

11.01 CLADRIBINE, Tablet 10 mg, Mavenclad[®], Merck Healthcare Pty Ltd

1 Purpose of submission

- 1.1 This Category 2 submission requested a revision to the equi-effective doses of cladribine versus fingolimod for the treatment of relapsing remitting multiple sclerosis (RRMS).
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) of cladribine administered over two years (plus two years of no treatment) compared to fingolimod administered over four years.
- 1.3 Table 1 provides a summary of the key components of the resubmission.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with 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 3.5 mg/kg, followed by observation only for two further years.
Comparator	The main comparator for cladribine is fingolimod 0.5 mg administered daily (over four years to match duration of therapeutic effect for cladribine).
Outcomes	Annual relapse rate, time-to-treatment switch, time-to-treatment discontinuation, time to first relapse, time to 6-month disability progression or improvement, EDSS measures, rates of no evidence of disease activity, proportion of patients relapse-free; proportion of patients switching treatment, proportion of patients discontinuing treatment, proportion of patients completing treatment
Clinical claim	Cladribine is non-inferior to fingolimod in terms of efficacy over four years. Cladribine is non-inferior to fingolimod in terms of safety over four years.

EDSS = expanded disability status scale; RRMS = relapsing remitting multiple sclerosis
Source: pp13-16, 25 and 36-37 of the resubmission.

2 Background

Registration status

- 2.1 Cladribine was TGA registered for RRMS in December 2017. The current TGA-approved indication for cladribine tablets is:

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

Previous PBAC consideration

- 2.2 Cladribine was recommended at the July 2018 PBAC meeting for treatment of RRMS. This recommendation was made on a cost-minimisation basis against the comparator fingolimod based on equi-effective doses of the therapies over two years.
- 2.3 In November 2021, the sponsor sought a revision to the effective price of cladribine based on a CMA comparing two years of cladribine treatment to four years of fingolimod, which was not recommended by the PBAC.
- 2.4 Table 2 provides an overview of the matters of key concern from the November 2021 submission and details of how these issues were addressed in the resubmission.

Table 2: Summary of key matters of concern from November 2021 submission

Component	Matter of concern	How this submission addresses it
Clinical effectiveness – non-inferiority	There were significant issues impacting comparability of the extension phases of the CLARITY and FREEDOM studies, upon which the submission's claim of non-inferiority was based (paragraph 7.4, cladribine PSD, November 2021).	New evidence was presented from a prospective registry data study (GLIMPSE), two retrospective analyses of registry data (Maglashvili 2022 and CLARENCE), PBS 10% sample data and German IQVIA longitudinal data. Not adequately addressed. The included studies provided limited data to allow a comparison of the efficacy and safety of cladribine versus fingolimod over a four-year treatment duration.
Clinical effectiveness – surrogate outcomes	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. The PBAC noted no evidence was presented to support a claim that treatment with cladribine solely accounts for the observed rate of DMT switching (paragraph 7.5, cladribine PSD, November 2021).	The resubmission reported that in a study of 110,326 RRMS patients from 1997 to 2016, the main reason for treatment discontinuation and/or switching was lack of efficacy, followed by lack of tolerance, side effects, convenience and disease progression in that order (Hillert et al. 2021). ^a The resubmission reported that in GLIMPSE, cladribine treated patients had a lower annualised relapse rate in years 3 and 4 ($p=0.02$) and an improved time to treatment switching and discontinuation (both $p<0.001$) compared to fingolimod. Not adequately addressed given data limitations.
Clinical effectiveness - RWE	The PBAC noted observational RWE studies did not include any comparative evidence versus fingolimod (paragraph 7.5, cladribine PSD, November 2021).	The GLIMPSE study of MSBase Registry data presents comparative evidence of cladribine tablets versus other DMTs in routine clinical use over 3 or 4 years of treatment. Partially addressed. While comparative data was presented, it provided limited data over 4 years of treatment.
Clinical effectiveness – applicability to Australia	The PBAC 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 (paragraph 7.6, cladribine PSD, November 2021).	The GLIMPSE study captured a large proportion of Australian patients. The resubmission also presented an Australian-specific PBS 10% sample analysis to support the GLIMPSE study findings. Partially addressed. The proportion of Australian patients in GLIMPSE was reduced in the propensity score matching process (42.9% of patients receiving cladribine and 20.6% of patients receiving

Component	Matter of concern	How this submission addresses it
		fingolimod). The PBS 10% sample did not provide comparative efficacy data.
Economic evaluation	The PBAC noted that the submission presented a 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 that 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 CMA 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 (paragraph 7.9, cladribine PSD, November 2021).	The resubmission included PBS 10% sample data that captured Australian patients who have been treated with cladribine and fingolimod for over 4 years to derive fingolimod compliance, patient discontinuation, and treatment switching for both cladribine and fingolimod over the 4-year period. Partially addressed. The PBS 10% sample data included a limited number of patients who received four years of cladribine treatment. (Out of the 310 patients who commenced treatment with cladribine, only 29 (9%) patients received 4 years of treatment. In comparison, 511 (52%) patients received 4 years of fingolimod treatment out of 978 patients who commenced treatment).
Financial estimates	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 (paragraph 7.10, cladribine PSD, November 2021).	Partially addressed. PBS services data 2019-2022 was used to estimate script numbers for the financial estimates, however it is not known if the use of cladribine tablets has stabilised to allow use of a logarithmic trend equation as used in the resubmission.

DMT = disease modifying therapy; RRMS = relapsing-remitting multiple sclerosis; RWE = real world evidence; PSD = public summary document; CMA = cost-minimisation approach

^a The resubmission also stated that the introduction of novel therapies may disrupt this pattern of treatment switching, but as switching therapies heightens relapse risk, it is sensible to assume that an individual switches treatment due to a lack of efficacy or tolerance, and that examining switching rates is a reasonable surrogate measure for treatment efficacy.

Source: Table 3, pp17-18 of the resubmission.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty ^{a,b}	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Cladribine, 10 mg tablet, 1 tablet	\$3,803.52 published \$ effective	1	1	1	Mavenclad
Cladribine, 10 mg tablet, 6 tablets	\$22,010.47 published \$ effective	1	6	1	Mavenclad
Cladribine, 10 mg tablet, 4 tablets	\$29,293.25 published \$ effective	2	8	1	Mavenclad

- 3.1 A requested restriction was not presented in the resubmission as no changes to the current PBS listing of cladribine tablets (PBS codes: 11603Q, 11604R and 11611D) were proposed.
- 3.2 The ESC noted the current restriction did not preclude the use of cladribine in years 3 and 4.
- 3.3 The AEMP proposed for one tablet of cladribine in the revised CMA was \$ [REDACTED], which is [REDACTED] % lower than the AEMP proposed in the November 2021 submission and [REDACTED] % higher

than the current AEMP (\$). The pre-PBAC Response proposed a revised lower price of \$ per tablet (% higher than the current AEMP).

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. 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, patients experience less recovery from relapses and accumulate underlying disability. Most RRMS patients progress to secondary progressive MS (SPMS), which is characterised by ongoing deterioration in function with interspersed relapses.

5 Comparator

- 5.1 As in the November 2021 cladribine submission, the resubmission nominated fingolimod as the main comparator. The resubmission's arguments in support of this nomination were: (1) the PBAC considered that fingolimod was a reasonable comparator at the November 2021 meeting, consistent with its view at the March 2018 meeting where cladribine was initially recommended; (2) the resubmission reported that 2022 PBS Medicare utilisation statistics demonstrated that fingolimod 500 microgram capsules have the highest market share by number of scripts (42.13%); and (3) the administration of fingolimod as an oral tablet matches that of cladribine. The evaluation and ESC considered that fingolimod remains an appropriate comparator but, as previously acknowledged by the PBAC, cladribine may replace any of the PBS subsidised RRMS treatments.
- 5.2 In the context of the cost-minimisation approach taken by the resubmission, 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. Given the established therapeutic relativities in RRMS, natalizumab, alemtuzumab, ocrelizumab, ozanimod and ofatumumab may also be alternative therapies. The ESC noted the established therapeutic relativities in RRMS include numerous higher efficacy tier agents, which were not considered by the resubmission.

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 a brief overview of updated data from the MSBase registry and discussed their clinical experience treating patients with cladribine in Australia. The clinician stated that lack of switching is considered a good indicator of the efficacy and tolerability of a treatment. The clinician further stated that cladribine may be selected for patients that are likely to be less compliant, so the clinician can be more confident that the treatment will be efficacious over the longer-term.

Consumer comments

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

Clinical studies

6.3 The resubmission was based on one prospective longitudinal study that compared registry data for patients with MS who were treated with cladribine tablets or other oral disease modifying therapies (DMTs) including fingolimod (GLIMPSE), and two retrospective database studies that investigated patients who received cladribine for MS (Magalashvili 2022; CLARENCE).

6.4 The resubmission also presented supportive data from an analysis of PBS 10% sample data for MS treatment services between 2011 and 2022, and longitudinal prescribing data from German patients with RRMS who were treated with cladribine tablets (IQVIA Longitudinal Prescription database).

6.5 Publication details of the included studies are provided in Table 3.

Table 3: Studies and associated reports presented in the resubmission for the included studies

Trial ID	Protocol title/ Publication title	Publication citation
GLIMPSE	Spelman T., et al. Comparative effectiveness of cladribine tablets versus other oral disease-modifying treatments for multiple sclerosis: Results from MSBase registry. Additional internal data.	<i>Mult Scler.</i> 2022; 29(2):221-235
Magalashvili 2022	Magalashvili D., et al. Cladribine treatment for highly active multiple sclerosis: Real-world clinical outcomes for years 3 and 4.	<i>J Neuroimmunol.</i> 2022; 15:372:577966.
CLARENCE	Brownlee, W., et al. Real-World Use of Cladribine Tablets (Completion Rates and Treatment Persistence) in Patients with Multiple Sclerosis in England: the CLARENCE Study. Additional internal data.	<i>Multiple Sclerosis and Related Disorders</i> 2023; 71: 104286.

6.6 The key features of the included evidence are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Included studies						
GLIMPSE	cladribine, n=699; fingolimod n=699 ^a	Prospective MSBase registry data from 31 countries; 4 years ^d	High	MS	ARR, time to first relapse, time to treatment switching, time to treatment discontinuation, time to 6 month improvement, time to 6 month confirmed disability progression	Not used
Magalashvili 2022	128 ^b	Retrospective analysis of Israeli database; 5 years	High	Highly active MS	ARR, EDSS, NEDA-2	Not used
CLARENCE	2,685 ^b	Retrospective analysis of English database; 5 years	High	Patients receiving cladribine	Treatment completion, treatment switch, EDSS	Not used
Supportive studies						
PBS 10% sample data	cladribine, n=310; fingolimod n=978	PBS services data; 2011 to 2022	High	RRMS	Number of patients, receiving cladribine, treatment switching, discontinuations, DMT received after switching	Treatment switching data
IQVIA LRx	848 ^c	German longitudinal prescription data; 4 years	High	MS	Treatment switches, average tablets per patient; patients receiving an additional cycle of cladribine	Not used

ARR = annualised relapse rate; EDSS = expanded disability status scale; LRx = Longitudinal Prescription database; MS = multiple sclerosis; NEDA = no evidence of disease activity; RRMS = relapsing remitting multiple sclerosis

^a Details not shown for patients who received dimethyl fumarate or teriflunomide. Data for July 2022 data cut, propensity score matched cohorts.

^b Studies investigated treatment with cladribine only.

^c Database captured German prescription data. Data only provided for patients who received cladribine.

^d The resubmission provided data for both the GLIMPSE July 2022 and August 2021 data cuts. The July 2022 data cut provided the potential for up to 4 years of follow-up.

Source: Sections 2.3 to 2.6 of the resubmission.

6.7 The resubmission stated that as the evidence presented in the November 2021 submission was not considered sufficient by the PBAC to support the 4-year efficacy claim of cladribine versus fingolimod, it was not represented in the current resubmission. Therefore, the comparison of the relevant arms of the cladribine CLARITY trial extension and the fingolimod FREEDOMS I and FREEDOMS II trial extensions were excluded from the resubmission, as were the previous RWE examples (Pfeuffer 2021, De Stefano 2020, Patti 2020 and Giovannoni 2020/2021). The evaluation considered this may be reasonable as the November 2021 submission did not present comparative data for cladribine and fingolimod treatment arms from the same study, and instead compared extension trial data from CLARITY (low dose cladribine followed by placebo treatment arm) with extension trial data from FREEDOMS I and II (fingolimod treatment arm).

Comparative effectiveness

- 6.8 To adjust for potential confounding in GLIMPSE, the cladribine cohort was propensity score matched to the fingolimod cohort using a pre-defined standard difference threshold (0.15) for 10 prespecified potential confounders (age, sex, duration of MS disease, expanded disability status scale (EDSS) score, count of relapses in the prior 12 and 24 months, number of prior DMTs since disease onset, being treatment naïve (yes/no), country and MS classification). For the baseline data of the GLIMPSE July 2022 data cut, the standardised difference for the unmatched cohort data was greater than 0.15 for all the potential confounders except for sex and whether patients were treatment naïve, indicating that the unmatched treatment cohorts were not well-balanced. Consequently, the evaluation and the ESC considered the results of the matched cohorts are likely to be of greater relevance than the unmatched cohorts when comparing treatment with cladribine and fingolimod. The ESC noted that it is unknown if all important confounders were captured and adjusted for, and that this was a considerable risk given the cohorts were not well-balanced. The pre-PBAC Response stated that baseline MRI data is another known potential confounder, and that while this was not a part of the minimum dataset in the MSBase registry, that fingolimod is highly unlikely to be prescribed to patients with worse disease activity and prognosis than cladribine.
- 6.9 The GLIMPSE baseline data for the July 2022 data set unmatched cohorts indicated that patients who received cladribine were older (mean age 43.77 years vs 38.01 years; standardised difference 0.497), had a longer mean disease duration (12.47 years vs 9.02; standardised difference 0.413), had a higher median EDSS score (2 vs 1.5; standardised difference 0.533), had a lower number of recent relapses (relapses in prior 12 months: 0.40 vs 0.53, standardised difference -0.189; relapses in prior 24 months: 0.59 vs 0.80, standardised difference -0.235) and had a higher mean number of prior DMTs (2.40 vs 1.61, standardised difference 0.333), compared to patients who received fingolimod. Patients in the cladribine and fingolimod cohorts also had a different country profile with patients receiving cladribine most commonly from Australia (53.6%), Canada (12.6%) and Spain (9.6%), whereas patients receiving fingolimod were most commonly from Turkey (51.5%), Australia (9.4%) and Canada (7.1%). The Pre-Sub-Committee Response (PSCR) considered the comparison of baseline characteristics of the unmatched cohorts to not be relevant. The ESC considered the information to be important context for the comparability of the cohorts and the extent of matching required.
- 6.10 The matched cohorts from the two GLIMPSE data cuts did not include the same patients (August 2021 data cut: cladribine, N=520 and fingolimod, N=520; July 2022 data cut: cladribine, N=699 and fingolimod, N=699). The propensity score matching appeared to be generally successful with the exception of the confounder 'country' for the July 2022 data set where a standardised difference of -0.223 was retained. Additionally, for the confounder country, the propensity score matching appeared to introduce some anomalies between the data sets. For example, despite there being

more patients in the July 2022 matched data set, the August 2021 data set contained 235 fingolimod treated patients from Turkey while there were only 148 fingolimod treated patients from Turkey in the July 2022 data set.

- 6.11 The resubmission presented the results for annualised relapse rate (ARR) for the matched and unmatched cohorts for both the August 2021 and July 2022 data cuts (Table 5). While ARR was found to be statistically significantly different between cladribine and fingolimod for both the matched and unmatched cohorts at the August 2021 data cut, this was no longer the case for the matched cohort at the July 2022 data cut.
- 6.12 The PSCR provided the results of updated analyses (to the July 2023 data cut from GLIMPSE) for ARR, proportion of patients relapse free, time to 6-month confirmed disability progression, proportion of patients persisting on treatment and proportion of patients who switched therapy. These results were not independently evaluated, however are relevant as they increase the amount of patient data available for these analyses, particularly for years 3 and 4 of treatment, which are most relevant to the clinical claim. These analyses are presented where relevant in the discussion below (Table 5 and Table 6).

Table 5: GLIMPSE, annualised relapse rate of matched and unmatched cladribine and fingolimod cohorts

Cohort	Drug	Number of relapses	On index DMT follow-up (years)	ARR (95% CI)	P value
July 2022 data cut					
Matched	Cladribine (n=699)	104	1074.35	0.0968 (0.0791, 0.1173)	0.0679
	Fingolimod (n=699)	139	1133.88	0.1226 (0.1031, 0.1447)	
Unmatched	Cladribine (n=882)	123	1401.85	0.0877 (0.0729, 0.1047)	0.0063
	Fingolimod (n=1554)	264	2235.11	0.1181 (0.1043, 0.1333)	
August 2021 data cut					
Matched	Cladribine (n=520)	47	498.28	0.0943 (0.069, 0.1254)	0.0156
	Fingolimod (n=520)	89	612.27	0.1454 (0.1167, 0.1789)	
Unmatched	Cladribine (n=633)	49	613.07	0.0799 (0.0591, 0.1057)	0.0002
	Fingolimod (n=1195)	201	1411.38	0.1424 (0.1234, 0.1635)	
July 2023 data cut (presented in the PSCR, not independently evaluated)*					
Matched	Cladribine (n=1,163)	218	2163.93	0.1007 (0.0878, 0.1150)	0.9562
	Fingolimod (n=1,163)	226	2255.07	0.1002 (0.0876, 0.1142)	

ARR = annualised relapse rate; CI = confidence interval; DMT = disease modifying therapy
Italicised figures extracted during the evaluation.

Source: Table 11, p39 of the resubmission and GLIMPSE MSBASE_AUGUST 2022 UPDATE_v5_6feb23 & PSCR Table 1. Only data for the matched cohort provided for the July 2023 data cut.

** Note that the results of the July 2023 data cut presented in Table 5 are derived from an analysis conducted by the GLIMPSE study investigator during preparation of the Pre-Subcommittee Response specifically for the purposes of informing the ESC and PBAC considerations. The analysis has not been independently evaluated and peer-reviewed for publication. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.13 While patients in GLIMPSE could have been followed for up to three years at the August 2021 data cut, Spelman 2022 reported that the median follow-up time for GLIMPSE was 1.14 years (interquartile range (IQR): 0.49–1.92) for the cladribine cohort and 1.28 years (IQR: 0.57–2.01) for the fingolimod cohort. Median on-treatment follow-up in the matched cohort (following propensity score matching) was 0.91 years (IQR: 0.11-1.50) for cladribine and 1.07 years (IQR: 0.42-1.77) for fingolimod. Therefore, while patients could potentially have been enrolled in GLIMPSE for up to three years at this data cut, the follow-up duration for most patients was substantially shorter. Consequently, the evaluation considered GLIMPSE provided limited data to substantiate the resubmission’s clinical claim that cladribine is non-inferior to fingolimod in terms of both efficacy and safety over four years. (These figures were not available for the subsequent July 2022 data cut where patients were followed for up to four years.)

6.14 The PSCR provided data based on an analysis of the GLIMPSE data at July 2023, stating that the data was consistent with that reported in the resubmission, and indicative of

no significant differences in annualised relapse rate, which was consistent with the July 2022 data. The Response also noted updated analyses on time to first relapse, time to 6-month confirmed disability progression and time to switch/discontinuation were undertaken. The ESC noted that the updated data did not include the proportion of patients who were relapse free.

- 6.15 The ESC noted that the ARR decreased with additional follow-up for fingolimod (from 0.1454 to 0.1002, ~30% reduction, based on the matched analysis) and conversely increased for cladribine (0.0943 to 0.1007, ~7% increase), which may suggest the extent of follow-up and small proportion with at least 4 years of follow-up is an important consideration.
- 6.16 Results for other outcomes measured in GLIMPSE are presented in Table 6 for the matched cladribine and fingolimod cohorts. The cladribine cohort displayed longer time to treatment switch and time to discontinuation.

Table 6: Outcomes for the comparison between matched cladribine and fingolimod cohorts

Outcome	Unadjusted Hazard Ratio (95% CI), p-value	Number of patients remaining at year 4
July 2022 data cut		
Time to first relapse	0.74 (0.55, 1.00), 0.051	CLAD = 3, FNG = 15
Time to treatment switch	0.30 (0.19, 0.38), <0.001	CLAD = 3, FNG = 15
Time to treatment discontinuation	0.19 (0.14, 0.27), <0.001	CLAD = 3, FNG = 15
Time to 6-month confirmed disability progression	1.45 (0.87, 2.39), 0.150	CLAD = 4, FNG = 10
Time to 6-month confirmed improvement	0.85 (0.57, 1.328), 0.440	CLAD = 5, FNG = 12
July 2023 data cut (not independently evaluated)*		
Time to first relapse	0.90 (0.72, 1.13), 0.363	CLAD = 61, FNG = 119
Time to treatment switch	0.29 (0.23, 0.37), <0.001	CLAD = 75, FNG = 133
Time to treatment discontinuation	0.22 (0.18, 0.28), <0.001	CLAD = 75, FNG = 130
Time to 6-month confirmed disability progression	1.19 (0.81, 1.77), 0.373	CLAD = 62, FNG = 111
Time to 6-month confirmed improvement	1.05 (0.71, 1.55), 0.808	CLAD = 27, FNG = 55

Source: Table 12, p41 of the resubmission and PSCR attachment GLIMPSE_MSBASE_JULY 2023 UPDATE_v1_19 (matched analyses cla vs fin).xlsx. July 2022 data cut patient numbers extracted from attachment GLIMPSE_MSBASE_AUGUST 2022 UPDATE_v5_6Feb23.xlsx.

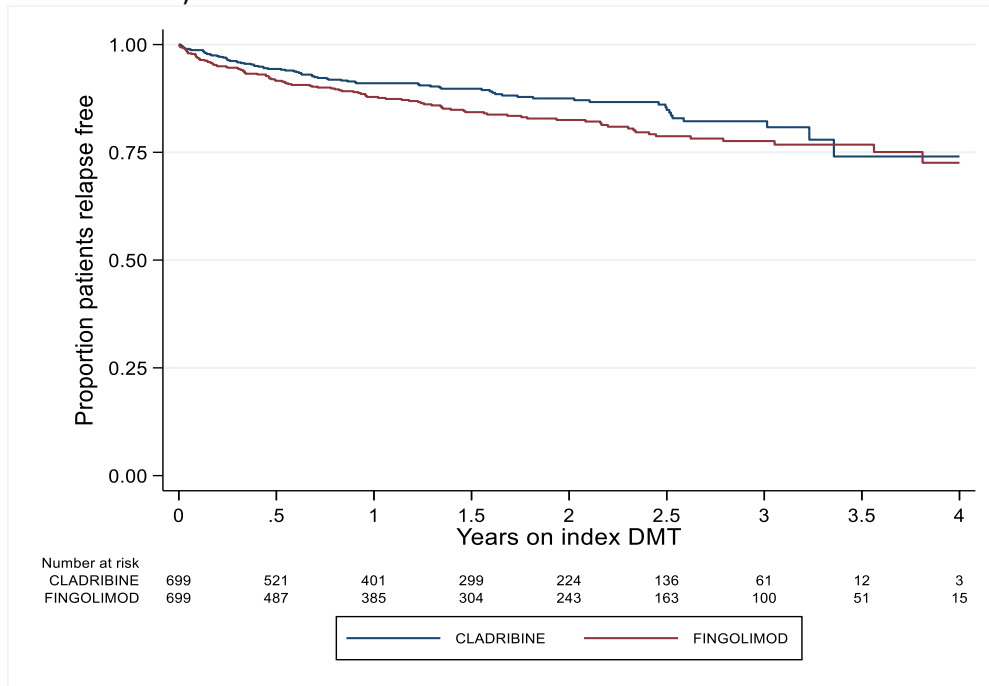
Abbreviations: CLAD = cladribine; FNG = fingolimod

* Note that the results of the July 2023 data cut presented in Table 6 are derived from an analysis conducted by the GLIMPSE study investigator during preparation of the Pre-Subcommittee Response specifically for the purposes of informing the ESC and PBAC considerations. The analysis has not been independently evaluated and peer-reviewed for publication. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.17 The GLIMPSE Kaplan-Meier graph of the probability of remaining relapse free is shown in Figure 1. The resubmission stated that for GLIMPSE, “it was assumed that patients in the MSBase registry follow their nation or territory’s indicated dosages, timings, methods of administration, etc, but this information is not available”. It therefore cannot be verified what cladribine and fingolimod dosage regimens were used by patients in GLIMPSE; although, as a high proportion of patients who received cladribine in GLIMPSE were from Australia (42.9% in the July 2022 data cut, matched cohort), it is possible that their dosage regimen aligned with Australian clinical

practice. However, as the cladribine dose schedule and how long patients took cladribine for in GLIMPSE were not documented and are essentially unknown, the applicability of GLIMPSE to Australian clinical practice remains unknown. The PSCR (pg. 3) stated the Sponsor sought advice from regulatory affairs branches who confirmed the dose of cladribine is consistent across the world and reiterated a substantial proportion of the matched GLIMPSE cohort were from Australia.

Figure 1: GLIMPSE, Kaplan-Meier graphs for proportion of patients remaining relapse free (July 2022 data cut, matched cohorts)

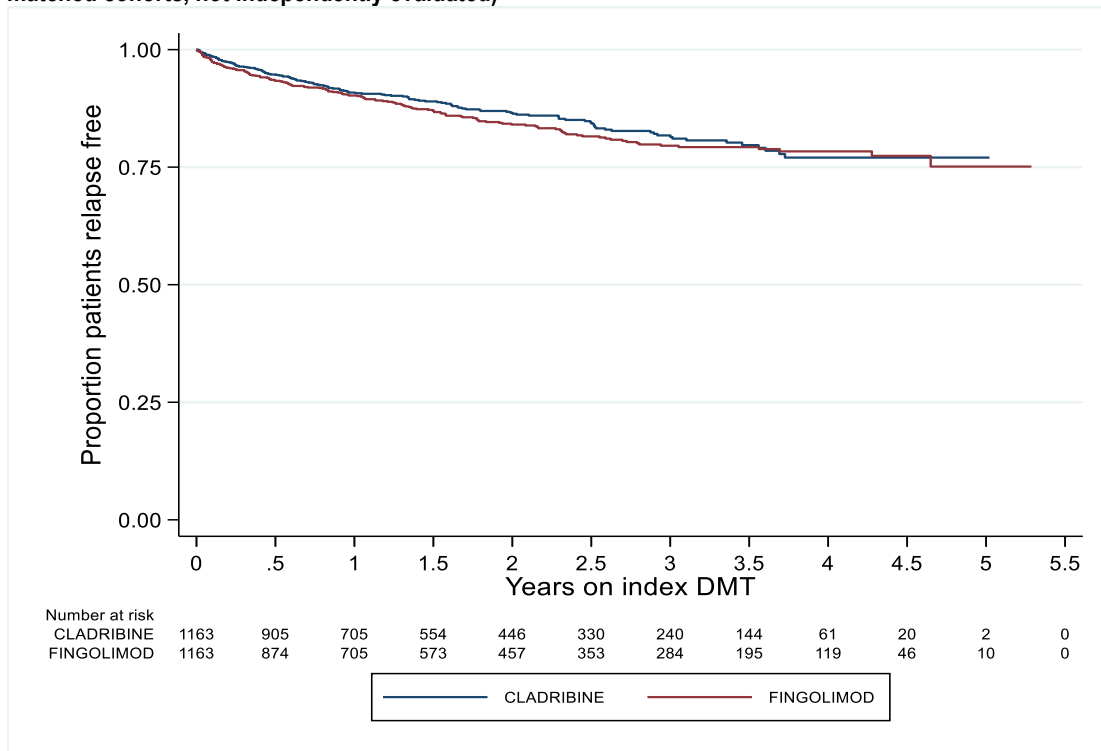


DMT = disease modifying therapy

Source: Figure 7, p43 of the resubmission

6.18 An updated Kaplan-Meier plot for proportion of patients remaining relapse free based on the July 2023 data cut (matched cohorts) from the PSCR is presented below.

Figure 2: GLIMPSE, Kaplan-Meier graphs for proportion of patients remaining relapse free (July 2023 data cut, matched cohorts, not independently evaluated)

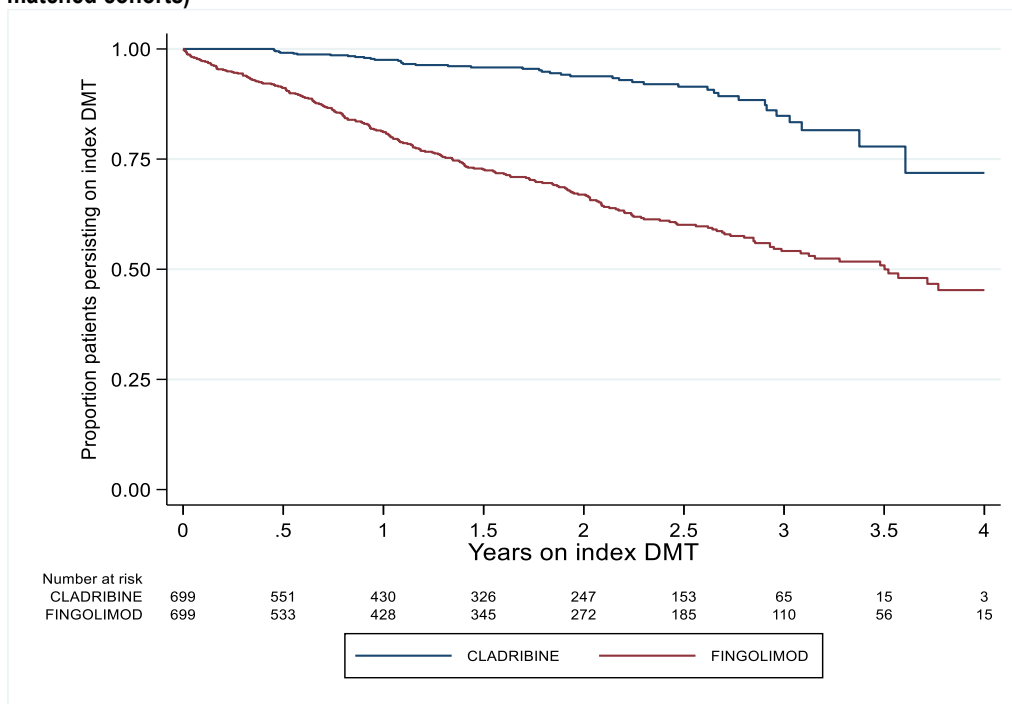


Source: Figure 1 of the PSCR.

Note that the results of the July 2023 data cut presented in Figure 2 are derived from an analysis conducted by the GLIMPSE study investigator during preparation of the Pre-Subcommittee Response specifically for the purposes of informing the ESC and PBAC considerations. The analysis has not been independently evaluated and peer-reviewed for publication. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.19 The GLIMPSE Kaplan-Meier graph for the proportion of patients persisting on treatment (i.e., time to treatment discontinuation) is shown in Figure 3.

Figure 3: GLIMPSE, Kaplan-Meier graph for proportion of patients persisting on treatment (July 2022 data cut, matched cohorts)



Source: Figure 6, p42 of the resubmission

- 6.20 For GLIMPSE, eligible patients were censored at treatment discontinuation or switch to another DMT, death, loss to follow-up or the start of a pregnancy (whichever occurred first). The number of patients who remained at risk decreased rapidly over time with only 3 patients receiving cladribine at risk at year 4. This data therefore provides limited evidence to demonstrate the efficacy of cladribine compared to fingolimod during the fourth year of cladribine treatment. Consequently, GLIMPSE provided limited data to substantiate the resubmission’s clinical claim that cladribine is non-inferior to fingolimod in terms of both efficacy and safety over four years. The PSCR clarified that patients were only censored at death or loss to follow-up.
- 6.21 While the resubmission claimed that time-to-treatment discontinuation is a surrogate measure of treatment persistence, previously "the PBAC ... 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" (paragraph 6.23, cladribine PSD, November 2021).
- 6.22 While GLIMPSE (July 2022 data cut, matched cohorts) found that patients taking cladribine had a statistically significantly longer time to treatment switch and time to treatment discontinuation compared to patients taking fingolimod, there was no significant difference in the proportion of patients remaining relapse-free. As no correlation was observed between patient relapse (the PBAC’s preferred outcome measure of sustained benefit for RRMS; paragraph 6.10, alemtuzumab PSD,

November 2018) and the proposed surrogate outcome, it suggests that treatment switch and treatment discontinuation may be a poor surrogate for patient relapse.

- 6.23 The PSCR stated the resubmission was based on patient outcome measures that have been accepted by the PBAC as relevant for RRMS therapies previously, including ARR, time to first relapse and time to confirmed disability progression. The ESC considered that time to treatment discontinuation was not an informative outcome, given cladribine is only taken in Weeks 1 and 5 of the first 2 years of therapy and therefore necessarily was defined differently versus that for fingolimod. The pre-PBAC Response stated that time to treatment switch provides a good indication of efficacy for comparing therapies, as it defines a point at which the people with RRMS no longer benefit from their existing treatment and are in need of a different treatment.
- 6.24 Magalashvili 2022 reported ARR for one year prior to cladribine initiation until year 4, as shown in Table 7.

Table 7: ARR in cladribine treated patients in years 3 and 4 – Sheba MS Registry

Relapse outcome	Cladribine treated MS patients – Years 3-4		
	mean (SD)	median	IQR
ARR 1 year prior, N = 61	1.6 ± 0.86	2.0	1.0-2.0
ARR Year 1, N = 61	0.34 ± 0.57	0.0	0.0-1.0
AAR Year 2, N = 61	0.14 ± 0.36	0.0	0.0-0.0
ARR Year 3, N = 61	0.36 ± 0.58 ^a	0.0	0.0-1.0
ARR Year 4, mean (SD) N = 35	0.17 ± 0.38 ^a	0.0	0.0-1.0
Relapse free	N (%)		
Relapse free Year 3,	42/61 (68.9%)		
Relapse free Year 4	29/35 (82.9%)		

ARR = annual relapse rate; IQR = interquartile range; SD = standard deviation

^a The decrease in mean ARR from the year prior to the study compared to years 3 and 4 was statistically significant, $p < 0.0001$.

Source: Table 13, p44 of the resubmission and Table 2 of Magalashvili 2022

- 6.25 Magalashvili 2022 reported that no evidence of disease activity (NEDA-2) was achieved for 59.0% (36/61) of patients in year 3, and for 74.3% (26/35) in year 4 of cladribine treatment. Table 8 provides further details.

Table 8: Clinical characteristics of cladribine treatment responders and non-responders by NEDA-2

Characteristic	Year-3, n=61		Year-4, n=35	
	Responders ^a n=36, 59%	Non-responders n=25, 41%	Responders ^a n=26, 74.3%	Non-responders n=9, 25.7%
Sex F/M, n	26/10	17/8	18/8	5/4
Sex F/M, %	72.2/27.8	68/32	69.2/30.8	55.6/44.4
Age, years	40.9	37.6	38.5	37.8
Disease duration, years	12.3	13.3	11.5	8.8
ARR 1 year prior	1.8	1.6	1.7	2.1
EDSS Baseline	3.8	3.5	3.5	4.0

ARR = annual relapse rate; EDSS = expanded disability status scale; F = female; M = male; NEDA-2 = no evidence of disease activity

^a No significant changes were found between clinical variables at the onset of cladribine treatment between responders and non-responders for Year 3 and Year 4.

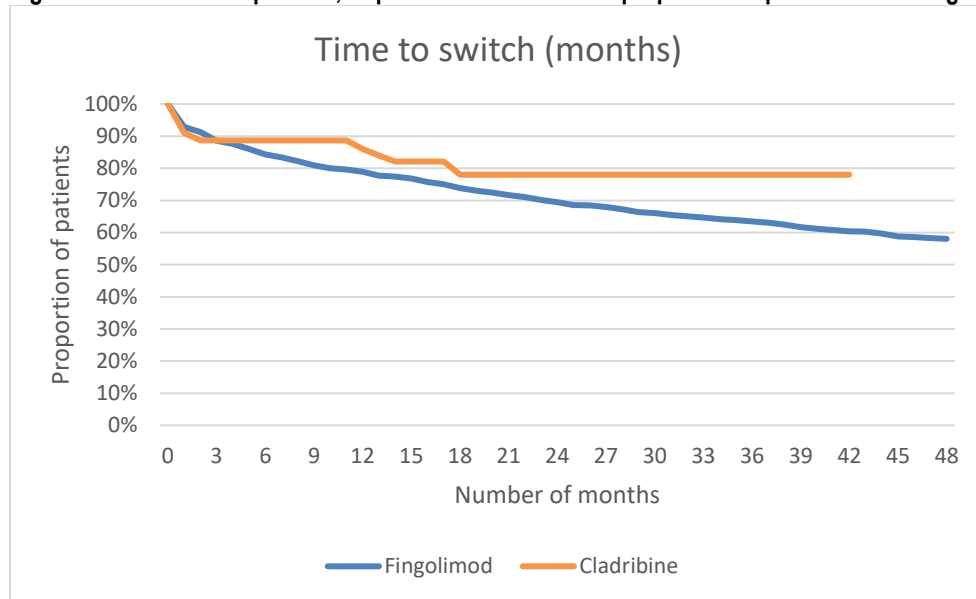
Source: Table 14, p44 of the resubmission and Table 4 of Magalashvili 2022

- 6.26 In CLARENCE, a total of 61% of patients completed treatment, with 11% discontinuing and the remaining 28% of patients having insufficient follow-up. In all, 93 % of patients

did not switch from cladribine treatment to another DMT during the course of the follow-up. i.e., 7% (194/2,685) of patients who received cladribine tablets switched to another DMT.

- 6.27 The PBS 10% sample data was used in the resubmission to provide Australian specific prescribing data for the use of cladribine and fingolimod. This data was obtained by extracting PBS data records from the available PBS 10% sample data for the treatment of MS. All publicly available records from 2011 to January 2023 were utilised, although cladribine was only PBS listed in 2019.
- 6.28 The resubmission reported that for the 327 patients whose first PBS script of cladribine was dispensed between January 2019 and January 2023:
- Of 188 patients for whom cladribine was initiated more than two years ago, ten (5.3%) received the third course of therapy, including one (0.5%) receiving the fourth course of therapy.
 - Of 117 patients receiving cladribine who have at least 3 full years of data, nine (7.7%) received the third course of therapy, including one (0.9%) receiving the fourth course of therapy.
- 6.29 While this data was unable to be verified during the evaluation, it appears that some patients received additional cladribine treatment beyond the recommended dose. The cladribine PI states “Patients should receive no more than two treatment courses over two consecutive years. The recommended dose should not be exceeded. Following completion of the two treatment courses, no further cladribine treatment is required in years 3 or 4”.
- 6.30 In the PBS 10% data sample, the proportion of patients remaining on cladribine or fingolimod treatment after initiation, i.e., patients who have not switched to an alternative DMT, is shown in Figure 4. The resubmission reported that at 42 months, a greater proportion of fingolimod treated patients had switched compared to cladribine treated patients.

Figure 4: PBS 10% sample data, Kaplan-Meier curve of the proportion of patients remaining on indexed treatment ^{a b}



^a Data for fingolimod patients is shown over 48 months, whereas data for cladribine treated patients is shown for 42 months.

^b Patients were censored if they were still on therapy as of 31 December 2022.

Source: Figure 10, p48 of the resubmission

6.31 The resubmission claimed that the PBS 10% sample data show that in years 3 and 4 after treatment initiation, a greater proportion of patients on fingolimod switched or discontinued treatment compared to patients on cladribine. The resubmission stated that cladribine had zero (0%) discontinuations or switch-outs in years 3 and 4, whereas fingolimod treated patients had 9.6% (63/658) and 9.0% (52/581), respectively. Table 9 provides further details.

Table 9: PBS 10% sample data, progression of patients on fingolimod or cladribine on PBS over previous 5 years

DMT		Year 1	Year 2	Year 3	Year 4	Year 5
Fingolimod	Start of period	978	753	658	581	511
	Switch outs	180	80	50	44	45
	Discontinuations	40	9	13	8	7
	Censored (still on therapy) ^a	5	6	14	18	17
	End of period	753	658	581	511	442
Cladribine	Start of period	310	236	157	103	29
	Switch outs	33	11	0	0	0
	Discontinuations	0	0	0	0	0
	Censored (still on therapy) ^a	41	68	54	74	29
	End of period	236	157	103	29	0

^a Patients who were still on therapy on 31 December 2022 were censored.

Source: Table 16, p48-49 of the resubmission

6.32 The data included in the 10% PBS sample covered different time spans for cladribine and fingolimod, due to the dates they were listed on the PBS. This resulted in the potential for these drugs to be used in different environments due to the timeframes involved. For example, from 2011 to 2018 there were a number of other DMTs listed on the PBS for the treatment of MS, which could have increased the potential for patients using fingolimod during these years to switch treatment. The PSCR argued

this suggestion was unsubstantiated as a similar number of new DMTs in the higher efficacy tier were listed in the period after the listing of cladribine (siponimod, ozanimod and ofatumumab) than were listed in the prior 6 years (alemtuzumab, daclizumab (now delisted) and ocrelizumab, and further argued that treatment selection in practice is often related to patients’ personal preferences for how certain treatments are delivered. The Response also argued the propensity score-matched analyses of the GLIMPSE study balanced over 10 potential confounding baseline characteristics, effectively mitigating the impact of any residual biases in the study.

- 6.33 While the resubmission did not re-present any data from the November 2021 submission, for reference, Table 10 provides an overview of the ARR and proportion of patients free from relapses, as reported in the November 2021 submission.

Table 10: 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)
Annualised relapse rate			
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
Proportion free from relapses, n/N (%)			
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% ^a	66.6% ^a

EXT = extension trial; LLPP = low dose cladribine followed by placebo.

^a patient numbers (n/N) not presented.

Source: paragraph 6.14, cladribine PSD, November 2021.

Comparative harms

- 6.34 Data regarding the incidence of adverse events experienced by patients with RRMS was not available for GLIMPSE. While Spelman 2022 reported that safety data were not considered as part of the current analysis and were only partially available, reasons for treatment discontinuation were reported where available. Overall, a greater proportion of patients in the matched fingolimod cohort discontinued treatment compared to patients in the cladribine cohort (August 2021 data set). This was the case for every reported discontinuation reason, except for “scheduled stop” where the same number of patients in each treatment arm discontinued. The most common reasons for discontinuing treatment were lack of improvement (cladribine 0.8%, fingolimod 11.0%) and adverse event (cladribine 0%, fingolimod 8.7%).
- 6.35 For the November 2021 submission, the PBAC considered that non-inferior safety was not adequately demonstrated. This was on the basis of the CLARITY and FREEDOMS trial extensions and because the submission did not explain the high rate of serious adverse events in the CLARITY extension (LLPP arm) compared to the arms of the pivotal trial (paragraph 6.27, cladribine PSD, November 2021). The data available for GLIMPSE and the other studies presented in the resubmission did not allow for a

comparison of individual adverse events or serious adverse events. Consequently, concerns regarding the high rate of serious adverse events seen in the CLARITY extension trial may persist.

Benefits/harms

6.36 The evidence presented in the resubmission did not allow for a quantitative comparison of the benefits and harms for the use of cladribine for the treatment of RRMS. Accordingly, a benefits/harms table was not presented.

Clinical claim

6.37 The resubmission described cladribine as non-inferior in terms of effectiveness compared to fingolimod over four years and non-inferior in terms of safety compared to fingolimod over four years. The evaluation considered that this claim was not adequately supported. The key issues were:

- There was limited data demonstrating the efficacy of cladribine versus fingolimod for the treatment of RRMS over 4 years. While GLIMPSE and the PBS 10% sample both allowed patients to be followed for four years, GLIMPSE reported a median on-treatment follow-up of 0.91 years (IQR: 0.11-1.50) for cladribine tablets and 1.07 years (IQR: 0.42-1.77) for fingolimod (matched cohorts, August 2021 data cut). For the PBS 10% sample, only 29 patients out of an initial cohort of 310 patients on cladribine were still being followed during year 4, with the remainder of the patients considered to be “switch outs” or “discontinuations” (defined for fingolimod as the patient not receiving another script for the drug for six months or when they switched to another therapy, and for cladribine this was defined as when the patient switched to a new therapy) or “censored” (i.e. still on therapy on 31 December 2022). Consequently, GLIMPSE provided limited data to substantiate the resubmission’s clinical claims that cladribine is non-inferior to fingolimod in terms of both efficacy and safety over four years.
- For GLIMPSE, the four-year data for ARR (matched cohorts, July 2022 data cut) found no statistically significant differences between cladribine and fingolimod. The PBAC has previously stated its preference for the outcome of proportion of patients remaining relapse-free as an outcome of sustained benefit (paragraph 6.10, alemtuzumab PSD, November 2018).
- While the time to treatment switch and time to treatment discontinuation data for GLIMPSE indicated favourable results for cladribine versus fingolimod, previously 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 (paragraph 7.5 cladribine PSD, November 2021).
- GLIMPSE (July 2022 data cut, matched cohorts) found that patients taking cladribine had a statistically significantly longer time to treatment switch and time

to treatment discontinuation compared to patients taking fingolimod, yet there was no significant difference in the proportion of patients remaining relapse-free for these treatments. As a correlation was not observed between patient relapse and the proposed surrogate outcomes, it suggests that treatment switch and treatment discontinuation may be a poor surrogate for patient relapse.

- The nature of the cladribine dosage schedule makes treatment discontinuation more difficult to assess for cladribine compared to fingolimod or other DMTs, which necessitated the use of different definitions of time to treatment discontinuation for cladribine compared to fingolimod. Consequently, these measures may not be equivalent between cladribine and other DMT.
- In clinical practice the inclination to switch treatments is likely to be correlated with the choice of treatment for RRMS. If a patient is considered likely to need or want to switch treatment in the next 3 to 4 years, it is less likely they would be prescribed cladribine. Consequently, the characteristics of the patients prescribed cladribine in non-randomised studies may be different to the characteristics of patients prescribed fingolimod. This, in fact, was observed to be the case in GLIMPSE where the propensity score matching pre-defined standard difference threshold indicated differences in the unmatched cohorts for most of the ten pre-defined potential confounders other than sex and being treatment naïve (yes/no) and included age, duration of MS disease, expanded disability status scale (EDSS) score, count of relapses in the prior 12 and 24 months, number of prior DMTs since disease onset, country and MS classification).

- 6.38 The ESC considered that while the data may be suggestive of the proposition that 2 years of cladribine treatment (plus a period of no treatment) may be non-inferior to more than 2 years of fingolimod, the data provided was not robust. The ESC noted that the data from GLIMPSE was not randomised and, based on updated data in the PSCR, for the outcome of proportion relapse free, only 5% (n=61) of the cladribine cohort and 10% (n=119) of the fingolimod cohort remained at risk at 4 years.
- 6.39 The PBAC considered the clinical claim of non-inferior comparative efficacy and safety of cladribine for two years (with two year of no treatment) and fingolimod over four years was not adequately justified.

Economic analysis

- 6.40 During the evaluation the sponsor provided an updated CMA workbook for evaluation. The updated CMA included modified cladribine and fingolimod switch data, as the switch data used in the model had initially been inconsistent with the clinical data presented.
- 6.41 As in the November 2021 submission, the resubmission presented a CMA of cladribine compared to fingolimod over four years. The most notable change in the CMA in the resubmission was the use of PBS 10% sample data to determine treatment switching for cladribine and fingolimod (timing of switching and the treatment received after

switching) and compliance for fingolimod. Additionally, unlike in the November 2021 CMA, cost offsets for health professional time were not included in the base case.

6.42 Table 11 provides a summary the key components of the CMA.

Table 11: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on the clinical evidence presented, effectiveness of cladribine is non-inferior to fingolimod for MS outcomes over a four-year period.
Therapeutic claim: safety	Based on the clinical evidence presented, safety of cladribine is likely to be non-inferior to fingolimod over a four-year period.
Evidence base	PBS 10% sample data ^a
Equi-effective doses	Cladribine 3.5 mg/kg over 2 years administered as one treatment course of 1.75 mg/kg per year (consisting of 2 treatment weeks per year) = Fingolimod 500 mcg once daily over 4 years.
Compliance rate	Cladribine: 100% (as used in July 2018 and November 2021 cladribine submissions) Fingolimod: 85.90% (based on PBS 10% sample data)
Direct medicine costs	Two years of cladribine tablets medicine costs is no more expensive than four years of fingolimod treatment costs.
Other costs or cost offsets	The CMA included offsets for the cost of subsequent DMTs received after treatment with cladribine or fingolimod in patients who switched treatment at any point during the 4-year period, based on the PBS 10% sample data. The pre-PBAC Response presented a revised CMA with the switching assumptions and cost offsets removed. For MS outcomes, some cost offsets in healthcare professional time as shown by the Time and Motion study (Appendix 1 to the resubmission) were included in the sensitivity analysis.
Discounting	No discount rate was applied because no outcomes were modelled, and it was not necessary to discount the costs used in the economic evaluation. The ESC noted the costs were discounted in the CMAs for onasemnogene abeparvovec (paragraph 8.11, September 2021 PSD) and zanubrutinib (paragraph 6.66, March 2023 PSD).

MS = multiple sclerosis

^a The resubmission incorrectly stated that the evidence base was "Indirect analysis using randomised controlled trials for MS as well as match-adjusted indirect comparison in the GLIMPSE study of real-world data".

Source: Table 22, p60 of the resubmission.

6.43 The CMA assumed non-inferiority over a four-year time horizon. The PBAC rejected this claim for the cladribine submission in November 2021 (paragraph 7.1, cladribine PSD, November 2021). If the clinical claim of non-inferiority over four years is not accepted, a cost-minimisation over four years remains inappropriate.

6.44 The proposed equi-effective dose was:

- 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; and
- Fingolimod 500 mcg once daily over 4 years.

This equated to a proposed equi-effective dose of 280 mg of cladribine and 627.06 mg of fingolimod.

6.45 In the CMA in the November 2021 submission, the proposed equi-effective dose was 280 mg of cladribine and 697 mg of fingolimod. The difference in fingolimod dose was due to a change in assumed compliance rate, which was based on the PBS 10% sample

data in the resubmission. The PBS 10% sample data did not report compliance data for cladribine, and this was assumed to be 100% as in previous submissions. In the July 2018 submission where cladribine was recommended by the PBAC, the equi-effective dose presented was 280 mg of cladribine and 348 mg of fingolimod (i.e. for the 2-year CMA of cladribine and fingolimod) (paragraph 5.12, cladribine PSD, July 2018).

- 6.46 As in the November 2021 submission, treatment switching was not addressed in the consideration of equi-effective doses but rather included as an offset in the current resubmission. The PBAC previously considered that “(t)his 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 previously noted that inclusion of any rate of treatment switching would only be appropriate if non-inferiority is demonstrated” (paragraph 6.35, cladribine PSD, November 2021). The PSCR stated that the switching rates applied in the CMA were derived from the prescription data of the PBS 10% sample and that this adequately reflects treatment practice in Australia. The ESC considered that this issue remains relevant to the resubmission.
- 6.47 Unlike the November 2021 submission where patients were assumed to only switch treatment after 2 years of cladribine or fingolimod, the resubmission claimed that the PBS 10% sample data demonstrated that patients could switch treatment in years 1 to 4. The cladribine and fingolimod switch rates used in the CMA are shown in Table 12.

Table 12: PBS 10% sample data, cladribine and fingolimod switch rate per year ^a

DMT	Cladribine tablets		Fingolimod	
	Patients, n	% switch	Patients, n	% switch
Total patients year 1	269		973	
Patients who switched treatment year 1	33	12.3%	220	22.6%
Total patients year 2	168		747	
Patients who switched treatment year 2	11	6.5%	89	11.9%
Total patients year 3	103		644	
Patients who switched treatment year 3	0	0.0%	63	9.8%
Total patients year 4	29		563	
Patients who switched treatment year 4	0	0.0%	50	8.9%

^a Switch rate incorporates patients reported as either switching or discontinuing in the PBS 10% sample data.

Source: Tables 26 and 27, pp 64 and 65 of the resubmission and Mavenclad Cost Min Analysis PBAC Nov 2023 (revised 20230802).xlsm

- 6.48 While the resubmission used the current PBS 10% sample data to provide the switch rate for cladribine and fingolimod patients in this resubmission CMA, several concerns remain with the use of this data:
- The PBS 10% sample data contained limited data for patients receiving cladribine after year 2, with only 29 of the original 310 patients receiving cladribine remaining active during year 4 of treatment (9.4%). In comparison, 511 of the original 978 patients receiving fingolimod remained active during year 4 of treatment (52.2%).

- Switch rates may be overestimated due to the inclusion of 'discontinuations' in the total number of patients classified as having switched from cladribine or fingolimod to another RRMS treatment. This may favour cladribine as a total of 0 patients on cladribine were classified as discontinuations over years 1 to 4, compared to a total of 75 patients for fingolimod.
 - Patients discontinuing treatment with fingolimod would generally be expected to continue on a different DMT. However, the assumption that patients who discontinue treatment immediately start another treatment inherently overestimates costs, as there may be some lag time between discontinuation and initiation of a new treatment. This favours cladribine as higher rates of switching were used for fingolimod in the CMA.
 - The nature of the cladribine dosage schedule makes it more difficult to assess discontinuation for cladribine compared to fingolimod or other DMTs, thereby necessitating the use of different definitions to define discontinuation for cladribine compared to fingolimod. Consequently, these measures may not be equivalent.
 - The data included in the 10% PBS sample covered different time spans for cladribine and fingolimod due to the dates they were listed on the PBS. This resulted in the potential for these drugs to be used in different environments due to the timeframes involved. For example, from 2011 to 2018 there were a number of other DMTs listed on the PBS for the treatment of MS thereby increasing the potential for patients using fingolimod to switch treatment during these years. The PSCR argued that new DMT listings on the PBS are not drivers of patient treatment choices and therefore not impactful on the CMA.
- 6.49 The resubmission reported that some patients captured in the PBS 10% data sample received additional cladribine treatment beyond the recommended dose. i.e., third and fourth dose courses. These additional doses should be accounted for in the CMA and/or the uncertainty associated with the use of additional (off label) cladribine dose courses should be addressed through a risk-sharing arrangement (RSA). As the third and fourth courses of cladribine were not included in the CMA presented in the resubmission, they were included in a sensitivity analysis conducted during the evaluation. The PSCR stated the sponsor was amenable to revising the base case CMA with this adjustment and noted that this resulted in a base case cost-minimised effective price of \$| per 10 mg tablet.
- 6.50 The pre-PBAC Response presented a revised CMA with the switching and treatment assumptions removed and as an alternative to an RSA, the Response proposed increasing the proportion of patients taking cladribine up to 10% in years 3 and 4.
- 6.51 To incorporate the cost of the alternate RRMS treatments that patients switched to after cladribine or fingolimod as a cost offset, the treatment options were categorised into three tiers: high efficacy tier, low efficacy tier and fingolimod tier. While

fingolimod is cost-minimised to several DMTs categorised as “high efficacy”, the resubmission stated that fingolimod was assigned its own tier due to its pricing being different from the other high efficacy tier treatments.

- 6.52 The annual cost for each of the alternate RRMS therapies reported by the PBS 10% sample data was calculated using their respective Product Information or estimated based on the PBS Therapeutic Relativity Sheets. The annual cost of each alternate treatment was bundled into an average treatment cost for each tier with each of the treatments within each tier given equal weighting. Then the average treatment cost of the tiers was used to calculate the weighted average cost per year of alternate treatment following switching or discontinuation from cladribine and fingolimod.
- 6.53 It may have been inappropriate for fingolimod to be included in its own tier in the CMA rather than in the high efficacy tier as fingolimod has been cost-minimised to or considered non-inferior to the drugs in the high efficacy tier and the clinical claim made in the resubmission was that cladribine has non-inferior efficacy and safety compared to fingolimod. If fingolimod had been put into the high-efficacy tier, its (lower) price may have less impact (as the price of the tier was calculated using an average, with the price of all drugs having equal impact. However, a sensitivity analysis conducted during the evaluation found that reclassifying fingolimod into the high efficacy tier had a low impact on the price of cladribine calculated in the CMA.
- 6.54 The resubmission stated there were three stages in the stepped analysis:
- Step 1: Calculation of the total medicine cost for fingolimod over two years;
 - Step 2: Calculation of the total medicine cost for fingolimod over four years; and
 - Step 3: Calculation of the base case model for the cost-minimised price of a one tablet pack of cladribine based on an equivalent total healthcare cost for fingolimod over four years, including the cost for switch patients.
- 6.55 Table 13 presents the details of the CMA (step 3).

Table 13: CMA of cladribine versus fingolimod over 4 years

	Cladribine	Fingolimod
Mg per maximum quantity	10.00	14.00
Maximum quantity over 4 years	28.00	45.00
Total patients in year 1 (n)	252	973
Patients who switched treatment year 1 (%)	16.7%	22.6%
Total patients in year 2 (n)	149	747
Patients who switched treatment year 2 (%)	4.0%	11.9%
Total patients in year 3 (n)	84	644
Patients who switch in year 3 (%)	0.0%	9.8%
Total patients in year 4 (n)	0	562
Patients who switch in year 4 (%)	0.0%	8.9%
Weighted average alternate treatment costs (\$)		\$12,128.48
Weighted average cost of treatment Year 1(\$)		\$11,022
Weighted average cost of treatment Year 2(\$)		\$10,870
Weighted average cost of treatment Year 3(\$)		\$10,839
Weighted average cost of treatment Year 4(\$)		\$10,826
Total cost of treatment with switch for 4 years (effective AEMP) (\$)		\$43,557.40
Equi-effective EMP (cladribine cost-minimised against fingolimod treatment cost over four years) (\$)		\$951.05

EMP = Ex-manufacturer price

Source: Table 39, p 72 of the resubmission and Mavenclad Cost Min Analysis PBAC Nov 2023 (revised 20230802).xlsm

6.56 The proposed effective EMP per pack of cladribine tablets based on the calculated price of one cladribine tablet from the updated CMA is shown in Table 14.

Table 14: Cladribine tablets effective EMP pricing details

Drug name	Comparator	Pack quantity	Maximum quantity (packs)	Proposed Effective AEMP
Cladribine	fingolimod	1	1	\$
Cladribine	fingolimod	4	2	\$
Cladribine	fingolimod	6	1	\$

EMP = Ex-manufacturer price

Source: Table 40, p73 of the resubmission and Mavenclad Cost Min Analysis PBAC Nov 2023 (revised 20230802).xlsm

6.57 The revised proposed effective EMP as presented in the pre-PBAC Response, based on the assumptions in paragraph 6.50 was \$| per 10 mg tablet.

6.58 In July 2018, the PBAC recommended the listing of cladribine for treatment of RRMS on a cost-minimisation basis against fingolimod based on a claim that two years of cladribine treatment is non-inferior in efficacy to two years of fingolimod treatment (paragraph 6.1, cladribine PSD, July 2018). While still requesting non-inferiority between cladribine and fingolimod, the resubmission has requested (a) a re-specification of the intervention previously accepted by the PBAC (i.e. change from 2 years of cladribine to 2 years of cladribine plus 2 years of no treatment and change in comparator treatment duration to 4 years of fingolimod; (b) re-specification of the therapeutic relativities; and (c) re-assessment the cost-effectiveness of cladribine compared to fingolimod on that basis.

6.59 Table 15 provides a summary of the key sensitivity analyses. Inclusion of third and fourth courses of cladribine in line with the PBS 10% sample data was found to have the most impact on the price of cladribine calculated in the CMA.

Table 15: CMA sensitivity analysis

Parameter combination	Cladribine tablets Effective EMP (1 tablet pack)
Base case (proposed)	\$
Incorporation of additional third and fourth courses of cladribine based on the PBS 10% sample data (patients with at least 3 years follow-up) ^a	\$
Exclude ozanimod from the “high efficacy tier calculation	\$
Include ofatumumab in the “high efficacy” tier calculation	\$

EMP = Ex-manufacturer price

^a In the PBS 10% sample data, of the 117 patients receiving cladribine who have at least 3 full years of data (i.e., patients whose first PBS script was dispensed in January 2020 or earlier, nine (7.7%) received the third course of therapy, including one (0.9%) receiving the fourth course of therapy.

Source: Table 43, p75 of the resubmission and calculations conducted using Mavenclad Cost Min Analysis PBAC Nov 2023 (revised 20230802).xism

6.60 Overall, even if non-inferiority over four years was accepted, the resubmission's CMA likely overestimated the cladribine cost-minimised price due to:

- The exclusion of third and fourth courses of cladribine used by Australian patients, as observed in the PBS 10% sample data.
- The inclusion of discontinuations in the PBS 10% switch data. While the resubmission stated that due to the chronic, progressive nature of RRMS, it was assumed that these patients would initiate another treatment if they discontinued treatment with cladribine or fingolimod, it was not explained why these patients would not have been classified as “switch outs” in the report of the PBS 10% switch data (Attachment 1 of the resubmission);
- The inclusion of ozanimod in the high efficacy tier, despite the PBS 10% sample data recording that no patients switched to ozanimod from cladribine or fingolimod; and
- The exclusion of the cost of ofatumumab from the high efficacy tier, despite the PBS 10% sample data recording that some patients switched to ofatumumab from cladribine and fingolimod.

While each of these had a relatively small impact, combined they contributed to the uncertainty of the CMA.

6.61 There was additional uncertainty surrounding the results of the CMA due to:

- Weighting all of the drug costs evenly within each of the high and low efficacy tiers;
- Compliance for cladribine was assumed to be 100% while compliance for fingolimod was assumed to be 85.90%. The fingolimod compliance rate was based on PBS 10% sample data, which did not report this data for cladribine.
- The PBAC previously considered it unclear if specific 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 (paragraph 6.35, cladribine PSD, November 2021). While a relatively low proportion of patients on cladribine were observed to switch treatment in the PBS 10% sample data, the switch rate was

higher for fingolimod (and data for fingolimod was also included in the equi-effective dose calculations).

- Previously, the ESC noted that inclusion of any rate of treatment switching would only be appropriate if non-inferiority is demonstrated (paragraph 6.35, cladribine PSD, November 2021).
- No discounting was applied to costs and outcomes in the CMA although the therapeutic claim was based on four years of cladribine treatment.

Cladribine cost/patient/course

6.62 The drug cost per patient per course of cladribine is \$[redacted] based on an effective EMP of \$[redacted] per tablet and a dosage of 28 tablets over two years of treatment. This compares to \$[redacted] for four years of fingolimod based on an effective AEMP of \$[redacted] and 627.06 mg dispensed over four years (0.5 mg/day x 365.25 days x 4 years of treatment x 85.90% compliance). Applying the updated cladribine price offer in the pre-PBAC Response (\$[redacted]), the drug cost per patient per course would be \$[redacted].

6.63 Table 16 presents the drug cost per patient for cladribine and fingolimod.

Table 16: Drug cost per patient for cladribine and fingolimod (original submission price – not PSCR updated)

	Cladribine studies	Cladribine model	Cladribine financial estimates	Fingolimod trial dose and duration ^c	Fingolimod model	Fingolimod financial estimates
Mean dose	280 mg over two years of treatment followed by two years of observation ^b			0.5 mg/day	0.5 mg/day	0.5 mg/day
Mean duration				24 months	4 years	4 years
Cost/patient/course ^a	\$[redacted]			\$21,874.15	\$43,557.40	\$43,557.40

Source: compiled during the evaluation

^a Cladribine dose is based on the patient's body weight. An average body weight of 76.6 kg was assumed throughout the resubmission, which resulted in a 280 mg dose of cladribine over two years.

^b 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 3.5 mg/kg, followed by observation only for two further years.

^c Presented for a duration of 2 years, consistent with the stepped CMA.

Source: Tables 37, 38 and 39, pp71-72 of the resubmission and Mavenclad Cost Min Analysis PBAC Nov 2023 (revised 20230802).xlsm

6.64 The drug cost per patient for both cladribine and fingolimod were lower in the resubmission than in the November 2021 submission, predominantly due to price reductions for fingolimod due to reference price reductions and a First New Brand (FNB) Statutory Price Reduction (SPR) and a lower proposed price for cladribine.

6.65 As the CMA used AEMP, the impact of wholesaler and pharmacy markups were not captured in the CMA. While fingolimod would require dispensing every month (12 scripts per year, 48 scripts over the 4-year treatment duration), cladribine would require approximately 6 scripts over the 4-year treatment duration (assuming an average patient weight of 76.6kg).

Estimated PBS usage & financial implications

6.66 This resubmission was not considered by DUSC.

6.67 Table 17 presents the data sources used in the resubmission.

Table 17: Data sources and parameter values applied in the utilisation and financial estimates

Parameter	Input	Source	Comment
Market size of cladribine data			
Cladribine market growth rate	2023 - 5.50% 2024 - 2.71% 2025 - 2.23% 2026 - 1.89% 2027 - 1.64% 2028 - 1.44% 2029 - 1.28%	Growth rates were calculated using a logarithmic trend equation based on cladribine PBS services data from 2019 to 2022.	Annual cladribine PBS use changed by +32% in 2020, -6% in 2021 and +6% in 2022. As it appears that cladribine use may not follow a consistent trend, this data may not provide a reliable base to calculate projected annual growth rate to 2029. In the November 2021 submission a market growth rate of 3% was used, in line with the Deed of Agreement for cladribine. This has been investigated in sensitivity analysis during the evaluation.
Proportion of cladribine units expected to be affected by effective price change (uptake rate in utilisation and cost model)	2022-2027 – 100%	The proposed listing would result in an effective price change for all units.	Reasonable.
Proportion of cladribine patients expected to remain treatment free after 2-year treatment regimen	Year 3 – 100% Year 4 – 100%	PBS 10% Medicare Sample Dataset	While the PBS 10% data indicated that no patients receiving cladribine would switch treatments during years 3 and 4, 4-year data was captured for a limited number of patients (29/310 patients initiating treatment) compared to fingolimod (511/978 patients initiating treatment). Consequently, the assumption that all patients on cladribine do not switch treatment in years 3 and 4 may not be robust. However, as this same assumption has been made for both proposed and affected cladribine, it thereby minimises the overall impact.
Costs^{a b}			
Cladribine, 10 mg (pack size 1 tablet, maximum quantity 1 pack)	Public AEMP - \$3,641.39 Public DPMQ - \$3,803.52 Current effective AEMP - \$ Current effective DPMQ - \$ Proposed effective AEMP - \$ Proposed effective DPMQ - \$	Requested effective prices from revised CMA. Requested effective price, based on	The financial estimates were updated to include the proposed cladribine AEMP and DPMQ from the revised CMA. Proposed cladribine prices were likely over-estimated.

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Parameter	Input	Source	Comment
Cladribine, 10 mg (pack size 4 tablets, maximum quantity 2 packs, repeats 1)	Public AEMP - \$14,565.56 Public DPMQ - \$29,293.25 Current effective AEMP - \$ Current effective DPMQ - \$ Proposed effective AEMP - \$ Proposed effective DPMQ - \$	CMA price for 1 tablet. Public prices to remain the same.	The PSCR proposed a lower AEMP of \$ per tablet to account for use of cladribine in years 3 and 4 in the PBS 10% sample.
Cladribine, 10 mg (pack size 6 tablets, maximum quantity 1 pack)	Public AEMP - \$21,848.34 Public effective DPMQ - \$22,010.47 Current effective AEMP - \$ Current effective DPMQ - \$ Proposed effective AEMP - \$ Proposed effective DPMQ - \$		The pre-PBAC Response proposed a further reduction in the AEMP to \$. The financial estimates below are based on the original submission, unless otherwise noted.
Patient co-payment	PBS: \$21.68 RPBS: \$6.60	PBS statistics for 2022 for the current cladribine items (11603Q, 11604R, 11611D)	The resubmission included a PBS general co-payment of \$41.30. This was changed to \$30.00 during the evaluation.

AEMP = Approved ex-manufacturer price; CMA = cost-minimisation approach; DPMQ = dispensed price maximum quantity; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Published PBS prices effective July 2023.

^b Effective AEMP from updated CMA (provided by sponsor during evaluation). Effective DPMQ were calculated during the evaluation to align with the updated CMA.

Source: Tables 48 and 49, pp79-80 of the resubmission

- 6.68 The resubmission used a market-share approach to estimate cladribine utilisation. The resubmission reasonably claimed that the proposed effective price change to cladribine is not expected to affect the utilisation of fingolimod or any other DMTs.
- 6.69 The estimated financial implications to the PBS/RPBS were calculated by subtracting the current net cost of cladribine to the PBS/RPBS from the proposed net cost of cladribine to the PBS/RPBS, as shown in Table 18.

Table 18: Estimated financial implications of cladribine for the PBS/RPBS

	2024	2025	2026	2027	2028	2029
Estimated net cost to cladribine (proposed)						
Total script numbers - cladribine	1	1	1	1	1	1
Cost to PBS/RPBS	2	3	3	3	3	3
Patient co-payments	4	4	4	4	4	4
Net cost to PBS/RPBS	2	2	3	3	3	3
Estimated net cost to cladribine (impact)						
Total script numbers - cladribine	1	1	1	1	1	1
Cost to PBS/RPBS	5	5	5	5	5	5
Patient co-payments	4	4	4	4	4	4
Net cost to PBS/RPBS	5	5	5	5	5	5
Estimated financial implications of proposed cladribine listing for the PBS/RPBS (submission)						
Cost of cladribine (proposed)	2	2	3	3	3	3
Cost of cladribine (impacted)	4	4	4	4	4	4
Net cost to PBS/RPBS	6	6	6	6	6	6
Estimated financial implications of proposed cladribine listing for the PBS/RPBS (PSCR updated)						
Cost of cladribine (proposed)	2	2	2	2	2	2
Cost of cladribine (impacted)	4	4	4	4	4	4
Net cost to PBS/RPBS	7	7	7	7	7	7
Sensitivity analyses for the financial estimates (original submission price)						
Cladribine market growth rate (base case: 5.5% to 1.3%)	6	6	6	6	6	6
- 3% per year ^a						
- 5% per year						

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

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 30 million to < \$40 million

³ 40 million to < \$50 million

⁴ net cost saving

⁵ 20 million to < \$30 million

⁶ \$10 million to < \$20 million

⁷ \$0 to < \$10 million

Source: Tables 52, 54 and 55, pp82-86 of the resubmission and worksheet 5. Impact – net, Cladribine_UCM-Release-3-Workbook-v1081 PBAC November 20233. PSCR updated estimates compiled by the Secretariat using revised AEMPs/DPMQs of \$█/\$█ (1 pack), \$█/\$█ (4 pack, max qty 2) and \$█/\$█ (6 pack).

- 6.70 The resubmission estimated that there would be no change in net processing costs for Services Australia and no net changes to MBS items. This was reasonable as no change in scripts was expected. This was also consistent with the CMA base case in which no cost offsets due to healthcare resource use were included.
- 6.71 The total cost to the PBS/RPBS of listing cladribine was estimated in the resubmission to be \$10 million to < \$20 million in Year 6, and a total of \$70 million to < \$80 million in the first 6 years of listing. At the revised PSCR price (AEMP \$█), the total cost of listing to the PBS/RPBS of listing cladribine was estimated to be \$0 million to < \$10 million in Year 6, and a total of \$50 million to < \$60 million in the first 6 years of listing. The price for cladribine was reduced further in the pre-PBAC response but revised financial estimates were not provided.
- 6.72 For the November 2017 submission that sought PBS listing of cladribine on a cost-minimisation basis compared to fingolimod over a 4-year treatment duration, the

PBAC noted that the financial analysis estimated a significant net cost to the PBS, “which undermines the first principles of a cost minimisation analysis” (paragraph 7.1, cladribine PSD, November 2017). While this issue may remain a concern in the resubmission, the resubmission sought to establish that cladribine has been undervalued and that the cost-effectiveness of cladribine should be based on a higher price than at present. The PSCR and pre-PBAC Response further argued that compared to the other DMTs it replaces, cladribine has in fact been cost saving for the PBS/RPBS because in years 3 and 4, there is no drug cost associated with treatment (although ESC noted there was evidence of off label prescribing in this period), whereas the other DMTs require ongoing administration and continue to accrue costs and even after the requested price increase, remains cost saving to the PBS/RPBS.

6.73 While the resubmission estimated that the proposed change in price of cladribine would result in a net cost to the PBS/RPBS:

- The resubmission claimed that the current effective price of cladribine tablets does not account for patients not needing active treatment in years 3 and 4, and therefore the net costs for the proposed change should not be considered as an incremental cost to the PBS/RPBS, but rather as savings foregone as a result of recognising the efficacy in years 3 and 4 of cladribine therapy.
- The resubmission noted that the proposed effective price of cladribine tablets was derived from cost-minimisation to the current price of fingolimod and that the fingolimod price has recently decreased and may now be lower than other high-efficacy DMTs. The resubmission claimed that cost-minimisation of cladribine to the current price of fingolimod offsets the financial impact from the revised equi-effective doses of cladribine tablets to an extent, and the listing of cladribine tablets should be considered cost-saving in comparison to the other high-efficacy DMTs (other than fingolimod) that it replaces.

6.74 While the use of cladribine may potentially be cost saving at the current price, it is unlikely to remain cost saving at the proposed increased price. If the sponsor wished for the above issues to be accounted for in the proposed price of cladribine tablets, then it would have been appropriate to include them in the economic analysis, with the impact on the proposed cladribine price included in the financial estimates. However, as the resubmission did not include these calculations, any impact of these issues remains unquantified.

Financial Management – Risk Sharing Arrangements

6.75 The resubmission did not present any information relating to Risk Sharing Arrangements.

6.76 The resubmission reported that some patients captured in the PBS 10% data sample received additional cladribine treatment beyond the recommended dose. i.e., third and fourth doses. The evaluation and the ESC considered that it may be appropriate

to address the uncertainty associated with the use of additional (off label) cladribine doses through a Risk Sharing Arrangement.

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 for the treatment of relapsing-remitting multiple sclerosis (RRMS), on the basis that the evidence presented did not satisfactorily establish that two years of treatment with cladribine (plus two years of no treatment) is non-inferior to four years of treatment with fingolimod. The PBAC considered the key clinical evidence, a propensity score matched analysis of the MSBase registry data (GLIMPSE), was not reliable for the purposes of establishing non-inferiority over four years given the potential for confounding and the small number of patients on treatment for four years.
- 7.2 The PBAC considered the nominated comparator of fingolimod was reasonable, consistent with its view when it recommended cladribine at its March 2018 meeting. However, the PBAC also considered the other disease modifying therapies (DMTs) in the higher efficacy tier for RRMS including natalizumab, alemtuzumab, ocrelizumab, ozanimod and ofatumumab were relevant alternative therapies. The PBAC noted only evidence versus fingolimod was presented in the resubmission.
- 7.3 The PBAC recalled cladribine was recommended for listing on the basis that cladribine and fingolimod were non-inferior over two years, based on a comparison of the randomised phases of the CLARITY (cladribine) and FREEDOMS (fingolimod) trials, and that it had not recommended amending the existing equi-effective doses following consideration of a submission at its November 2021 meeting.
- 7.4 The PBAC noted that the resubmission provided new clinical evidence from the MSBase registry (GLIMPSE), including a propensity score matched analysis of this data, as well as data from two retrospective database studies that investigated patients who received cladribine (Magalashvili 2022; CLARENCE), and longitudinal prescribing data from a 10% sample of PBS data and from German patients treated with cladribine (IQVIA database).
- 7.5 The PBAC noted the key evidence presented in the resubmission was the propensity score matched analysis of MSBase (GLIMPSE) where patients starting treatment with cladribine or fingolimod (either naïve or switched) were matched based on potential outcome determinants against the probability of receiving cladribine or fingolimod. There were three analyses presented for GLIMPSE: a published analysis with a data cut of August 2021, an analysis with a July 2022 data cut and an analysis presented in the PSCR (and hence not evaluated) with a data cut of July 2023. The PBAC noted the two evaluated matched analyses (August 2021 and July 2022) did not include the same cohort of patients (paragraph 6.10).

- 7.6 The PBAC noted for the July 2022 data cut, prior to matching there were a number of important differences across the cladribine and fingolimod cohorts (paragraph 6.8-6.9), and considered there may be important confounders that were not adjusted for in the matched analysis. Patients in the cladribine and fingolimod cohorts had a different country profile with patients receiving cladribine most commonly from Australia (53.6%), whereas patients receiving fingolimod were most commonly from Turkey (51.5%) followed by Australia (9.4%). The PBAC noted although the propensity score matching was generally successful, the matching did not appear to adequately adjust for the confounder 'country' with a difference larger than the 0.15 nominated standardised difference retained (0.223).
- 7.7 The PBAC noted relatively few patients in all three analyses received treatment for four years. For example, in the July 2022 analysis of the proportion of patients remaining relapse free, 3 patients (0.4%) in the cladribine cohort and 15 patients (2%) in the fingolimod cohort remained at risk at four years. Although this increased to 61 patients (5%) and 119 patients (10%), respectively, in the July 2023 analysis, the number of patients with 4 years of follow-up remained small. The PBAC further noted that the annualised relapse rate (ARR) varied across the three analyses, with the rate decreasing for fingolimod by approximately 30% over the three analyses, and conversely increasing for cladribine by approximately 7% (paragraph 6.15). Overall, the PBAC considered there was limited data to inform the comparative efficacy of cladribine and fingolimod over a four year period.
- 7.8 With regards to the additional evidence sources presented in the submission, the PBAC considered:
- The data from Magalashvili 2022 (paragraphs 6.24-6.25, Tables 6-7) was of limited value given there was no comparator and noting the attrition rate in years 3 and 4;
 - While the treatment switch rate was low for cladribine in the CLARENCE study (paragraph 6.26), the analysis was of limited value given there was no comparator; and
 - Although the analysis of the 10% sample of PBS data (paragraphs 6.27-6.31, Table 9) indicated that the switch rate for cladribine was lower than for fingolimod, this was based on an unadjusted comparison and hence was of limited value as it was not possible to determine whether the patient populations being compared were similar.
- 7.9 The PBAC considered that based on the available evidence, the clinical claim of non-inferior comparative efficacy of cladribine for two years (with two year of no treatment) and fingolimod over four years was not adequately supported.
- 7.10 The PBAC considered the existing equi-effective doses for cladribine and fingolimod remained appropriate.
- 7.11 The PBAC noted that the resubmission presented a cost-minimisation approach (CMA)

of cladribine administered over two years (plus two years of no treatment) compared to fingolimod administered over four years. The price for cladribine proposed in the pre-PBAC response was reduced based on a revised CMA with switching assumptions and associated cost offsets removed. However, the PBAC considered the CMA presented was not reasonable, as the clinical evidence submitted did not adequately demonstrate the non-inferiority of cladribine and fingolimod over four years.

- 7.12 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

Since PBS listing in January 2019, it is Merck's view that a growing body of real-world evidence in Australia and internationally consistently demonstrates that the effectiveness of Mavenclad is sustained in years 3 and 4 and the majority of patients do not need additional treatment in these years. The unique dosing of the therapy reduces the treatment burden for Australians living with relapsing-remitting multiple sclerosis and in Merck's view, reduces costs for the healthcare system compared to other therapies that require continuous dosing. Merck will continue to work closely with the PBAC to amend the PBS listing of Mavenclad.