current cladribine costs.
- 6.64 The submission stated it estimated utilisation and costs using a mixed model approach.
- 6.65 Table 13 presents the data sources used in the submission.

**Table 13: Data sources and parameter values applied in the utilisation and financial estimates (in the submission)**

Data	Value	Source	Comment
<b>Eligible population</b>			
Number treated with cladribine	2019: 900 2020: 850 2021: 876 2022: 902 2023: 929 2024: 957 2025: 985 2026: 1,015 2027: 1,045	Years 2019 and 2020 were estimated from the PBS 10% data sample	These patient numbers were used to derive the number of fewer patients who would use fingolimod in Years 3 and 4 post-cladribine, and assuming 12.45 fingolimod scripts per year. The submission noted the decrease in patients between 2019 and 2020 was due to the impact COVID-19 as the restrictions on hospitals and clinics prohibited many new patients from initiating cladribine treatment or had patients delay their second year of treatment.
Cladribine scripts, 2021	1 tablet: 1,133 4 tablets: 1,320 6 tablets: 1,594	PBS 10% data sample.	Reasonable.
Market growth	3%	Deed of Agreement	The submission stated that projected annual growth rate could not be determined from the PBS services, as there were only two calendar years of data available. Cladribine use increased by 24% from 2019 to 2020, and the submission considered it would be unrealistic to expect a similar growth rate for the following six years. Therefore, the growth rate accepted in the Deed of Agreement for cladribine between the Commonwealth and the sponsor was applied to the model. According to the Deed, the combined cladribine + fingolimod market was expected to grow annually by 3%.
% remaining treatment free after two years of cladribine	Year 3 – 70% Year 4 – 55.6%	Patti (2020)	The evaluation and the ESC considered that the Patti (2020) estimates were not applicable to the Australian setting and could overestimate how long patients remain without initiating subsequent treatment.

Source: Table 63, p90 and Table 65, pp91-92 of the submission

MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

6.66 Table 14 presents the estimated financial implications of increasing the price of cladribine, at the price proposed in the submission.

**Table 14: Estimated use and financial implications (based on price proposed in the submission)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
<b>Estimated financial implications of cladribine at new price</b>						
Cost to PBS/RPBS less copayments	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>3</sup>
<b>Estimated financial implications for fingolimod and cladribine at current price</b>						
Cost to PBS/RPBS less copayments	-█ <sup>2</sup>	-█ <sup>2</sup>	-█ <sup>2</sup>	-█ <sup>2</sup>	-█ <sup>2</sup>	-█ <sup>3</sup>
<b>Cladribine offsets (cladribine at existing price)</b>						
Net cost to PBS/RPBS	-█ <sup>4</sup>	-█ <sup>4</sup>	-█ <sup>5</sup>	-█ <sup>5</sup>	-█ <sup>5</sup>	-█ <sup>5</sup>
<b>Fingolimod offsets</b>						
Fewer fingolimod patients	-█ <sup>1</sup>	-█ <sup>1</sup>	-█ <sup>1</sup>	-█ <sup>1</sup>	-█ <sup>1</sup>	-█ <sup>1</sup>
Fewer fingolimod scripts	-█ <sup>6</sup>	-█ <sup>6</sup>	-█ <sup>6</sup>	-█ <sup>6</sup>	-█ <sup>6</sup>	-█ <sup>6</sup>
Net cost to PBS/RPBS	-█ <sup>7</sup>	-█ <sup>7</sup>	-█ <sup>7</sup>	-█ <sup>7</sup>	-█ <sup>7</sup>	-█ <sup>7</sup>
<b>Increased cost of cladribine to PBS/RPBS</b>						
	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	-█ <sup>8</sup>	-█ <sup>8</sup>	-█ <sup>8</sup>	-█ <sup>8</sup>	-█ <sup>8</sup>	-█ <sup>8</sup>

Source: Tables 68 and 70, pp93-94, Tables 71 and 72, pp95-96, and Table 73, p96 of the submission.

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

<sup>a</sup> based on PBS 10% statistics of currently listed cladribine scripts

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> \$40 million to < \$50 million

<sup>3</sup> \$50 million to < \$60 million

<sup>4</sup> \$20 million to < \$30 million

<sup>5</sup> \$30 million to < \$40 million

<sup>6</sup> 10,000 to < 20,000

<sup>7</sup> \$10 million to < \$20 million

<sup>8</sup> \$0 to < \$10 million

6.67 The submission estimated a net saving to the PBS/RPBS over the first six years of listing. The additional extra cost of cladribine to the PBS/RPBS was estimated to be \$90 million to < \$100 million over 6 years. That is, the submission estimated that, at the current price, cladribine would cost the PBS/RPBS \$100 million to < \$200 million over 6 years; while the total cost, at the newly requested price would be \$200 million to < \$300 million over 6 years before offsets.

6.68 As outlined in paragraph 6.54 above, the Pre-PBAC Response offered an effective AEMP of \$█ for one 10mg tablet of cladribine. At that price (with no other assumptions changed), the additional extra cost to the PBS/RPBS of cladribine would be \$30 million to < \$40 million over 6 years (accounting for offsets), or an additional \$200 million to < \$300 million over 6 years before offsets.

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

- 6.69 The submission stated that in accordance with the letter from the Department and new signed deed, dated by the sponsor 1 July 2021, the current risk sharing arrangement (RSA) for cladribine will be removed effective August 2021.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend amending the existing equi-effective doses of cladribine and fingolimod (and other disease modifying therapies (DMTs)) for the treatment of relapsing-remitting multiple sclerosis (RRMS), on the basis that the evidence presented did not satisfactorily establish that 2 years of treatment with cladribine (plus 1 or 2 years of no treatment) is non-inferior to either 3 or 4 years of treatment with fingolimod. The PBAC considered the clinical evidence, primarily based on extension phases of studies and real-world evidence (RWE), was not reliable for the purposes of establishing non-inferiority due to a lack of comparability between the studies included in the naïve comparison, and a lack of direct measures of the comparative effectiveness of cladribine and fingolimod in years 3 and 4.
- 7.2 The PBAC considered the nominated comparator of fingolimod was reasonable, consistent with its previous view when it recommended cladribine at its March 2018 meeting. However, the PBAC also considered the other DMTs in the higher efficacy tier for RRMS including natalizumab, alemtuzumab, ocrelizumab, ozanimod and ofatumumab were also relevant alternatives.
- 7.3 The PBAC recalled its previous recommendation that cladribine and fingolimod were non-inferior over 2 years, based on a comparison of the randomised phases of the CLARITY (cladribine) and FREEDOMS (fingolimod) studies. The Committee reaffirmed its previous view that the randomised phases of these studies were comparable for the purposes of establishing the currently accepted basis of listing and equi-effective doses of cladribine and fingolimod over 2 years.
- 7.4 The PBAC noted that the submission's claim that 2 years of treatment with cladribine plus 2 years of no treatment is non-inferior to 4 years of treatment with fingolimod was based on a naïve comparison of the point estimates from the extension phases of the CLARITY and FREEDOMS studies. The PBAC considered there were significant issues that impacted the comparability of the extension phases of these studies, including:
- In the extension phase of the CLARITY study, patients who received the 3.5mg/kg dose of cladribine were re-randomised to 3.5mg/kg cladribine or placebo following a gap in treatment (the median duration of this gap was 40.3 weeks), with 71% of patients in this arm entering the extension study. The PBAC considered that the risk of being randomised to placebo and the gap between completing the main study and entering the extension study resulted

in a high risk of selection bias for the cohort of patients who returned to the extension phase. The PBAC considered that patients who performed better on treatment with cladribine or those with less severe disease would be more likely to volunteer for the extension study. As such, the PBAC re-iterated its previous view that the enrolled population in the extension study was likely not reflective of the full CLARITY population; and

- In the FREEDOMS extension study all participants in the fingolimod 0.5 mg arm were eligible to continue on fingolimod 0.5 mg and hence the potential for selection bias was less than for the CLARITY extension study.

Given these differences between the extension phases of the CLARITY and FREEDOMS studies, combined with the relapsing/remitting nature of the condition, the PBAC considered the claim of non-inferiority (based on a naïve comparison of point estimates from these studies) over a period longer than two years was not supported.

7.5 The PBAC noted that the submission presented RWE regarding the rates at which alternative disease modifying therapies (DMTs) were initiated following 2 years of treatment with cladribine. The Committee also noted that input from consumers and clinicians generally supported the claim that some patients do not require additional treatment in their third year after commencing cladribine. However, the PBAC considered that the rate of commencing alternative DMTs is not a direct measure of the durability of effect of cladribine in years 3 and 4 and considered that it was unclear if this was a reasonable surrogate measure. For example, given the natural history of RRMS, the PBAC considered it was plausible that some patients would experience few or no relapse events in the period for which the RWE was presented, therefore the rate of commencing an alternative DMT could not be solely attributed to the effects of cladribine. The PBAC noted no evidence was presented to support a claim that treatment with cladribine solely accounts for the observed rate of DMT switching. Further, the PBAC noted these observational RWE studies did not include any comparative evidence versus fingolimod. Overall, the PBAC considered these studies did not support the non-inferiority of cladribine versus fingolimod over a period longer than 2 years.

7.6 The PBAC noted that the RWE evidence indicated that a proportion of patients remain untreated with an alternative DMT for a period after 2 years of treatment with cladribine. However, the PBAC considered there were issues with the RWE provided (in addition to the issues outlined in the paragraph above), including:

- It was unclear how the data were collected and considered that given the design of these studies there were likely substantial risk of bias issues;
- The Committee considered the RWE presented may not be applicable to the Australian context, as the studies were small and conducted in countries with different health systems to Australia. The PBAC agreed with the ESC with regards to the specific issues for individual RWE studies noted in paragraph

6.24; and

- The PBAC considered the issues noted above applied to the Patti 2020 study which was used to inform the DMT switch rates in the submission's economic analysis, as it was a small study of only 34 relevant participants conducted in Italy. The PBAC considered it was unlikely the results would be generalisable to the Australian context.

- 7.7 The PBAC noted the additional information presented in the sponsor hearing and pre-PBAC response regarding a recently conducted (but unpublished) analysis of Australian patients in the MSBase registry with RRMS who had initiated on cladribine or other oral DMTs (including fingolimod). The PBAC considered that the additional information was potentially informative but noted only limited detail was provided and the data could not be evaluated.
- 7.8 The PBAC considered the existing equi-effective doses and therapeutic relativities for cladribine and fingolimod remained appropriate.
- 7.9 The PBAC noted that the submission presented a cost minimisation approach (CMA) over a time horizon of 4 years with offsets for a proportion of patients switching to fingolimod (as a proxy for other DMTs) in years 3 and 4. The pre-PBAC Response presented a revised price proposal which appeared to exclude the fourth year from the price calculations and continued to rely on the DMT switch rates from the Patti 2020 study in year 3. The PBAC considered the cost minimisation approach presented in the submission and pre-PBAC response were not adequately supported as the clinical data and RWE did not adequately demonstrate the non-inferiority of cladribine and fingolimod over longer than two years.
- 7.10 The PBAC considered the utilisation and financial estimates were not reliable due to the limitations with the CMA and the data informing the assumptions around the rates and timing of initiating alternative DMTs following 2 years of treatment with cladribine, as outlined above.
- 7.11 The PBAC noted that this submission is not eligible for an Independent Review as it was not seeking a change to the listing that includes a new indication, objectively different subtype of disease or new population.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

The sponsor had no comment.