



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Cladribine

Proprietary Product Name: Mavenclad

Sponsor: Merck Serono Australia Pty Ltd

June 2018

TGA Health Safety
Regulation

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- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
AMC	Absolute monocyte count
AML	Acute myelogenous leukaemia
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ARR	Annualised relapse rate
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical classification
AUC	Area under the plasma concentration time curve
AUC _{0-inf}	Area under the plasma concentration time curve from time 0 to infinity
BPF	Brain parenchymal fraction
BVMT-R	Brief Visuospatial Memory Test Revised
CBC	Complete blood count
CDMS	Clinically definite multiple sclerosis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS	Clinical isolated syndrome
CLCR	Creatinine clearance
CLL	Chronic lymphocytic leukaemia
C _{max}	Maximum plasma concentration
CNS	Central nervous system

Abbreviation	Meaning
CPMS	Chronic progressive multiple sclerosis
CTCAE	Common Terminology Criteria for Adverse Events
CU	Combined Unique
DAE	Discontinuation due to adverse event
DCK	Deoxycytidine kinase
DER	Drug event report
DMD	Disease modifying drug
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDSS	Expanded Disability Status Score
EQ-5D	EuroQuol 5-dimension
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
Gd	Gadolinium
Gd+	Gadolinium-enhancing
hCG	Human chorionic gonadotropin
HCL	Hairy cell leukaemia
HDA	High disease activity
HDPE	High density polyethylene
HLLL	Cladribine high/low dose
HLPP	Cladribine high dose/placebo
HP β CD	Hydroxypropyl betadex (2-hydroxypropyl- β -cyclodextrin)
HR	Hazard ratio
HRQL	Health Related Quality of Life

Abbreviation	Meaning
HRU	Health Resource Utilization
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IFN	Interferon
IMP	Investigational medicinal product
ITP	Initial treatment period
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
IVRS	Interactive voice response system
JCV	John Cunningham virus
KFS	Kurtzke Functional Systems
LC-MS	Liquid chromatography-mass spectrometry
LLLL	Cladribine low/low dose
LLN	Lower limit of normal
LTBI	Latent tuberculosis infection
MCDA	Multi criteria decision analysis
MedDRA	Medical Dictionary of Regulatory Activities
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSQOL-54	Multiple Sclerosis Quality of Life-54
MSSS	Multiple sclerosis severity score
NONMEM	Nonlinear Mixed Effects Modelling
OR	Odds ratio
PASAT	Paced Auditory Serial Addition Test

Abbreviation	Meaning
PBVC	Percentage brain volume change
PD	Pharmacodynamic
PGx	Pharmacogenetics of pharmacogenomics
PI	Product Information
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
p.o.	Oral/by mouth (per os)
PopPK	Population pharmacokinetic
PPLL	Placebo/cladribine low dose
PPMS	Primary progressive multiple sclerosis
PY	Patient years
RD	Risk difference
RI	Renal impairment
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SIR	Standard incidence ratio
SOC	System order class
SPMS	Secondary Progressive Multiple Sclerosis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TEAE	Treatment emergent adverse event
t_{\max}	Time to maximum plasma concentration
ULN	Upper limit of normal

Abbreviation	Meaning
UTI	Urinary tract infection

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	5 December 2017
<i>Date of entry onto ARTG</i>	11 December 2017
<i>Active ingredient:</i>	Cladribine
<i>Product name:</i>	Mavenclad
<i>Sponsor's name and address:</i>	Merck Serono Australia Pty Ltd 25 Frenchs Forest Road East Frenchs Forest NSW 2086
<i>Dose form:</i>	Tablet
<i>Strength:</i>	10 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	Packs of 1, 4, 5, 6, 7, 8, 9 or 10 tablets
<i>Approved therapeutic use:</i>	<i>(RRMS) to reduce the frequency of clinical relapses and to delay the progression of physical disability.</i> <i>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.</i>
<i>Route of administration:</i>	Oral (PO)
<i>Dosage:</i>	The recommended cumulative dose of Mavenclad is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. Patients should receive no more than 2 treatment courses over two consecutive years. The recommended dose should not be exceeded. Following completion of the 2 treatment courses, no further cladribine treatment is required in year 3 and year 4 (refer to Clinical Trials). Reinitiation of therapy after year 4 has not been studied.
<i>ARTG number:</i>	166483

Product background

This AusPAR describes the application by the sponsor, the sponsor, to extend the indications of cladribine 10 mg tablets (Mavenclad) by the addition of: *'to reduce the frequency of clinical relapses and to delay the progression of physical disability'* and removal of *'for a maximum duration of 2 years'* from the approved indication and update the Product Information (PI) per the revised Risk Management Plan (RMP) based on the updated clinical data set. The sponsor is also re-launching the product; it was first registered in Australia on 9 September 2010, for *'the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS) for a maximum duration of 2 years'* but subsequently withdrawn from the market on 22 June 2011.

A change in tradename was also approved by the TGA during the evaluation process. The tradename Movectro has now been replaced with Mavenclad (application date 19 May 2017).

The proposed indication in this application is:

Mavenclad is indicated for the treatment of relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical relapses and to delay the progression of physical disability.

It is administered orally over a 2 year period according to an interrupted short course protocol, followed by 2 year monitoring. The recommended total cumulative dose is 3.5 mg/kg bodyweight over the 2 year treatment period. Daily doses during active treatment are 10 mg or 20 mg.

Cladribine is a nucleoside analogue of deoxyadenosine. It differs from deoxyadenosine by a chlorine substitution in the 2-position in the purine ring. Cladribine is a prodrug and is phosphorylated to its active form, 2-chlorodeoxyadenosine triphosphate. Cladribine is an immunomodulatory agent which increases the rate of lymphocyte cell death which results in depleted lymphocyte populations.

New data included the final reports of the 3 clinical studies which were ongoing at the time of the market withdrawal in 2011 (Studies CLARITY EXT, ORACLE MS and ONWARD), the final report of the Study RECORD MS registry and interim data from a prospective long-term follow-up registry set up by the sponsor (PREMIERE).

Information on the condition being treated

Relapsing remitting multiple sclerosis (RRMS) is the most common variant of multiple sclerosis (MS) and is characterised by recurrent acute exacerbations followed by partial or complete recovery. During the acute MS exacerbations, inflammation occurs to myelin (the insulating layer on axons) and to the axons themselves in the central nervous system (CNS). The regions of damage are localised and vary between patients, resulting in a variable neurological presentation. The damage results in plaques or scars which can be detected by magnetic resonance imaging (MRI). The most common symptoms reported in RRMS include episodic bouts of fatigue, numbness, vision problems, spasticity or stiffness, bowel and bladder problems, and problems with cognition (learning and memory or information processing).

Overall, MS affects over 23,000 patients in Australia and more than two million diagnosed worldwide. Most people are diagnosed between the ages of 20 to 40 years but it can affect younger and older people too.¹ Roughly three times as many women have MS as men. 70 to 75% percent of people with MS initially begin with a relapsing-remitting course.

¹ MS Australia. <https://www.msaustralia.org.au>, accessed 6th April 2017

MS reduces life expectancy by a few months and 15 years from diagnosis 60% of patients will be ambulatory without assistance (some of whom may have little disability); approximately 20% will be bedridden or institutionalised, and 20% may require a wheelchair, crutches or a cane to ambulate.² Up to a third of patients will not develop persistent disability and will have only intermittent, transient episodes of symptoms.

Current treatment options

The management of RRMS involves rehabilitation, symptomatic treatments and disease modifying treatments. There are no curative treatments. Cladribine is classed as a disease modifying treatment. The alternative currently available disease modifying treatments for RRMS are detailed in Table 1, shown below.

Table 1: Currently available disease modifying treatments for RRMS

Type of treatment	Available treatments
Injectable therapies	Interferon beta-1b Interferon beta-1a Glatiramer Daclizumab
Infusion therapies	Natalizumab Alemtuzumab Mitoxantrone
Oral therapies	Dimethyl fumarate Teriflunomide Fingolimod
Other treatments	Azathioprine CCSVI Cyclophosphamide Dalfampridine Glucocorticoids Intravenous immunoglobulin Laquinimod Rituximab Ocrelizumab Stem cell transplantation

A published comparison of efficacy for the disease modifying treatments for RRMS is extracted from Fogarty (2016);³ and displayed below in Figure 1.

² Rolak L. Multiple Sclerosis: It's Not The Disease You Thought It Was. *Clinical Medicine and Research* (2002) 1; 57-60

³ Fogarty E, Schmitz S, Tubridy N, Walsh C, Barry M. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis. *Multiple Sclerosis and Related Disorders* (2016) 9; 23-30

Figure 1: Comparative efficacy for disease modifying treatments for RRMS

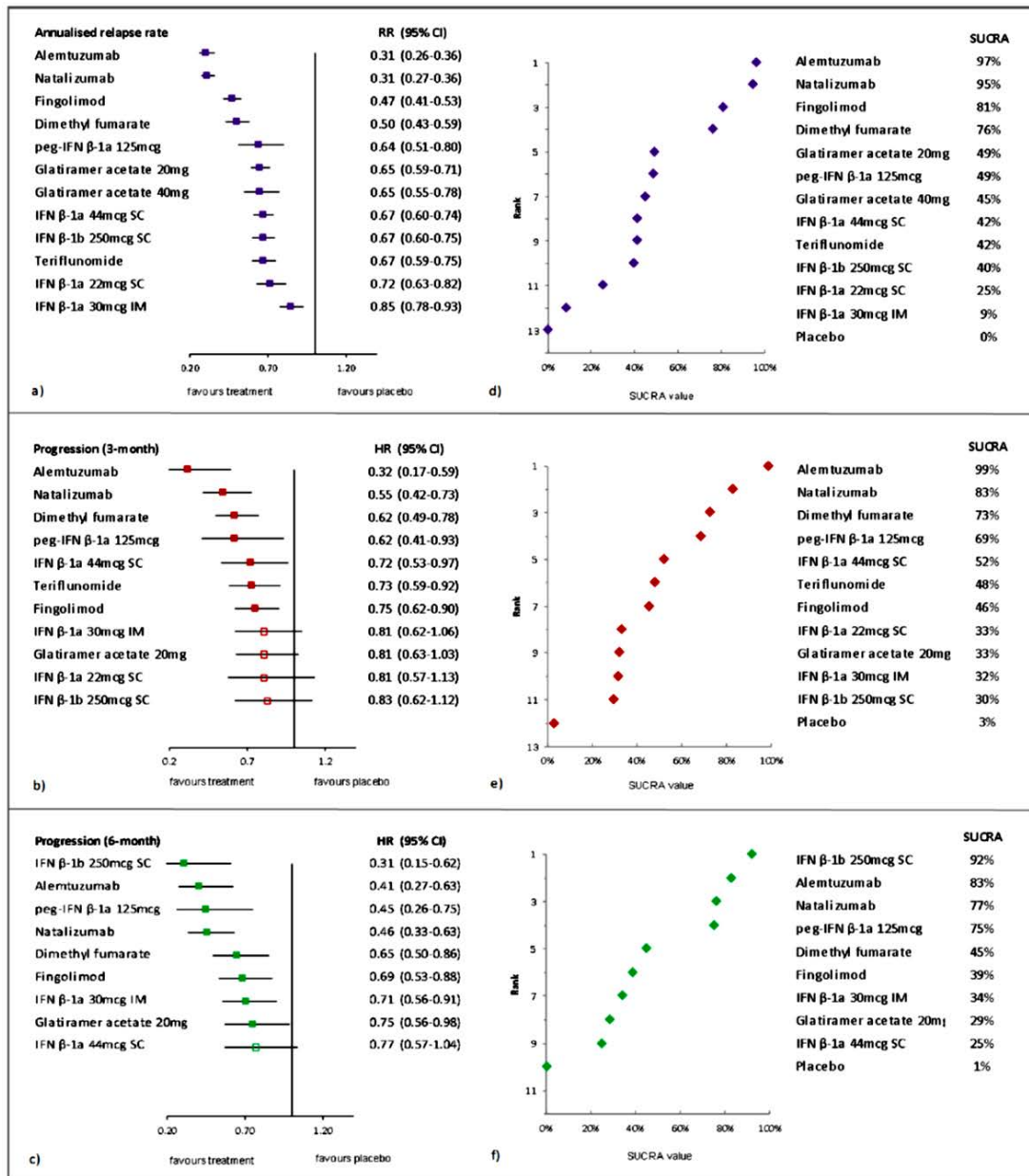


Fig. 3. a-c. Forest plots of treatments versus placebo for a) Annualised relapse rate, b) Disability progression confirmed at three months c) Disability progression confirmed at six months. Relative treatment effects (rate ratios for annualised relapse rate, hazard ratios for disability progression) are represented by coloured nodes, and corresponding 95% credible intervals are represented by solid lines. Bars to the left of the central vertical line of no difference indicate superiority of the treatment over placebo. Hollow nodes represent pairwise comparisons where the 95% credible interval spans the central vertical line of no difference. d-f. Network ranking plots for d) Annualised relapse rate, e) Disability progression confirmed at three months c) Disability progression confirmed at six months. Treatments are ranked according to the surface under the cumulative ranking curve (SUCRA). SUCRA values provide the hierarchy for the treatments and placebo, and show the cumulative probability (expressed as a percentage) of a treatment being among the best options. The y-axis shows the possible ranks from r=1 up to r=11 and the x-axis shows the cumulative probabilities that the corresponding treatment is among the top r treatments. The larger the SUCRA value the better the treatment. IFN β=interferon beta; IM=intramuscular; SC=subcutaneous; RR=rate ratio; HR=hazard ratio; CI=credible interval.

Compared to placebo, a 50% reduction in annualised relapse rate can be achieved with alemtuzumab, natalizumab, fingolimod and dimethyl fumarate. Compared to placebo, the HR (95% CI) for 3 month disease progression is 0.32 (0.17 to 0.59) for alemtuzumab, 0.55 (0.42 to 0.73) for natalizumab, 0.62 (0.49 to 0.78) for dimethyl fumarate and 0.62 (0.41 to 0.93) for peg-IFN β-1a 125 µg. Compared to placebo, the HR (95% CI) for 6 month disease progression is 0.31 (0.15 to 0.62) for peg-IFN β-1b 250 µg, 0.41 (0.27 to 0.63) for alemtuzumab, 0.45 (0.26 to 0.75) for peg-IFN β-1a 125 µg, and 0.46 (0.33 to 0.63) for natalizumab.

Table 2: Comparative efficacy of cladribine

• DMD Therapy and dose	• Time to 3-month sustained disability progression over a 2 year period				
	• Ratio	• Hazard	• CI 95%	• p-value	• Disability progression-free (% vs placebo)
Cladribine 3.5 mg/kg	0.67		0.48, 0.93	0.018	86 vs 81
Cladribine 5.25 mg/kg	0.69		0.49, 0.96	0.026	87 vs 81
IFN- β (Rebif [®]) 44 μ g ¹	0.63*		0.43, 0.91	0.013	73 vs 62
Fingolimod (Gilenya [®]) 0.5 mg ²	0.70		0.52, 0.96	0.02	82 vs 76
Fingolimod (Gilenya [®]) 0.5 mg ³	0.83		0.61, 1.12	0.227	75 vs 71
Dimethyl fumarate (Tecfidera [®]) 240 mg bid ⁴	0.62		0.44, 0.87	0.005	84 vs 73
Dimethyl fumarate (Tecfidera [®]) 240 mg bid ⁵	0.79		0.52, 1.19	0.25	87 vs 83
Teriflunomide (Aubagio [®]) 7 mg ⁶	0.76		0.56, 1.05	0.08	78 vs 73
Teriflunomide (Aubagio [®]) 14 mg ⁶	0.70		0.51, 0.97	0.03	79 vs 73
Teriflunomide (Aubagio [®]) 7 mg ⁶	0.95		0.68, 1.35	0.762	87 vs 79
Teriflunomide (Aubagio [®]) 14 mg ⁶	0.68		0.47, 1.00	0.044	84 vs 79

Sources for other DMDs: 1 PRISMS study data on file at Merck Serono (PRISMS, 2001) ; 2 FREEDOMS study (Kappos et al, 2010); 3 FREEDOMS II study (Calabresi et al, 2012); 4 DEFINE study (Gold et al, 2012); 5 CONFIRM study (Fox et al, 2012); 6 TEMSO study (O'Connor et al, 2011) and 7 TOWER study (Confavreux et al, 2014).

Note: Table copied from statement of foreign registration status

Regulatory status

Movectro was registered in July 2012 after its approval in September 2010. The approved indication was treatment of relapsing-remitting multiple sclerosis (RRMS) for a maximum of two years. It has not been marketed in Australia and there was a worldwide withdrawal of Movectro in 2011.

Two other products containing cladribine are registered: Leustatin, sponsored by Janssen-Cilag was registered in 1994 and Litak, sponsored by Orphan Australia, was registered in June 2004. Both are indicated for the treatment of hairy cell leukaemia and second line treatment of patients with B-cell chronic lymphocytic leukaemia in whom treatment with alkylating agents has failed. Leustatin is given intravenously (IV) and Litak by subcutaneous (SC) injection.

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

- The disproportionate numbers of patients developing malignancies in the cladribine treatment arms of clinical studies, compared with placebo.
- The risk of developing Grade 3 or 4 lymphopaenia, which was thought to be associated with an increased risk of infection. The prolonged recovery time from lymphopaenia in some patients was thought to expose these patients to risks.
- The subsequently proposed patient population (patients with high disease activity) consisted of what the committee considered to be too small a proportion of the patients who had been studied in the clinical development programme.
- In the above context, it was considered that the optimal dose and the revised treatment regimen had not been adequately investigated in the target patient population.

Similar applications to the original New Drug Application were withdrawn in Switzerland in 2010, Canada in 2011 and New Zealand in 2011.

Applications similar to the present application were submitted in the European Union (EU) (June 2016) and Canada (December 2016). The sponsor intends to submit similar applications in the US in 2018 and Switzerland in 2017.

In the EU cladribine was recommended for approval by the CHMP in June 2017 with the indication of '*treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features*'.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

Table 3: Registration timeline for Submission PM-2016-03923-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2017
First round evaluation completed	6 July 2017
Sponsor provides responses on questions raised in first round evaluation	1 August 2017
Second round evaluation completed	13 October 2017
Delegate's Overview	25 October 2017
Sponsor's response to Delegate's Overview	3 November 2017
Advisory Committee meeting	Not applicable
Registration decision	5 December 2017
Entry onto ARTG	11 December 2017
Number of TGA working days from commencement of evaluation to registration decision*	176

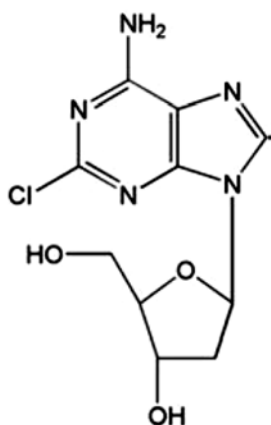
* Statutory timeframe: 255 working days.

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

Drug substance

Cladribine is a nucleoside analogue of deoxyadenosine. It differs from deoxyadenosine by a chlorine substitution in the 2-position in the purine ring. Cladribine is a prodrug and is phosphorylated to its active form, 2-chlorodeoxyadenosine triphosphate. It has the following chemical structure, as shown in Figure 1.

Figure 1: Chemical structure of cladribine

Decomposition increases over time at acidic pH. The ionisation behaviour of the molecule over the pH range 0 to 12 is characterised by a single pKa of approximately 1.21.

Drug product

Mavenclad tablets are uncoated, white, round and biconvex, and engraved with 'C' on one side and '10' on the other side. Each tablet of Mavenclad contains 10 mg cladribine. The tablets also contain hydroxypropylbetadex, sorbitol and magnesium stearate.

IV. Nonclinical findings

Introduction

The nonclinical submission comprised only of pharmacokinetics studies and did not provide direct nonclinical data to support the extension of indication request. Thus, the suitability of the extension of indication was to be based on the accompanying clinical data.

Pharmacokinetics

The sponsor submitted 11 new studies which included permeability and absorption and metabolism and interaction data.

Absorption and distribution

The sponsor submitted two in vitro studies demonstrating the uptake of cladribine by cryopreserved human hepatocytes and human lymphocyte isolates. The uptake of cladribine by hepatocytes was not concentration dependent and unaffected by transport inhibitors and therefore appeared to be a passive process. The study also found a concentration related increase in cytotoxicity, particularly at the highest dose (251 μM). In contrast, the kinetics of cladribine uptake into human lymphocytes was related to the concentration in the cell suspension (at least up to 3 h), with a high initial uptake (< 1 h) followed by a plateau and subsequent decrease past 3 h post-exposure. This study demonstrated that the 30 to 40 fold increase in intracellular radioactively labelled ([¹⁴C])-cladribine observed at anticipated clinical concentrations (0.1 μM) decreased in magnitude with increasing extracellular [¹⁴C]-cladribine. No inhibition studies were

conducted to determine the impact of transporters on cladribine uptake into the human lymphocytes.

Metabolism studies

The sponsor submitted one new metabolism study, profiling the metabolites in plasma and whole blood of mice, monkeys and humans. Of the 13 detected metabolites, 8 remained unidentified. The remaining 5 identified metabolites and pathways were as follows: 2-chloroadenine (M169) produced by oxidative cleavage; hydroxyl-2-chloroadenine or N-oxide of 2-chloroadenine (M185) produced by N-oxidation or hydroxylation of M169; hydroxy-cladribine (M301-1) formed by mono-hydroxylation of cladribine; 2-chloro-hypoxanthine (M170) formed by oxidative cleavage of 2-chloro-inosine (M286), which in turn is an oxidative product of cladribine. While the levels of metabolites in plasma and blood cells were comparable between monkey and human (despite variability between the two fractions), 2-chlorohypoxanthine, 2-chloro-inosine and hydroxy-cladribine were largely not detected in mouse samples (a small amount of hydroxy-cladribine was however reported in mouse blood cells).

Of the five identified metabolites, 2-chloroadenine was previously detected in plasma of mice and monkeys, and hydroxy-cladribine was detected during metabolite profiling of the human hepatic S9 fractions;⁴ and microsomes. The estimated levels of these metabolites were comparable with those reported in the previous evaluation. In addition, the sponsor also proposed that the metabolism of 2-chloro-inosine (M-286) to 2-chlorohypoxanthine (M170) was driven by adenosine deaminase (ADA), a metabolic pathway reported by Bierau et al.⁵ that was not previously associated with cladribine metabolism.

Interaction studies

The sponsor presented several studies showing cladribine mediated inhibition or induction of cytochrome P450 (CYP450) enzymes. Weak inhibition of CYP2B6 and CYP3A4 was reported in preparations of cultured human hepatocytes at doses up to 250 μM as determined by reduced messenger ribonucleic acid (mRNA) expression. However, the levels of inhibition were not significant and comparable with those observed for the same enzymes in previously evaluated studies. Similarly, weak induction of CYP1A2 was reported in cultured human hepatocytes at high doses (compared to the positive control). The level of induction of CYP1A2 was comparable with the levels reported in studies evaluated by the TGA previously.

Transporter interaction studies demonstrated that cladribine was a substrate for the breast cancer resistance protein (BCRP) in Caco-2 and CPT-B1 cells lines (up to 50 μM concentrations). Cladribine also acted as a minor inhibitor of BCRP (50% inhibitory concentration (IC_{50}) 150 μM). Inhibition was also noted in renal transporters (multidrug resistance protein 5 (MRP5) and organic anion transporter 3 (OAT3)) at an IC_{50} of 64 μM for MRP5 and 39% inhibition for OAT3 at 100 μM , respectively. The clinical significance of these inhibitory interactions are likely to be minimal given the highest inhibition was reported at a concentrations significantly greater than the clinical peak plasma concentration (C_{max}). A small dose related increase in organic cation transporter 2 (OCT2) mediated transport was reported. No transporter interactions were noted with MRP2, MRP4, OAT1 or OCT4.

⁴ The S9 fraction is the product of an organ tissue homogenate (usually liver) used in biological assays. The S9 fraction is most frequently used in assays that measure the metabolism of drugs.

⁵ Bierau J., Determination of the deoxycytidine kinase activity in cell homogenates with a non-radiochemical assay using reversed-phase high performance liquid chromatography Identification of a novel metabolite of 2-chlorodeoxyadenosine, J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 2004; 805:339-346.

Nonclinical summary and conclusions

- The nonclinical submission comprised of pharmacokinetic studies related to permeability and absorption, and metabolism and transporter interaction. No nonclinical data related directly to the extension of indication were submitted.
- Two in vitro studies demonstrated uptake of cladribine into human hepatocytes and lymphocytes. Hepatocyte uptake was passive and independent of known transport processes. Lymphocyte uptake was time dependent and related to concentration of cladribine in culture.
- Metabolite profiling in mouse, monkey and human whole blood reported 13 metabolites of which 8 were unidentified and 2 were reported in previously evaluated studies. Overall, levels of metabolites were comparable between monkey and human whole blood compared with mouse. No new human specific metabolites were identified.
- No significant induction or inhibition of human CYP450 isozymes was observed. However, cladribine was however found be a substrate for the BCRP in Caco-2 and CPT-B1 cells lines, and a weak inhibitor of BCRP. Inhibition of the renal transporters MRP5 and OAT3, as well as a slight stimulation of OCT2 mediated transport was also noted. The concentrations at which all of the interactions were observed were of limited clinical significance.
- As no nonclinical data directly related to the extension of indication was submitted, the decision to approve such a request will rely on the clinical data.
- Amendments to the draft PI were also recommended.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor stated the following clinical rationale for developing cladribine for the treatment of MS:

'Because of cladribine's actions on the immune system, a potential clinical utility in the treatment of multiple sclerosis (MS) was postulated. Initial clinical studies on MS were performed by the Scripps Research Institute, using a parenteral formulation and, based on observations from these, Merck developed an oral cladribine formulation for the treatment of MS.'

The rationale for the present application is that additional data are now available that the sponsor considers support the longer term efficacy and safety of cladribine.

Guidance

The following regulatory guidance applies to the present application:

- Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/771815/2011, Rev 2; 26 March 2015.

- Guideline on Reporting the Results of Population Pharmacokinetic Analyses. CHMP/EWP/185990/06

Contents of the clinical dossier

Scope of the clinical dossier

The new clinical data are:

- CLARITY EXT, ORACLE MS and ONWARD
- The final report of RECORD MS registry
- Interim data from a prospective long-term follow-up registry set up by the sponsor (PREMIERE)

Previously submitted data included:

- Nine clinical pharmacology studies: Study IXR-102-09-186, Study 25803, Study 26127, Study IXR-101-09-186, Study 6226/6414, Study 93-220, Study JK-6251-1, Study 26486 and Study 27967.
- One population pharmacokinetic study (dated May 2009 and assumed to have been included in the original dossier): Study 700568-013.
- Three Phase II efficacy studies: Study 2-CdA-MS-SCRIPC, Study 2-CdA-MS-001, and Study 2-CdA-MS-SCRIPP.
- One pivotal efficacy study: Study 25643 CLARITY.
- Two studies evaluable for safety only: Study 2-CdA-MS-SCRIPB and Study 2-CdA-MS-SCRIPA.

Paediatric data

There are no paediatric data in the submission. The sponsor has a waiver for a Paediatric Investigation Plan from the EMA. The sponsor provides the following statements:

'In 2009, a waiver for the condition multiple sclerosis was granted for cladribine (EMEA-000383-PIP01-08, A). The waiver applies to all subsets of the paediatric population from birth to less than 18 years of age for tablet, oral use, on the grounds that the specific medicinal product is likely to be unsafe in the paediatric population.

In an E-mail on 15 April 2015, the EMA has confirmed that the Decision P/101/2009 of 19 May 2009 is still valid, and, as the Opinion granted for PIP EMEA-000383-PIP01-08 is a full waiver, no PIP compliance check would be required prior to the Marketing Authorisation Application'.

Good clinical practice

The studies submitted in the clinical dossier are stated to have conformed to Good Clinical Practice (GCP) and appear to have conformed to GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Studies providing pharmacokinetic (PK) information are outlined in the Table 4, below.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK- Single dose	Study 6226 / Study 6414	
	-Multi-dose	Study 93-220	
		Study JK-6251-1	
	Food effect	Study 26127	
PK in special populations	Target population §- Single dose	Study IXR-109-09-186	
		Study 25803	
		Study IXR-101-09-186	
PK interactions	IFN- β -1a	Study 26486	
	Pantoprazole	Study 27967	
Population PK analyses	Target population	Study 700568-013	

* Indicates the primary PK aim of the study; † bioequivalence of different formulations; § subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

The original data submission did not include PK data for patients with renal impairment, hepatic impairment, age < 18 years or age > 65 years. No new data for these populations has been included in the current application.

In the opinion of the evaluator there are statements in the PI that are not supported by the data these statements are:

- The statement '*A population pharmacokinetic analysis did not show any effect of age (range 18 to 65 years) or gender on cladribine pharmacokinetics.*' is included in the pharmacokinetics section relating to special populations. The statement is ambiguous and should be rephrased as: *The effects of age < 18 years or > 65 years on cladribine pharmacokinetics has not been studied.*
- The following statement also appears in the pharmacokinetics section: '*Based on a population pharmacokinetic analysis including patients with normal renal function and with mild renal impairment, total clearance in patients with mild renal impairment (CLCR = 65 mL/min) is estimated to decrease by 18%. The predicted decrease in cladribine clearance is 30% in patients with moderate renal impairment (CLCR = 40 mL/min) and 40% in patients with severe renal impairment (CLCR = 20 mL/min).*' In the opinion of the evaluator this statement is not supported by the data in the submission because the model used in the population pharmacokinetic study was not validated sufficiently to support simulations, particularly in populations that were not represented in the covariate data.

Pharmacodynamics

Studies providing pharmacodynamic data

The sponsor provided one modelling and simulation study in support of pharmacodynamics (PD) (Table 5).

Table 5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Population PD and PK-PD analyses	Target population	M&S Population Analysis Report Trial No.: 25643 (CLARITY), 27820 (CLARITY EXT); 28821 (ORACLE-MS):	*

* Indicates the primary PD aim of the study.

Evaluator's conclusions on pharmacodynamics

The sponsor has not provided sufficient data to enable reliable conclusions of the dose effect relationship. In the opinion of the evaluator this is because the dose effect relationship cannot be reliably described with only high dose and placebo data. Maximum effect appears to have been achieved at the 3.5 mg/kg dose level. Hence, in order to adequately describe the dose effect relationship, PD outcome data from lower doses are required.

Dosage selection for the pivotal studies

Dosage selection for the pivotal studies

Phase III pivotal studies investigating more than one dose regimen

Study 27820 CLARITY Extension has examined extended dosing regimens and is discussed in Attachment 2 under Section 7. The study examined cumulative doses of 7 mg/kg and 8.25 mg/kg.

Evaluator's conclusions on dose finding for the pivotal studies

The sponsor provided a modelling and simulation report using data from the clinical studies using the 3.5 mg/kg and 5.25 mg/kg dose levels (M&S Population Analysis Report Trial Nos. 25643 (CLARITY), 27820 (CLARITY EXT); 28821 (ORACLE-MS)). In the opinion of the evaluator, the population PK-PD modelling was not sufficiently robust to simulate lower doses.

The TGA's Advisory Committee on Prescription Medicines (ACPM; now called Advisory Committee on Medicines (ACM)) considered that the lowest effective dose had not been determined. The sponsor has not provided any new data examining lower doses in clinical trials.

Efficacy

Studies providing efficacy data

There were two pivotal studies conducted in patients with the proposed indication of RRMS, Study 25643 CLARITY and Study 27820 CLARITY Extension.

There were five other efficacy studies:

- Study 2-CdA-MS-SCRIPC, a Phase II study in patients with RRMS.
- Study 2-CdA-MS-001, a Phase III study in patients with PPMS.
- Study 2-CdA-MS-SCRIPP, a Phase II study in patients with Chronic Progressive MS (CPMS).
- Study 28821 ORACLE, a Phase III study in patients with a first clinical event at high risk of converting to MS.
- Study 26593 ONWARD, a Phase IIb in patients with active MS.

Evaluator's conclusions on efficacy

The sponsor has demonstrated efficacy compared to placebo in Study 25643 CLARITY which has been previously submitted and evaluated.

Efficacy was demonstrated using qualifying relapse rate as the primary efficacy outcome measure. Disability progression was measured using EDSS. There was a statistically and clinically significant benefit for cladribine in comparison with placebo for both of these outcome measures. Hence there are sufficient data to support: *'to reduce the frequency of clinical relapses and to delay the progression of physical disability'* being included in the indication.

There are limited data in support of removing the 2 year limit on treatment. Although Study 27820 CLARITY Extension is supportive of the cladribine low/low dose (LLLL) (total dose 7 mg/kg over 4 years) treatment group over the cladribine high/low dose (HLLL) (8.5 mg/kg over 4 years) and does provide some support for extending the duration of treatment and total exposure to 7 mg/kg over 4 years, there are a number of limitations to the study. These limitations are:

- Study 27820 CLARITY Extension did not have a primary efficacy outcome measure and was not designed primarily to demonstrate efficacy.
- The sponsor argues for efficacy based on a post hoc selection of 'key' efficacy variables.
- The overall efficacy results were inconsistent and the statistically significant findings were not clearly of clinical significance.
- The MRI outcome measures were more convincing of efficacy than the clinical outcome measures.

The sponsor has not provided any data that explores the lowest effective dose. This was identified as a major issue at the time of initial approval but has not subsequently been addressed by the sponsor.

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

Pivotal and/or main efficacy studies

There were two pivotal studies conducted in patients with the proposed indication of RRMS, Study 25643 CLARITY and Study 27820 CLARITY Extension.

There were five other efficacy studies:

- Study 2-CdA-MS-SCRIPC, a Phase II study in patients with RRMS.
- Study 2-CdA-MS-001, a Phase III study in patients with PPMS.
- Study 2-CdA-MS-SCRIPP, a Phase II study in patients with chronic progressive MS (CPMS).
- Study 28821 ORACLE, a Phase III study in patients with a first clinical event at high risk of converting to MS.
- Study 26593 ONWARD, a Phase IIb in patients with active MS.

Studies with evaluable safety data: dose finding and pharmacology

There were nine clinical pharmacology studies: Study IXR-102-09-186, Study 25803, Study 26127, Study IXR-101-09-186, Study 6226/6414, Study 93-220, Study JK-6251-1, Study 26486 and Study 27967.

The safety data from the clinical pharmacology studies are limited by the short duration of drug exposure and follow-up.

Studies evaluable for safety only

Study 2-CdA-MS-SCRIPB

Study 2-CdA-MS-SCRIPB was a Phase II, double blind, placebo controlled, parallel group crossover study in patients with primary progressive MS (PPMS). The study was of 12 months duration and was conducted in 11 patients. The study included patients with PPMS, aged between 21 and 55 years age and able to ambulate a minimum of 25 feet. The study treatments were:

1. Cladribine 2.1 mg/kg (0.07 mg/kg/day SC for 5 days per course, for 6 courses)
2. Cladribine 0.7 mg/kg (0.07 mg/kg/day SC for 5 days per course, for 2 courses), followed by an additional four courses in the second phase
3. Placebo, followed by cladribine 2.1 mg/kg (0.07 mg/kg/day SC for 5 days per course, for 6 courses) in the second phase.

The efficacy outcome measures were the Expanded Disability Status Scale (EDSS), Scripps Neurological Rating Scale (SNRS) and MRI brain scan at the end of each 6 month phase. The safety outcome measures included AEs, clinical laboratory tests and vital signs. There were 11 patients entered into the study, ten entered the second phase and a further two discontinued during the second phase. There were eight females, three males and the age range was 35 to 55 years.

During the initial phase treatment-emergent adverse events (TEAEs) were reported in seven (87.5%) patients treated with cladribine and three (100%) treated with placebo. The commonest TEAE was urinary tract infection in four subjects in the cladribine group. Lymphopaenia occurred in all the cladribine treated patients. TEAEs were reported in all

patients in the retreatment phase. One patient developed herpes zoster infection. There were no deaths or serious adverse events (SAEs). No hypothesis tests were performed on the efficacy data.

Study 2-CdA-MS-SCRIPA

Study 2-CdA-MS-SCRIPA was an open label, Phase II, 'proof-of-concept' study in patients with PPMS. The study was conducted at a single centre in the US from December 1989 to May 1998. The study included male or female patients, aged 21 to 55 years, with PPMS and who were not severely disabled or wheelchair bound. The study treatment was cladribine 3.65 mg/kg (0.87 mg/kg/day over 7 days as a continuous infusion, for six courses, monthly). Three patients received half of this dose. The efficacy outcome measures were neurological symptoms and disability scores: EDSS and SNRS scales. The study included seven patients: five females and two males. Total exposure ranged from 1.21 to 5.10 mg/kg. The most commonly reported TEAE was nausea in four (57.1%) patients and insomnia was reported in four (66.7%) of six patients who entered the follow-up phase. There was one death due to cardiac arrest 3 years after last dose of cladribine. SAEs were reported in three patients (pancytopenia, gastrointestinal haemorrhage, bronchitis, pneumonia, pyelonephritis, sinusitis, haemoglobin decreased, MS, haemangioma and skin lesion). Three patients discontinued study treatment; one because of AE. Lymphocyte count shifted from normal to low in four (57.1%) patients and Grade 3/4 lymphocyte toxicity was recorded in six (85.7%) patients.

Study PREMIERE registry

The Study PREMIERE registry was a long term safety monitoring study. The study included patients who had participated in CLARITY, CLARITY Extension, ONWARD, ORACLE and Study 27967. The study is ongoing and the report providing interim data is dated May 2016. The data were collected using telephone contacts every 3 months for 2 years and then yearly. Data from 1153 patients are included in the registry but patients from Study 27967 and those with non-matching record numbers are excluded from the safety analysis, leaving 1,133 patients in the safety analysis. There were 941 patients who had received at least one dose of cladribine with a mean (SD) total dose of 4.742 (2.082) mg/kg. There were 192 patients who had received placebo with no cladribine exposure. In the cladribine group, 319 (33.9%) patients were subsequently exposed to other disease modifying drugs, predominantly IFN- β .

Study RECORD MS registry

A prospective, observational, post-authorisation study of cladribine tablets in cladribine-naïve patients in the Australian Patient Familiarisation Program. It is discussed in Attachment 2, Section 8.

Patient exposure

Integrated safety analysis

In the integrated safety analysis there were 1976 patients exposed to cladribine for a total of 8650.16 patient years of follow-up and 802 patients exposed to placebo for a total of 2361.13 patient years of follow-up. Cumulative dose was in the range > 0 to 3.5 mg/kg for 439 patients, > 3.5 to 5.25 mg/kg for 759, > 5.25 to 7.0 mg/kg for 418, > 7.0 to 8.75 mg/kg for 213 and > 8.75 mg/kg for 147 patients.

Clinical pharmacology studies

In Study IXR-102-09-186 there were 26 patients with MS exposed to single doses of three treatments: cladribine 3 mg orally, cladribine 10 mg orally and cladribine 3 mg IV.

In Study 25803 there were 16 patients with MS exposed to a single oral 10 mg dose and a single 3 mg IV dose.

In Study 26127 there were 16 subjects exposed to two single 10 mg doses of cladribine, one each in the fed and fasted states.

In Study IXR-101-09-186 there were 12 patients exposed to three oral and one IV single doses of 3 mg cladribine.

In Study 6226/Study 6414 there were 61 patients with haematological malignancies or solid tumours exposed to IV doses in the range of 2.5 to 21.5 mg/m²/day.

In Study 93-220, ten patients with advanced malignancy were exposed to cladribine 1 mg/mL oral solution, 0.28 mg/kg/day for 5 days, followed by a month break, then cladribine 1 mg/mL IV solution (Leustatin), 0.14 mg/kg/day administered IV over 2 hours, daily for 5 days.

In Study JK-6251-1 there were nine patients with lymphoid malignancies exposed to cladribine 1 mg/mL solution, 0.06 to 0.09 mg/kg/day continuous IV infusion for 7 days, for up to three courses.

In Study 26486 there were 17 patients with MS exposed to the combination of IFN- β -1a 44 μ g every second day and cladribine 10 to 20 mg daily for 5 days.

In Study 27967, 18 subjects received up to two single doses of cladribine 10 mg orally.

Pivotal studies

In Study 25643 CLARITY there were 454 subjects enrolled to have 5.25 mg/kg, and 390 (85.9%) patients received the full course of treatment; 430 subjects enrolled to have 3.5 mg/kg, and 395 (91.9%) patients received the full course of treatment; and 435 patients enrolled to receive placebo.

In Study 27820 CLARITY Extension there were 98 patients exposed to LLPP (total dose 3.5 mg/kg), 92 to Cladribine high dose/placebo (HLPP) (total dose 5.25 mg/kg), 186 to LLLL (total dose 7 mg/kg), 186 to HLLL (total dose 8.25 mg/kg) and 244 to Placebo/cladribine low dose (PPLL) (total dose 3.5 mg/kg).

Other efficacy studies

In Study 2-CdA-MS-SCRIPC there were 26 patients with RRMS exposed to 2.1 mg/kg over an 8 month period, and 23 exposed to placebo. Twelve patients were entered into an open label extension study and received a mean dose of 1.38 mg/kg over a mean duration of 22.8 months.

Studies for other indications

In Study 2-CdA-MS-001 there were 52 patients with PPMS exposed to cladribine 2.1 mg/kg, 53 patients exposed to cladribine 0.7 mg/kg and 54 patients given placebo.

In Study 2-CdA-MS-SCRIPP there were 48 patients with CPMS exposed to cladribine: 25 to cladribine 2.8 mg/kg and 23 to cladribine 1.4 mg/kg.

In Study 28821 ORACLE there were 204 patients with a first clinical event at high risk of converting to MS randomised to cladribine 5.25 mg/kg, 206 to 3.5 mg/kg and 206 to placebo. There were 99 (48.5%) who completed the full course for 5.25 mg/kg and 131 (63.6%) patients who completed for 3.5 mg/kg.

Study 26593 ONWARD there were 124 patients with active MS exposed to cladribine 3.5 mg in combinations with IFN- β , and 48 patients exposed to placebo.

Safety issues with the potential for major regulatory impact

For a discussion of lymphocyte suppression, liver toxicity, other haematology and haematological toxicity, and immunogenicity and immunological events see Attachment 2

as well as the *Evaluator's conclusion on safety* and the Delegate's summary of *Safety and Discussion* below.

Postmarketing data

The sponsor submitted one post-marketing study. Study EMR700568_015 Record MS was a prospective, observational, post-authorisation study of cladribine tablets in cladribine-naïve patients in the Australian Patient Familiarisation Program. The study was conducted at seven centres in Australia from February 2011 to September 2014. The study included patients with relapsing forms of MS. The outcome measures were serious adverse drug reactions and Grade 3/4 lymphopaenia. There were 35 patients included in the study. There were 31 (88.6%) females, four (11.4%) males, the age range was 23 to 69 years and the time since diagnosis ranged from 1 to 42 years. The majority had previously received disease modifying treatment: 30 (85.7%) patients. Twelve patients received concomitant disease modifying treatment: three (8.6%) with natalizumab, two (5.7%) with fingolimod, two (5.7%) with dimethyl fumarate, two with interferon- β -1a and two (5.7%) with glatiramer acetate. The total dose of cladribine ranged from 0.9 to 2.5 mg/kg (patients only received a maximum of two courses due to withdrawal of cladribine from the Australian market).

Two serious adverse drug reactions were reported, both in the same patient: lymphopaenia and prostatic cancer. The prostate cancer was reported 490 days after the last dose. The patient was a 61 year old male, who was also reported with hip fracture and acute myocardial infarction.

There were no deaths. Four patients were reported with Grade 3 lymphopaenia.

Evaluator's conclusions on safety

The safety data confirm a higher rate of adverse events in the cladribine treated population compared with placebo. Lymphopaenia is a very common adverse event and is dose related. Lymphopaenia is related to the mode of action of cladribine. Infections and infestations are more common with cladribine. Herpes infections are also more common with cladribine.

There appears to be a higher rate of malignancy with cladribine but there is an insufficient sample size in the reported data to establish statistical significance. The relationship between total dose/exposure and malignancy remains to be determined.

The sponsor proposes extensive changes to the Risk Management Plan, but as discussed in Attachment 2, many of the proposed changes are not supported by any new data.

The sponsor has not submitted new clinical data exploring the minimum effective dose, so it is not possible to comment whether the adverse event profile may be improved by dose reduction. There were few patients treated with more than four years of treatment (total dose 7 mg/kg) and long-term treatment (beyond four years) has not been sufficiently investigated.

In the draft PI document the sponsor has changed the recommendations with regard the waiting time following administration of live vaccines to commencement of cladribine, from 3 months to 4 to 6 weeks. The sponsor has not provided any data in support of this change.

First round benefit-risk assessment

First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
<p>The sponsor has demonstrated efficacy compared to placebo in Study 25643 CLARITY which has been previously submitted and evaluated.</p> <p>Efficacy was demonstrated using qualifying relapse rate as the primary efficacy outcome measure. Disability progression was measured using EDSS. There was a statistically and clinically significant benefit for cladribine in comparison with placebo for both of these outcome measures. Hence there are sufficient data to support: <i>'to reduce the frequency of clinical relapses and to delay the progression of physical disability'</i> being included in the indication.</p> <p>There are limited data in support of removing the 2 year limit on treatment. Study 27820 CLARITY Extension provides some support for extending the duration of treatment, and total exposure, to 7 mg/kg over 4 years.</p>	<p>The data in support of removing the 2 year limit on treatment are limited. Although Study 27820 CLARITY Extension is supportive of the LLLL (total dose 7 mg/kg over 4 years) treatment group over the HLLL (8.5 mg/kg over 4 years) and does provide some support for extending the duration of treatment and total exposure to 7 mg/kg over 4 years, there are a number of limitations to the study. These limitations are:</p> <ul style="list-style-type: none"> • Study 27820 CLARITY Extension did not have a primary efficacy outcome measure and was not designed primarily to demonstrate efficacy. • The sponsor argues for efficacy based on a post hoc selection of 'key' efficacy variables. • The overall efficacy results were inconsistent and the statistically significant findings were not clearly of clinical significance. • The MRI outcome measures were more convincing of efficacy than the clinical outcome measures. <p>The sponsor has not provided any data that explores the lowest effective dose. This was identified as a major issue at the time of initial approval but has not subsequently been addressed by the sponsor.</p>

First round assessment of risks

Risks	
<p>The safety data confirm a higher rate of adverse events in the cladribine treated population compared with placebo. Lymphopaenia is a very common adverse event and is dose related. Lymphopaenia is related to the mode of action of cladribine. Infections and infestations are more common with cladribine. Herpes infections are more common with cladribine.</p> <p>There appears to be a higher rate of malignancy with cladribine.</p>	<p>The sponsor has not submitted new clinical data exploring the minimum effective dose, so it is not possible to comment whether the adverse event profile may be improved by dose reduction.</p> <p>There were few patients treated with more than four years of treatment (total dose 7 mg/kg) and long term treatment (beyond four years) has not been sufficiently investigated.</p> <p>There is an insufficient sample size in the reported data to establish statistical significance for a higher rate of malignancy with cladribine.</p> <p>The relationship between total dose/exposure and malignancy remains to be determined.</p>

First round assessment of benefit-risk balance

The risk benefit for cladribine is favourable for the currently approved treatment regimen. The duration of treatment could be extended to four years but there are insufficient data to support a favourable risk-benefit balance for treatment beyond this.

First round recommendation regarding authorisation

The application to amend to indication for Mavenclad to:

Mavenclad is indicated for the treatment of relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical relapses and to delay the progression of physical disability.

should be rejected.

In the opinion of the clinical evaluator there are sufficient data to support the addition of

'to reduce the frequency of clinical relapses and to delay the progression of physical disability'

but not the removal of

'for a maximum duration of 2 years'.

The sponsor needs to clarify the proposed dosing regimen before the treatment duration can be determined, but in the opinion of the clinical evaluator it should not exceed four years.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to Clinical questions raised and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of cladribine (Mavenclad) in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of cladribine (Mavenclad) in the proposed usage are unchanged from those identified the first round evaluation.

Second round assessment of benefit-risk balance

The risk benefit for cladribine is favourable for proposed amended dosing regimen, which is:

'Mavenclad therapy comprises of 2 treatment courses over 2 years (Year 1 and Year 2; cumulative dose of 3.5 mg/kg over 2 years). Patients should receive no more

than 2 treatment courses over two consecutive years. The recommended dose should not be exceeded. Following completion of these 2 treatment courses, no additional treatment is needed in the subsequent 2 years (Year 3 and Year 4). Re-initiation of treatment with cladribine after Year 4 has not been studied.'

VI. Pharmacovigilance findings

- Merck Serono Australia Pty Ltd has submitted EU-RMP version 1.3 (18 June 2017; DLP 31 December 2016) and ASA version 6.0 (17 August 2017) in support of this application.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below:

Table 6: Summary of ongoing safety concerns

R=routine and A=additional

Summary of safety concerns (ASA v6.0)		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Severe (Grade \geq 3) lymphopaenia	✓	✓	✓	✓
	Herpes zoster infection	✓	✓	✓	✓
	Tuberculosis	✓	✓	✓	✓
Important potential risks	Severe infections (including severe viral infections)	✓	✓	✓	✓
	Progressive multifocal leukoencephalopathy	✓*	✓	✓	✓
	Opportunistic infections (other than PML and tuberculosis)	✓	✓	✓	✓
	Malignancies	✓	✓	✓	✓
	Teratogenicity/Adverse pregnancy outcomes	✓	✓	✓	✓
	Severe cytopaenias (including aplastic anaemia)	✓	-	✓	
Missing information	Long-term safety data in particular for malignancy risk	✓	✓	✓	-
	Use in patients with moderate to severe hepatic impairment	✓	-	✓	-
	Use in elderly patients	✓	-	✓	-
	Sequential use of other immunosuppressive or immunomodulatory agents after	✓	-	✓	-

Summary of safety concerns (ASA v6.0)		Pharmacovigilance		Risk Minimisation	
	cladribine treatment				
	Impact of exposure to prior immunomodulatory / immunosuppressive agents on subsequent risks following cladribine exposure	✓	✓	✓	–

* enhanced pharmacovigilance with the use of structured targeted follow up forms

Recommendations for the safety specification

- Use in moderate to severe renal impairment should be included as missing information, and the PI revised as directed by the clinical evaluator

Additional pharmacovigilance activities include:

- EMR 700568-012 PREMIERE patient registry (ongoing, global)
- MS 700568-0002 PASS (planned): Post-authorisation long term safety study, Australian patient involvement planned.
- MS 700568-0004: Pregnancy registry (planned)
- Educational materials for health care professionals (HCPs) and Patients will be distributed as additional risk minimisation activities
 - The patient guide includes a dose calendar to aid with treatment compliance.

Outstanding recommendations

The recommendations made in the first round evaluation are reconciled with consideration of the sponsor response. There are two new recommendations.

1. The sponsor has not satisfactorily addressed 'Use in paediatrics' in the Risk Management Plan or PI. The sponsor should monitor the risk of off-label paediatric use and the Delegate is requested to consider a stronger warning against use in paediatrics.
2. Use in moderate to severe renal impairment should be included as missing information and the PI revised as directed by the clinical evaluator.

Wording for conditions of registration

Suggested wording for the RMP condition of registration will be provided after the Delegate has advised on the paediatric warnings in the Product Information so that appropriate management of the potential for paediatric off-label use can be recommended.

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no quality evaluation for this submission. Submissions for changes to quality aspects of the product and for the tradename change were approved during the evaluation process.

Nonclinical

The nonclinical component of the submission comprised of pharmacokinetic studies related to permeability and absorption, and metabolism and transporter interaction. No nonclinical data related directly to the extension of indication were submitted. Two in vitro studies demonstrated uptake of cladribine into human hepatocytes and lymphocytes. Hepatocyte uptake was passive and independent of known transport processes. Lymphocyte uptake was time-dependent and related to concentration of cladribine in culture.

Amendments to the PI were recommended.

Clinical

Pharmacology

The population pharmacokinetic evaluation relates to Study 700568-013 contributed further to understanding of cladribine PK in particular the estimation of renal and non-renal clearance and the association of renal clearance with creatinine clearance (CRCL). This analysis included data from the previously submitted Studies 25803, 26127 and 25643 (CLARITY). Typical renal clearance was 23.1 L/hour and related to CRCL by $3.66 \times \text{CRCL}$ (L/hour). Typical non-renal clearance was 22.7 L/hour. The population PK (popPK) study confirmed the effects of food on bioavailability and IFN-1 on metabolic clearance that were observed in other studies.

Interaction studies showed no clinically significant PK interaction between cladribine and IFN β -1a or cladribine and pantoprazole.

There has been no assessment of the PK of cladribine in patients with moderate or severe renal impairment. Estimates were made on extrapolation from a study population with normal renal function to mild renal impairment.

There were no new data concerning PD. The maximum effect of cladribine appears to have been achieved at the 3.5 mg/kg dose level. The effect of lower doses has not been explored.

Efficacy

Study 25643 (CLARITY) has been previously evaluated and demonstrated superiority of cladribine in comparison with placebo for reduction in relapse rates, MRI findings indicative of disease activity and for reduction in the progression of disability. Total doses of 3.5 mg/kg and the 5.25 mg/kg were compared with placebo over a 96 week period. The last dose of study medication was given at Week 52 and patients were followed to Week 96. In that study, cladribine 3.5 mg/kg and 5.25 mg/kg treatment groups had a 33% and a 31% relative reduction in risk of developing disability progression over the 96 week trial period, respectively, compared with the placebo group (HR = 0.67, 95% CI (0.48, 0.93), $p = 0.018$; HR= 0.69, 95% CI (0.49, 0.96), $p = 0.026$, respectively). The proportion of patients progressing to sustained disability was 20.6% in the placebo group, 14.3% in the 3.5 mg/kg treatment group and 15.1% in the 5.25 mg/kg treatment group.

Study 27820 (CLARITY Extension) examined extended dosing regimens with cumulative doses of 7 mg/kg and 8.25 mg/kg. There were 5 dose groups and over the course of the CLARITY + CLARITY extension study total cladribine dose exposures ranged from 3.5 mg/kg to 8.25 mg/kg. While the last observation was made in December 2011 the study report included in this submission was not completed until April 2016. This was primarily a safety study but there were exploratory efficacy objectives.

This study included patients who had been enrolled in Study 25643 CLARITY and who had completed, with or without rescue therapy; who had no evidence of latent tuberculosis infection (LTBI) or TB as evidenced by skin test or chest X-ray, and normal haematologic parameters. Of the 1165 subjects who completed treatment in the CLARITY study, 867 (74.4%) enrolled in the extension study. Of the 867 patients, 806 were treated and were included in the intent-to-treat (ITT) and Safety analyses.

Cladribine (or matching placebo) was administered as two treatment courses (each of two treatment weeks separated by a month) separated by one year. The treatment groups are summarised as:

- LLPP: cladribine 3.5 mg/kg for CLARITY and placebo for CLARITY Extension: total dose 3.5 mg/kg
- HLPP: cladribine 5.25 mg/kg for CLARITY and placebo for CLARITY Extension: total dose 5.25 mg/kg
- LLLL: cladribine 3.5 mg/kg for CLARITY and 3.5 mg/kg for CLARITY Extension: total dose 7 mg/kg
- HLLL: cladribine 5.25 mg/kg for CLARITY and 3.5 mg/kg for CLARITY Extension: total dose 8.25 mg/kg
- PPLL: placebo for CLARITY and cladribine 3.5 mg/kg for CLARITY Extension: total dose 3.5 mg/kg

The total duration of observation was 120 weeks (216 weeks including the predecessor CLARITY study).

No clinical benefit from the additional exposure to cladribine was demonstrated in this study as assessed by annualised relapse rates and disability progression. The proportion of patients free of 3 month disability progression ranged from was 72.4% to 77.4% across the 5 dosing groups. There was no significant difference in change in EDSS scores during the study. MRI markers also did not suggest a benefit from increased exposure to cladribine.

This study allows an assessment of efficacy in patients given the current approved dose regimen with a total exposure of 3.5 mg/kg over 2 years (patients given low dose cladribine in the CLARITY study and subsequently given placebo in the CLARITY extension study). There were 98 patients in this group with a median duration of exposure to cladribine (in CLARITY and CLARITY extension) of 136.4 weeks (range 96 to 212 weeks). The annualised relapse rate during CLARITY extension was 0.15 and 71 (72.4%) of these patients did not experience 3 month disability progression during the study.

Study 28821 ORACLE was a Phase III, randomised, double blind, placebo controlled, parallel group efficacy and safety study in patients with a first clinical event at high risk of converting to MS. The study was terminated prior to full follow-up time because the sponsor had decided to cease further development of cladribine. A total of 617 subjects were randomised and 616 received at least 1 dose of blinded study medication; 204 subjects in the cladribine 5.25 mg/kg group, 206 subjects in the cladribine 3.5 mg/kg group, and 206 subjects in the placebo group.

The study's original primary objective was to evaluate the effect of oral cladribine versus placebo on the time to MS conversion according to the 2005 McDonald criteria;⁶ in subjects with a first clinical demyelinating event at high risk of converting to MS. To comply with a FDA request and to support a potential product labelling indication, the study's primary endpoint was switched with an existing secondary endpoint in Protocol Amendment 3 (8 January 2010). Thus, following Amendment 3, the study's primary objective was to evaluate the effect of oral cladribine on the time to clinical definite MS (CDMS) conversion according to the Poser criteria, defined by either a second attack or a sustained increase in the EDSS in subjects with a first clinical demyelinating event at high risk of converting to MS. The 2005 McDonald criteria endpoint was retained as a secondary endpoint.

It has not been proposed to include a description of this study in the PI. It appears to have been included primarily for assessment of safety.

Study 26593 (ONWARD) was a Phase IIb, multicentre, randomised double blind, placebo-controlled, safety, tolerability and efficacy study of add-on cladribine 3.5 mg/kg to IFN- β -1a or β -1b in RMS patients with active disease despite treatment with IFN- β therapy. It is not being proposed that cladribine be given with IFN- β and this study has not been proposed for inclusion in the PI. The primary endpoint was safety and tolerability. All efficacy endpoints were secondary (lesion activity, as measured by MRI, qualifying annualised relapse rates (ARR) and progression of disability by EDSS).

There were multiple major protocol changes during the study and it was terminated in October 2011 after all patients had completed the scheduled cladribine/placebo courses. The annualised relapse rate in the cladribine group + IFN- β was similar to that seen in the CLARITY study at 0.12.

Comparison of efficacy from the efficacy analysis of high disease activity (HDA) subpopulations

This was a post hoc analysis performed after a recommendation from the CHMP in December 2014. Criteria were applied in order to retrospectively identify such subjects and evaluate their response to oral cladribine in individual (single trial) and combined (multi-trial) cohorts. The post hoc analyses were performed on HDA subgroups from the CLARITY and ONWARD studies. HDA definitions are shown below.

Table 7: HDA definitions

Definition	HDA1	HDA2	HDA3	HDA4
	A and/or C	D	B and D	A and/or D
A. Subjects with ≥ 1 relapse in previous year while on DMD therapy and ≥ 1 T1 Gd+ or ≥ 9 T2 lesions	√			√
B. ≥ 1 T1 Gd+ or ≥ 9 T2 lesions			√	
C. Subjects with ≥ 2 relapses (no prior use of DMD at any time in subject's history or duration of previous DMD)	√			

⁶ The McDonald criteria are diagnostic criteria for multiple sclerosis (MS). These criteria are named after neurologist W. Ian McDonald.

Definition	HDA1	HDA2	HDA3	HDA4
	A and/or C	D	B and D	A and/or D
therapy < 1 year) and at least 1 T1 Gd+ lesion				
D. Subjects with ≥ 2 relapses in previous year regardless of treatment status		√	√	√

DMD=disease modifying drugs; Gd+=gadolinium enhanced; HDA=high disease activity.

All HDA analyses have been conducted as post-hoc analyses and statistical tests were not corrected for multiplicity. Based on this, all statistical results in the HDA analyses should be interpreted as being nominally significant.

The EDS scores at baseline in these various HDA subgroups were similar to the whole study population. Mean disease duration was approximately 5 years and mean age was mid to late 30s. The ARR for non HDA patients and each of the HAD subgroups in CLARITY is shown below.

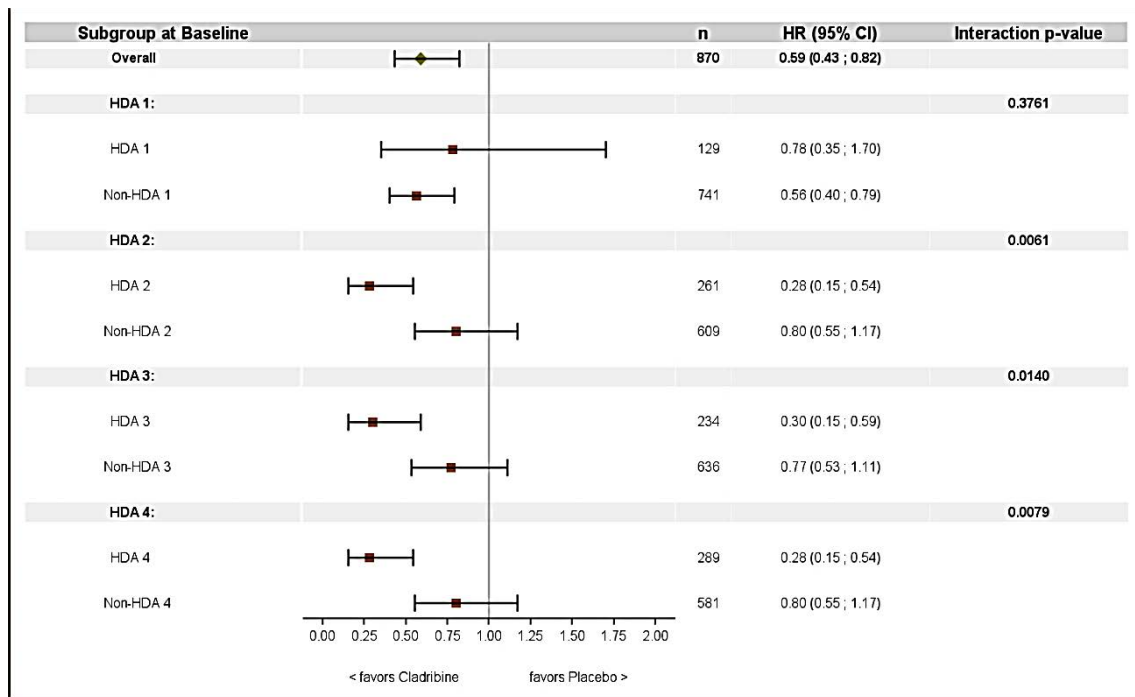
Table 6: HAD definitions

DB CLARITY	Overall N = 437	HDA1 N = 67	Non-HDA1 N = 370	HDA2 N = 131	Non-HDA2 N = 306	HDA3 N = 122	Non-HDA3 N = 315	HDA4 N = 149	Non-HDA4 N = 288
ARR adjusted	0.35	0.57	0.30	0.50	0.29	0.48	0.29	0.47	0.29
95% CI	0.31, 0.39	0.45, 0.73	0.26, 0.35	0.41, 0.60	0.24, 0.34	0.39, 0.58	0.25, 0.34	0.40, 0.57	0.24, 0.34

The ARR for HDA1, HDA2, HDA3, and HDA4 in patients treated with 3.5 mg/kg cladribine in CLARITY ranged from 0.38 to 0.32, indicating a relative risk reduction of 62% to 68% in ARR and are supportive of the relative risk ratios observed in the overall population (0.42, which indicated a relative risk reduction of 58%). The relative risk ratio for ARR for the corresponding non-HDA subgroup patients was 0.43 (relapse rates of 0.29 to 0.30 in the placebo group versus 0.13 to 0.14 the corresponding non HDA subgroup). This shows that while all patients benefit with reduced relapse rates, a greater benefit was seen for those with more active disease at Baseline.

Similarly for time to 3 month disability progression, The HRs for the HDA2, HDA3 and HDA4 subgroups were 0.28, 0.30 and 0.28, respectively, indicating a risk reduction of 72%, 70% and 72% in time to next 3 month confirmed EDSS progression, compared to the HR in the overall population of 0.59, indicating a risk reduction of 41%. The HR for time to next 3 month disability progression for the HDA1 and corresponding non-HDA groups were 0.78 (with a wide 95% CI) and from 0.56 to 0.80 respectively for the corresponding non-HDA subgroups. This result shows that while all patients benefit in terms of increased time to disability progression, patients with more active disease at baseline have the greatest benefit. This is shown in the figure below.

Figure 2: Hazard ratio of time to 3 month confirmed EDSS progression, HAD subgroups for 3.5 mg/kg versus placebo (CLARITY)



Safety

The major safety finding with increasing total exposure to cladribine is the increased rate of AEs related to lymphopaenia. This was dose dependent and in the highest total exposure group (8.75 mg/kg given as 5.25 mg in CLARITY + 3.5 mg in CLARITY extension) the study drug discontinuation rate was 25.3% compared with 22.6% in the 7 mg/kg (3.5 mg/kg in CLARITY and 3.5 mg CLARITY extension), 18.4% in patients receiving 3.5 mg/kg for the first time in CLARITY extension and 12.2% and 10.9% in the groups given placebo during CLARITY extension. At the end of the treatment phase in CLARITY extension, 40.9% of patients in the 8.25 mg total dose had Grade 3 or 4 lymphocyte toxicity (< 500/mm³) compared to 5.1% of patients in the 3.5 mg/kg during CLARITY and placebo in CLARITY extension (the LLPP group). Grade 3 or 4 white blood cell (WBC) toxicity (< 2000/mm³) was reported for no patients in the LLPP (total dose 3.5 mg/kg) group, one (1.1%) in the HLPP (total dose 5.25 mg/kg), 11 (5.9%) in the LLLL (total dose 7 mg/kg), 11 (5.9%) in the HLLL (total dose 8.25 mg/kg) and five (2.0%) in the PPLL (total dose 3.5 mg/kg).

A post hoc analysis of safety in the cladribine and Oracle studies did not show a relationship between highly active disease at baseline and the safety profile of cladribine. Safety of cladribine in patients with highly active disease was similar to that of the overall population.

Safety of concomitant INF- β with cladribine in the ONWARD study showed higher rates of discontinuation of treatment due to treatment emergent AEs with concomitant cladribine group as compared to the placebo (29.8% versus 8.3% respectively). This suggests continuing with INF- β in subjects who have received treatment courses of cladribine will result in about a third of patients needing to discontinue INF- β treatment due to AEs. The discontinuation rate due to AEs in the cladribine 3.5 mg/kg total dose group in the CLARITY study was 3.5%.

The RECORD study, conducted in Australia enrolled only 35 patients and was too small to identify less frequent safety risks. PREMIER is an ongoing prospective observational long-term safety registry for patients who had participated in CLARITY, CLARITY

extension, ONWARD, ORACLE and the interaction study with pantoprazole. The submission included data to from PREMIER to February 2015. Total duration of this registry is to be 8 years after the subjects' first enrolment into a cladribine clinical study or until 2018, whichever occurs first. It is intended to collect data on AEs including infections, malignancies, and lymphopaenia. Overall, of the 1,133 subjects in the Safety Set, 941 subjects received at least 1 dose of cladribine and 192 subjects never received cladribine (only received placebo (+ IFN- β placebo/observational period). Of subjects who received at least 1 dose of cladribine, mean (\pm standard deviation (SD)) total cumulative dose was 4.742 ± 2.082 mg/kg, and mean (\pm SD) time since the last dose at the time of the data cut (20 February 2015) was 240.8 ± 81.4 weeks. The table below highlights the TEAEs in this study.

Table 7: TEAEs reported from PREMIER

Number (%) of subjects with	Placebo (N = 192)	Cladribine (N = 941)	Total (N = 1133)
At least one AE	76 (39.6)	332 (35.3)	408 (36.0)
At least one AE leading to death	3 (1.6)	3 (0.3)	6 (0.5)
At least one SAE	8 (4.2)	37 (3.9)	45 (4.0)
At least one AESI: All Infection	7 (3.6)	35 (3.7)	42 (3.7)
At least one AESI: Severe Infection	2 (1.0)	6 (0.6)	8 (0.7)
At least one AESI: Herpetic Infection	5 (2.6)	29 (3.1)	34 (3.0)
At least one AESI: Opportunistic Infection (including tuberculosis)	6 (3.1)	31 (3.3)	37 (3.3)
At least one AESI: PML	0	0	0
At least one AESI: All malignant or unspecified tumours	1 (0.5)	11 (1.2)	12 (1.1)
At least one AESI: Malignant or unspecified tumours adjudicated by the independent tumour review board	1 (0.5)	7 (0.7)	8 (0.7)

Of particular note is the higher incidence of malignancy in the cladribine treatment group. (0.5% for placebo versus 1.2% for cladribine). The 11 malignant or unspecified tumours in patients given cladribine were: breast cancer (2), colon cancer Stage 0, lung neoplasm, metastases to lung, nasopharyngeal cancer, neoplasm of orbit, non-keratinising carcinoma of nasopharynx, papillary thyroid cancer, rectal adenocarcinoma, rectal cancer and thyroid neoplasm. The malignancy or unspecified tumour in the placebo group was a Stage 0 cervix carcinoma.

Risk management plan

EU-RMP version 1.0, 3 June 2016; data lock point (DLP) 29 February 2016 with Australian Specific Annex (ASA) version 5.0, 2 December 2016 was submitted.

The RMP evaluator considered the Summary of Safety concerns (ASA version 5.0) to be incomplete. That summary included severe lymphopaenia and herpes zoster infection as

identified risks, severe infections, opportunistic infections, malignancies, and teratogenicity/adverse pregnancy outcomes as important potential risks and long term safety data as missing information.

Additional risk minimisation activities are considered necessary by the sponsor and are being developed, including a Health Care Professional Guide and a Patient Guide. They are proposed to align with the EU materials (drafts submitted) and are intended to minimise all the important risks, except 'Malignancies'.

The RMP evaluator recommended additional safety concerns for the Safety Specification, requested details of the proposed pharmacovigilance activities, including whether Australian patients were to be included in a pregnancy registry and a post-authorisation safety study.

Recommendations by the RMP evaluator included patient directed risk minimisation tools, changes to the draft PI to better highlight risks and a request that the Australian educational material be provided.

Risk-benefit analysis

Delegate's considerations

No new data on the mechanism of action of cladribine in MS were submitted. It was noted by the Advisory Committee on Prescription Medicines (ACPM; now the ACM) at its consideration of the initial submission that a minimum effective dose of cladribine for MS had not been established. The approved 3.5 mg/kg dose level appears to achieve a maximum response. No new data to explore lower doses was included in this submission.

There were no new data concerning patients with renal impairment. The PopPK analysis included only patients with normal or mild renal impairment. An estimate of the exposure to cladribine for patients with moderate to severe renal impairment based on extrapolation from those with normal renal function or mild renal impairment was made and has been proposed for inclusion in the PI. This is not appropriate. Cladribine results in prolonged dose related lymphocyte suppression and there are major safety concerns with overexposure. A PK study in patients with moderate or greater renal impairment would be required if data on exposure in those patients were to be included in the PI.

The CLARITY extension study was primarily a safety study but the majority of patients were given additional doses of cladribine. No additional efficacy from higher cumulative doses over the initial 3.5 mg/kg over 2 years was demonstrated. Of note is that there were 98 patients who received the current dose regimen in the initial CLARITY study and who were followed for efficacy in CLARITY extension having received no additional cladribine. The annualised relapse rate in these patients was similar to the annualised relapse rate in the CLARITY study, strongly suggesting continued benefit up to 6 years after commencing treatment with cladribine. The risk of disability progression over the 96 weeks of the CLARITY study for patients given 3.5 mg cladribine was 33%. Disability progression occurred in 27.6% over the course of the extension study, again indicating sustained benefit from cladribine given only in the CLARITY study. These results strongly support continuing benefit from the current dose regimen.

The post hoc efficacy analyses of the CLARITY study clearly shows that more benefit in terms of reduced relapse rates and reduction in the risk of disability progression for patients with higher disease activity at baseline compared with other patients, though benefit was shown for all patients. The Delegate does not consider the difference in extent of benefit over the course of 2 years is sufficient to amend the indications to prevent patients without highly active disease at Baseline from receiving cladribine. It is appropriate to disclose the extent of difference in benefit shown in the post hoc analyses

of the CLARITY study in the Clinical Trials section of the PI. This will allow for maximal choice of treatments for patients. Cladribine treatment is to be initiated only by neurologists skilled in the management of MS and thus able to appropriately select patients.

A report of the ORACLE study was included in the submission. Cladribine is potentially very toxic and it would be clearly inappropriate for it to be given to patients who do not have a poor prognosis without aggressive treatment. Those patients were eligible for inclusion in this study. Prevention of conversion to clinically definite MS is not an appropriate endpoint for current studies in the treatment of MS. Similarly with the ORACLE study it was not possible to determine if there was increased efficacy from the combination of continued INF- β in patients who had been given cladribine.

It is clear that careful surveillance for infection and lymphopaenia is required for all patients who have received cladribine. While 75% of patients given the current dose regimen had lymphocyte counts within the normal range at Week 90 after their last dose (144 weeks after commencing treatment with cladribine) patients with persistent lymphopaenia should continue to be monitored until lymphocyte counts return to the normal range. Whether surveillance for AEs including malignancy can be reduced over time is not able to be determined from the data presented.

Request for ACM advice

This application was not referred to the Advisory Committee on Medicines (ACM).

Response from sponsor

Outstanding issues from RMP evaluation report

The following have been identified as outstanding issues from the RMP evaluation report:

- Paediatric population
- Moderate to severe renal impairment
- Educational material: Patient Guide
- Implementation plan: Schedule of effectiveness assessment reports

Paediatric population

Per the second round clinical evaluation report, the revised wording for Paediatric Use in the proposed PI is believed satisfactory. The sponsor agrees to include the paediatric population as important missing information of the Safety Concerns in the ASA.

Moderate to severe renal impairment

The sponsor agrees to include moderate to severe renal impairment as important missing information of the Safety Concerns in the ASA.

Educational material: Patient Guide

The RMP evaluation report made 3 recommendations for amendments of the Patient Guide. The sponsor accepts all recommendations and the final version of the Patient Guide will be submitted with the ASA.

Implementation plan: Schedule of effectiveness assessment reports

Expected dates for submission of effectiveness assessment reports were requested. Approximate timelines will be included in the implementation plan for submission with the ASA.

Review of the Product Information requests for amendments

The sponsor accepts all recommendations made by the Delegate on the proposed PI.
The draft PI has been amended.

Advisory committee considerations

This application was not referred to the Advisory Committee on Medicines (ACM).

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of approve the registration of Mavenclad tablet blister pack containing 10 mg cladribine for the new indication:

(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.

Specific conditions of registration applying to these goods

The EU-RMP (version 1.3, 18 June 2017, DLP 31 December 2016) with Australian Specific Annex (version 6.0, 17 August 2017) amended as agreed in your response to the TGA (date: 3 November 2017) must be implemented. Your assurance that the RMP (with ASA) will be updated as agreed and provided to the TGA for review and approval prior to product launch, is noted. Please ensure that the revised documentation is submitted to the TGA at least 3 months prior to the planned product launch date to ensure adequate time for assessment.

Attachment 1. Product Information

The PI for Mavenclad approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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