PUBLIC SUMMARY DOCUMENT
Product: Cladribine, tablet, 10 mg, Movectro®
Sponsor: Merck Serono Australia Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) Authority Required listing for initial and continuing treatment of relapsing–remitting multiple sclerosis (RRMS) initiated by a neurologist, in an ambulatory patient who has experienced at least two documented attacks of neurological dysfunction, believed to be due to multiple sclerosis in the preceding two years who meets certain criteria.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This presentation of cladribine had not been previously considered by the PBAC.

3. Registration Status

Cladribine 10 mg tablets were TGA registered on 2 September 2010 for the treatment of relapsing-remitting multiple sclerosis for a maximum duration of two years.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Authority Required
Initial treatment by a neurologist of clinically definite relapsing-remitting multiple sclerosis in an ambulatory (without assistance or support) patient who has experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years. The diagnosis must be confirmed by magnetic resonance imaging of the brain and/or spinal cord and the date of the scan included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient.

A maximum quantity of 10 tablets will be issued with the initial authority, with no repeats.

Authority Required
Continuing treatment of clinically definite relapsing-remitting multiple sclerosis in a patient previously issued with an authority prescription for this drug and who does not show continuing progression of disability while on treatment with this drug. A maximum quantity of 10 tablets will be issued with each continuing authority. Patients can receive a maximum of one initial and one continuing authority within a 48 week period.

Note: Reimbursed treatment is limited to four courses over two years.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Multiple Sclerosis (MS) is a chronic autoimmune inflammatory, demyelinating disease of the central nervous system (CNS) marked by an aberrant activation of specific T and B cells. It can affect any part of the brain or spinal cord at any time. Usually initial symptoms improve (sometimes completely), only to worsen again, or occur in some other part of the brain or spinal cord. The recovery events are known as remissions and the deterioration events as relapses. Symptoms include impaired vision, weakness and paralysis of muscle, numbness, loss of balance and muscle coordination, slurred speech, bladder and bowel problems, memory loss, depression and mood swings.

It causes disability and premature death in over 16,000 Australians, 87% of whom are of working age and three quarters of whom are women. The onset of MS is typically from 20 to 40 years of age.

The submission proposed that the place in therapy of cladribine 10 mg tablets would provide an alternative treatment option to natalizumab for patients with relapsing remitting multiple sclerosis.

6. Comparator

The submission nominated natalizumab as the main comparator. The PBAC did not accept natalizumab as the appropriate main comparator, *see Recommendation and Reasons.*
The submission presented an indirect comparison of the effectiveness and safety of cladribine versus natalizumab and interferon beta.

7. Clinical Trials

The submission presented one randomised trial comparing cladribine with placebo (CLARITY), one randomised trial comparing natalizumab with placebo (AFFIRM) and one randomised trial comparing interferon beta 1a (Rebif®) with placebo (PRISMS) in patients with RRMS.

The submission presented an indirect comparison of cladribine versus natalizumab and versus interferon beta, using placebo as the common reference.

The table below details the published trials presented in the submission:

Trial ID / First author	Protocol title/ Publication title	Publication citation
Direct randomised trials: cladribine versus placebo		
CLARITY Giovannoni G et al.	A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis"	New England Journal of Medicine 2010, 362 (5), pp416-426.
Direct randomised trials: natalizumab versus placebo		
AFFIRM Balcer LJ et al.	Natalizumab reduces visual loss in patients with relapsing multiple sclerosis.	Neurology 2207, 68 (16) pp1299-1304
Calabresi PA et al.	The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL	Neurology 2007, 69 pp1391-1403
Giovannoni G et al.	Natalizumab improves physical disability in patients with relapsing multiple sclerosis	Journal of Neurology 2009, 256 (S124), p350
Havrdova E et al.	Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study	The Lancet Neurology 2009, 8 (3) pp254-260
Herbert J et al.	Effects of natalizumab on relapses and MRI outcomes in	Multiple Sclerosis 2009,

	hispanic patients with relapsing multiple sclerosis.	15 (9) pS232
Hutchinson M et al.	The efficacy of natalizumab in patients with relapsing multiple sclerosis: Subgroup analyses of AFFIRM and SENTINEL	Journal of Neurology 2009, 256 (3) pp405-415
Kappos L et al.	Clinical effects of natalizumab on multiple sclerosis appear early in treatment course, regardless of baseline disease activity.	Journal of Neurology 2010, 257 ppS22-S23
Kieseier BC et al.	Natalizumab improves quality-of-life outcomes in patients with highly active multiple sclerosis	Journal of Neurology 2009, 256 ppS124-S125
Kieseier BC et al.	The effect of natalizumab therapy on quality of life outcomes in multiple sclerosis patients with non-highly active disease.	Multiple Sclerosis 2009, 15 (9) pS246
Miller DH et al.	MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS	Neurology 2007, 68 (17) pp1390-1401
Munschauer F et al.	Natalizumab improves disability on the multiple sclerosis functional composite in a randomised, double-blind, placebo-controlled study of patients with relapsing multiple sclerosis	Multiple Sclerosis 2009, 15 (9) ppS124-S125
Polman CH et al.	A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis.	New England Journal of Medicine 2006, 354 (9) pp899-910
Rudick RA et al.	Health-related quality of life in multiple sclerosis: Effects of natalizumab	Annals of Neurology 2007, 62 (4) pp335-346
Direct randomised trials: interferon beta-1a (Rebif®) versus placebo		
PRISMS	PRISMS: The story of a pivotal clinical trial series in	Current Medical
Cohen BA & Rivera VM.	multiple sclerosis.	Research and Opinion 2010, 26 (4) pp827-838
Ebers GC/PRISMS Study Group.	Randomised double-blind placebo-controlled study of interferon (beta)-1a in relapsing/remitting multiple sclerosis	The Lancet 1998, 352 (9139) pp1498-1504
Francis G. S. et al.	Interferon (beta)-1a in MS: Results following development of neutralizing antibodies in PRISMS.	Neurology 2005, 65 (1) pp. 48-55
Freedman MS & Forrestal FG.	Canadian treatment optimization recommendations (TOR) as a predictor of disease breakthrough in patients with multiple sclerosis treated with interferon (beta)-1a: Analysis of the PRISMS study	Multiple Sclerosis 2008, 14 (9) pp1234-1241
Gold R. et al.	The long-term safety and tolerability of high-dose interferon (beta)-1a in relapsing-remitting multiple sclerosis: 4-Year data from the PRISMS study	European Journal of Neurology 2005, 12 (8) pp649-656
Hughes RAC.	Interferon-beta 1a (REBIF) in the treatment of relapsing-remitting multiple sclerosis: the clinical results of a large multicentre study.	Multiple Sclerosis 1997, 3 (Suppl), p269. No.S020
Kappos L et al.	Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS	Neurology 2006, 67 (6) pp944-953
Li DKB & Paty DW.	Magnetic resonance imaging results of the PRISMS trial: A randomized, double-blind, placebo-controlled study of interferon-(beta)1a in relapsing- remitting multiple sclerosis	Annals of Neurology 1999, 46 (2) pp197-206
Liu C & Blumhardt LD.	Randomised, double blind, placebo controlled study of interferon (beta)-1a in relapsing-remitting multiple sclerosis analysed by area under disability/time curves	Journal of Neurology Neurosurgery and Psychiatry 1999, 67 (4) pp451-456.
Liu C & Blumhardt LD.	Randomized, double-blind, placebo-controlled study of subcutaneous interferon beta-I a relapsing-remitting multiple sclerosis: A categorical disability trend analysis.	Multiple Sclerosis 2002, 8 (1) pp10-14.
Oger J et al.	Prospective assessment of changing from placebo to IFN beta-1a in relapsing MS: The PRISMS study",	Journal of the Neurological Sciences 2005, 237 (1-2) pp45-52
Patten SB &	Interferon beta-1a and depression in relapsing-remitting	Multiple Sclerosis 2001,

Metz LM.	multiple sclerosis: an analysis of depression data from the PRISMS clinical trial	7 (4) pp243-248
Patten SB & Metz LM.	Hopelessness ratings in relapsing-remitting and secondary progressive multiple sclerosis	International Journal of Psychiatry in Medicine 2002, 32 (2) pp155-165
Paty DW.	Interferon-beta 1a (REBIF) in the treatment of relapsing-remitting multiple sclerosis: the MRI results of a large multicentre study",	Multiple Sclerosis 1997, 3 (Suppl) p269 No. S021

8. Results of Trials

The results of the primary outcome of the CLARITY, AFFIRM and PRISMS trials, the annualised relapse rate, together with the results of the indirect comparison of cladribine and natalizumab (Tysabri®)and cladribine (Movectro®)and interferon beta-1a (Rebif®)are shown in the table below.

Annualised relapse rates reported in the placebo controlled trials

Measured at	Cladribine	Placebo	Comparator[a]	RRR RR[b] (95% CI)	Indirect RR (95% CI) Clad v Comp
CLARITY: Cladribine versus placebo					
Total number of relapses Annualised rate at 96 weeks[c]	N=433 109 0.14 (0.12, 0.17)	N=437 252 0.33 (0.29, 0.38)	NA	RRR=57.6% **RR=0.43** **(0.34, 0.54)**	NA
AFFIRM: Natalizumab versus placebo					
1 year[c]	NA	N=315 0.78 (0.64, 0.94)	N=627 0.27 (0.21, 0.33)	RRR=65.4% **RR=0.35** **(0.26, 0.47)**	NA[e]
2 years[d]	Excluding relapses after rescue therapy and sustained progression				
	NA	N=315 0.73 (0.62, 0.87)	N=627 0.23 (0.19, 0.28)	RRR=68.5% **RR=0.32** **(0.26, 0.40)**	1.34 (0.98, 1.84)
	Including relapses following initiation of rescue therapy				
	NA	N=315 0.64	N=627 0.22	RRR=65.6% RR=NR	NC
PRISMS: Interferon beta-1a versus placebo					
2 years[c]	NA	N=187 Mean=2.56[f] 1.28[g]	N=184 Mean=1.73[f] 0.87[g]	RRR=33.0% **RR=0.68** **(0.61, 0.75)[g]**	**0.64** **(0.46, 0.89)**

RRR=relative risk reduction compared with placebo; RR=relative risk; Clad=cladribine; Comp=comparator; NA=not applicable; NC=not calculable

Italicised text indicates additions made during the evaluation

[a] natalizumab or interferon beta
[b] compared with placebo
[c] primary outcome
[d] secondary outcome
[e] inconsistent time point measurements
[f] mean number of relapses
[g] calculated by the submission, calculation of RR/HR could not be verified

The above results of annualised relapse rates reported in the placebo controlled trials indicated that cladribine, natalizumab and interferon beta-1a are all superior to placebo for the outcome of annualised relapse rate.

For PBAC's comments on these results, see Recommendation and Reasons.

The PBAC noted that orally administered cladribine tablets were generally well-tolerated. Overall, only slightly more patients in the cladribine group reported an adverse event (AE) (80.7% v 73.3%) or a serious adverse event (SAE) (8.4% v 6.4%), and demonstrated a low rate of discontinuations due to AEs (3.5% v 2.1%). Natalizumab was associated with significantly increased risks of allergic reactions (9% v 4%, p=0.012) and infusion-related reactions (24% v 18%, p=0.04). Both cladribine and natalizumab were associated with more cases of cancer than placebo (cladribine 6 v 0, natalizumab 5 v 1).

9. Clinical Claim

The submission claimed cladribine as non-inferior in terms of comparative effectiveness and has a different safety profile to natalizumab. The PBAC did not accept the clinical claim of non-inferiority with natalizumab.

The submission claimed cladribine as superior in terms of comparative effectiveness and superior to interferon beta-1a, in terms of the primary outcome of reduction in relapse rate compared with placebo. The PBAC considered the claim was uncertain.

For PBAC's view of these claims, see Recommendation and Reasons.

10. Economic Analysis

A modelled cost-utility analysis was presented. The model was a Markov model in which patients entered the model on treatment in a particular Expanded Disability Status Score (EDSS) health state (based on the proportional split of patients in each EDSS category at baseline in the placebo arm of the CLARITY trial).

There were 31 health states included in model:

- 10 EDSS (0-9) health states representing patients with RRMS, on treatment;
- 10 EDSS (0-9) health states representing patients with RRMS, off treatment;
- 10 EDSS (0-9) health states representing patients with SPMS, off treatment; and
- 1 health state for death.

Patients moved through the model according to transition probabilities derived from the London-Ontario data set. A treatment effect was applied to these transitions such that patients may progress an EDSS health state or progress to Secondary Progressive multiple sclerosis (SPMS). The cycle length of the model was one year. Patients remained in a given health state and accrued costs, utilities and disutilities associated with that health state.

In the base case of the modelled economic evaluation, the submission assumed that cladribine is non-inferior to natalizumab and as such, applied the treatment effect reported for natalizumab in terms of efficacy and safety.

The Sponsor commissioned a community based time-trade-off (TTO) survey to estimate societal preferences with regard to short course oral treatments compared to subcutaneous and intravenous therapies for patients with MS.

A total of five health states (vignettes) were developed with input from the literature and clinicians: an anchor state (untreated), a treated state (treatment not disclosed), a subcutaneous treatment health state, an IV treatment health state and a short course oral tablet

health state. Treatment efficacy and safety were assumed to be the same, regardless of the treatment administered.

The PBAC noted from the Time Trade Off survey there would be a preference for short-course oral treatment compared with IV infusion or subcutaneous injection, however the PBAC considered the magnitude of this preference was in question. The results of the survey indicated substantial utility decrements for IV infusion and SC injection compared with oral therapy (-0.129 and -0.103, respectively).

For the stepped economic evaluation for cladribine versus natalizumab the incremental cost/extra QALY gained over 2 years was dominant.

The results of the stepped economic evaluation for cladribine versus interferon-1a, the incremental cost/extra QALY gained was in the range $105,000-$200,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

It was estimated that the additional cost to the PBS for cladribine tablets is in the range of $10 – $30 million per year.

12. Recommendation and Reasons

The PBAC agreed there is a high clinical need for an oral therapy for multiple sclerosis (MS). However, there is uncertainty over the usefulness of cladribine given treatment is limited to two years and due to safety concerns, as recognised by the FDA and the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP).

The Committee recalled that natalizumab was recommended for listing under section 100 because it is administered by intravenous infusion. Given that cladribine is administered orally, a section 100 listing was not considered necessary. Further, the Highly Specialised Drug Working Party did not consider that the highly specialised drug criteria had been met and therefore did not support supply through section 100.

The PBAC did not accept natalizumab as the appropriate main comparator, although agreed that this comparison was of interest. Thus, the Committee considered the appropriate main comparator to be interferon beta, the most commonly used first line treatment for MS, as cladribine is most likely to be used first line and noting that natalizumab is most commonly reserved for second line treatment.

With respect to the indirect comparison with interferon beta-1a (Rebif®), the PBAC noted that cladribine may be more effective than the comparator in terms of reducing the annualised relapse rate. However, given the differences in the annualised relapse rate reported for the placebo arms in the trials (0.33 in the CLARITY trial compared with 1.28 in the PRISMS trial), it is uncertain whether these trials and their populations are sufficiently comparable to inform a meaningful indirect comparison. The PBAC therefore considered there was uncertainty about a claim for superiority of cladribine over interferon beta-1a.

Concerning the comparison with natalizumab, the PBAC did not accept the claim of non-inferiority based on the non-significant differences for the indirect comparison. The reported

annualised relapse rates amongst the placebo arms in each of the trials differ, which suggests that the populations in the trials are not exchangeable and therefore could indicate that the conduct of such an indirect comparison is not appropriate. Based on the entry criteria for the trials, the likelihood of relapse may be higher in the natalizumab trial (AFFIRM) and (in conjunction with the definition of relapse being more stringent in CLARITY) natalizumab may be likely to show a greater improvement in the primary outcome of annualised relapse rate, than is cladribine.

Further, the minimally important clinical difference in relapse rates was not defined and although the pre-Sub-Committee Response proposed a difference of 25%, based on the CLARITY trial, which specified this rate for establishing superiority over placebo, this rate would likely be higher than a nominated non-inferiority criterion for comparison between active treatments.

Furthermore, although, the indirect comparison of cladribine and natalizumab indicates no differences between treatments RR=1.34 (95%: 0.98, 1.84) the indirect comparison indicates that the relapse rate for cladribine is 34% (and up to 84%) greater than that for natalizumab over two years, and this comparison almost reaches statistical significance (lower CI of 0.98).

Given that, the PBAC did not accept the clinical claim of non-inferiority with natalizumab, the Committee did not consider the modelled economic evaluation to be appropriate. Similarly, the validity of the modelled economic evaluation against interferon beta-1a was questionable, given the doubts for the claim for superiority of cladribine over interferon beta-1a. In addition, the incremental cost per extra QALY gained between $105,000 - $200,000 was considered unacceptably high.

The PBAC noted a number of issues raised concerning the economic evaluations. The PBAC agreed that it is not appropriate to model a trade-off in survival for differences in quality of life due to differences in mode of administration. The PBAC did not consider it feasible that the utility decrement associated with mode of administration would be approximately equivalent to the difference in utility applied for patients in EDSS 0 and 2 and greater than any utility difference between adjacent EDSS scores (with the exception of EDSS 6 and 7, EDSS 7 and 8 and EDSS 8 and 9). The PBAC also noted that disutility decrements for intravenous administration of natalizumab and subcutaneous administration of interferon beta-1a were not offset by the disutility and costs for the risk of cancer for cladribine.

A further concern with the model was the use of the London-Ontario data set to estimate the natural progression of MS and to derive the transition probabilities for disease progression. The PBAC considered that the clinical situation of patients with MS was now quite different from that in the study period where data were collected from 1972 to 1984. The Committee agreed that it would have been more appropriate to use the transition probabilities from the CLARITY trial in the modelled economic evaluation, given that it ran for 96 weeks and the model runs for two years.

The PBAC therefore rejected the submission because of use of an inappropriate comparator, uncertain clinical benefit and uncertain and unacceptable cost effectiveness in comparison with the appropriate comparator.

Recommendation:

Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Merck Serono Australia is considering its position regarding any future course of action.