CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	22561
PDUFA Goal Date	March 29, 2019
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Reviewer Name(s)	Charlotte Jones, MD, PhD, MSPH
Team Leader	Donella Fitzgerald, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 26, 2019
Subject	Evaluation of Need for a REMS
Established Name	Cladribine
Trade Name	Mavenclad
Name of Applicant	EMD Serono, Inc.
Therapeutic Class	Multiple Sclerosis
Formulation(s)	10mg tablet
Dosing Regimen	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.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Mavenclad (cladribine) is necessary to ensure the benefits outweigh its risks. EMD Serono Inc (Serono) submitted a New Drug Application (NDA 022561) for a new dosage form for cladribine with the proposed indication for treatment of patients with a relapsing form of multiple sclerosis or active secondary progressive disease (b) (4) (b) (4). The serious risks associated with Mavenclad include embryo-fetal toxicity, malignancy, lymphopenia, infections, and liver injury.

The applicant did not submit a proposed REMS or risk management plan with this application, but proposed to communicate and mitigate the risks through labeling, a Medication Guide and pharmacovigilance. The agency is plans to require a pregnancy registry, a pregnancy outcomes study, and an observation study evaluating malignancies in the postmarketing setting.

DRISK and Division of Neurology Products (DNP) agree that a REMS is not necessary to ensure the benefits of Mavenclad outweigh its risks. Relapsing MS is a serious disease with significant disability and increased mortality that lacks universally effective treatments. The risks of Mavenclad are similar to other medications used to treat MS. If approved, the indication for Mavenclad will be indicated for patients with relapsing or active secondary progressive MS who have had an inadequate reponse to (b) (4) other MS indicated medications and further supports a favorable its benefit risk profile. Additionally, the intravenous formulation of cladribine is included in national guidelines for the treatment of MS.[1] This suggests that providers may already be aware of the importance of mitigating the risks of Mavenclad with monitoring laboratory values, effective contraception, routine cancer surveillance and pretreatment screening, vaccination and prophylaxis for infections.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Mavenclad (cladribine) is necessary to ensure the benefits outweigh its risks. Serono submitted a New Drug Application (NDA 022561) for the oral formulation of cladribine (Mavenclad) with the indication for treatment of patients with a relapsing form of multiple sclerosis (RMS) and active secondary progressive multiple sclerosis. This application is under review in the Division of Neurology Products (DNP). The applicant did not submit a proposed REMS or risk management plan with this application beyond labeling, including a Medication Guide, and routine pharmacovigilance and the Agency will require postmarketing registries for malignancy and pregnancy.[2]

2 Background

2.1 PRODUCT INFORMATION

New drug application (NDA) 02256 is an application for Mavenclad for the treatment of RMS. Mavenclad is a synthetic chlorinated purine nucleoside analog of the naturally occurring nucleoside deoxyadenosine. Its proposed mechanism of action in MS is lymphocyte suppression by causing DNA

strand breaks and interfering with DNA synthesis. The lymphocyte depletion leads to its associated anti-inflammatory effects. Cladribine is approved by the FDA as an intravenous formulation (Leustatin and multiple generics) for the treatment of active hairy cell leukemia. This review is for an oral formulation of cladribine (Mavenclad).[2] For the proposed MS indication Mavenclad is to be given as a cumulative dose of 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, (b) (4) (b) (4) 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. Following completion of the 2 treatment courses. Labeling will include that after the two year course not to administer in years 3 and 4 due to an increase in malignancy risk and that the safety and efficacy of further treatment has not been studied.[a,3] Mavenclad, was approved by the European Medicines Agency in 2017 for the treatment of adult patients with highly active RMS as defined by clinical or imaging features. It is also approved in Canada.[2]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 22561 relevant to this review:

- 05/27/2010: NDA 22561 submission for cladribine tablets for treatment of RMS received.
- 02/28/2011: Complete response issued due to safety concerns for an association with an increased risk of malignancy.[4]
- 08/19/2011: Applicant withdrew NDA 22561
- 05/31/2018: Applicant submitted Resubmission/After Withdrawal for NDA 22561.[2]

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

MS is a chronic inflammatory demyelinating disease that effects 100-150 people per 100,000 people in the United States.[b] Typical presenting signs are unilateral optic neuritis, with painful, monocular visual loss, brain stem or cerebellar syndromes with painless double vision difficulties or vertigo or balance problems, partial transverse myelitis with predominantly sensory symptoms.[5] Symptoms typically develop over the course of hours to days and then remit, although remission may be incomplete and relapses occur for many patients.[5] A relapsing course is the most common form of MS with 90% experiencing a secondary progressive course 10- 20 years after disease onset.[6,7] From patient's perspectives the incomplete remission with increasing disability over time, including cognitive

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

impairment, contributes significantly to quality of life in MS.[8,9c] Along with the impact MS has on the activity of daily living these patients also experience higher mortality compared to their age cohort.[10,11]

3.2 Description of Current Treatment Options

Treatment of MS is divided into two broad categories, symptomatic and disease modifying. The disease modifying therapies (DMTs) for relapsing MS reduce the frequency of relapses as well as accumulation of lesions on MRI resulting in decreased disability.[12] The factors the American Academy of Neurology suggests clinicians should consider with patients when deciding which medication to use are safety, efficacy and method of administration.[1] Since Mavenclad is an oral formulation with significant risks, Appended Table 1 shows the FDA approved DMTs that are either oral formulations or have significant efficacy but are not first line drugs, since these are the best comparators to Mavenclad when assessing benefit: risk. This also documents that the risks of embryofetal toxicity, lymphopenia, malignancy, infection and hepatoxicity, are risks associated with other FDA approved products recommended by the American Academy of Neurology for treatment of MS with increasing risk being seen in drugs approved for use in patients who have failed first line treatment. Although several drugs have been approved there is still a need for effective treatment for patients with MS, particularly the population who have failed other treatments. It is anticipated that patients with MS will be maintained on disease modifying treatment for years with those who transition from relapsing remitting to progressive having fewer treatment options.[1]

4 Benefit Assessment

The Division of Neurology Products (DNP) has decided to limit the current review to a review of safety with efficacy having been previously established in the prior review cycle in 2010.[13] At that time, it was determined that a single pivotal study, CLARITY (NCT00213135), supported the efficacy of Mavenclad. The CDTL concluded:

> *"There are no unresolved clinical or statistical issues related to efficacy. The effect of cladribine has been robustly demonstrated.*[d]

The sponsor conducted one adequate and well-controlled pivotal efficacy study, the CLARITY trial (#25643). CLARITY was a phase 3, placebo-controlled, three-arm, randomized (1:1:1), double-blind, multi-center study to evaluate the efficacy and safety of two doses of cladribine (3.5 mg/kg cumulative dose and 5.25 mg/kg cumulative dose) over 96 weeks in 1326 adult RRMS patients enrolled at 155 centers in 32 countries.

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

CLARITY provides substantial evidence for the effectiveness of both doses of cladribine on relapse rate when compared with placebo (0.15 for cladribine 5.25 mg/kg, 0.14 for cladribine 3.5mg/kg, and 0.33 for placebo), the primary outcome of the trial. There was no statistically significant difference between active treatment groups, but treatment with both doses resulted in a highly significant (p<0.001) difference in relapse rate when compared with placebo. Relative relapse rate reductions were 54.5% for high-dose cladribine and 57.6% for low-dose cladribine. These findings are both statistically and clinically meaningful. Multiple sensitivity and additional analyses of the primary endpoint confirmed the robust effect of both doses of cladribine."[4]

5 Risk Assessment & Safe-Use Conditions

Two thousand four hundred and twenty-four subjects exposed to Mavenclad constituted the full safety database. The safety database included data from the studies in Appended Table 2, and the safety assessed using the following cohorts:

- Oral Placebo-Controlled Double-Blind cohort: included safety data from the placebo-controlled double-blind period of the studies with Mavenclad.
- Monotherapy Oral cohort: included safety data from all studies that used Mavenclad as oral monotherapy.
- All Exposed cohort: included safety data from all phase II/III studies with any formulation of cladribine.

Common adverse events seen more frequently in Mavenclad treated than placebo treated subjects included lymphopenia and upper respiratory infections. The serious risks associated with Mavenclad treatment include embryofetal toxicity, malignancy, lymphopenia, infections, and liver injury.[e2]

5.1 DEATHS

In the placebo-controlled trials 7 of 1458 (0.5%) of Mavenclad exposed patients died while 2 of 745 (0.3%) of placebo subjects died (Table 1). In all studies of Mavenclad exposed subjects there were twenty-one deaths. Five deaths were related to malignancy, four deaths were related to infections, other causes of death included accidents (five), cardiac arrest (two), suicide (two), respiratory arrest (one), myocardial infarction(one) and unknown cause of death (one).[14]

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Table 1 Deaths in Placebo Controlled Trials[14]

Treatment Group	Subject Number	Total Cladribine Dose	Cause of Death	Relationship to Study Treatment*
Cladribine 5.25 mg/kg	CLARITY (b) (6)	0.875 mg/kg	Tuberculosis	Likely related
	CLARITY (b) (6)	1.75 mg/kg	Drowning	Unlikely related
Cladribine 3.5 mg/kg	CLARITY (b) (6)	1.75 mg/kg	Pancreatic carcinoma metastatic	Likely related
	CLARITY (b) (6)	1.88 mg/kg	Ovarian Cancer	Likely related
	CLARITY (b) (6)	3.5 mg/kg	Myocardial infarction	Cannot rule out if related
	ORACLE MS (b) (6)	0.94 mg/kg	Cardiorespiratory arrest	Confounded by brain stem lesions at baseline
	MS-Scripps (b) (6)	2.8 mg/kg iv (equivalent to 3.5 mg/kg oral)	Hepatitis B	Likely related
Placebo	CLARITY (b) (6)	0	Completed suicide	Not on cladribine
	CLARITY (b) (6)	0	Hemorrhagic stroke	Not on cladribine

*FDA reviewer's assessment

5.2 MALIGNANCIES

At the time of the initial review in 2010 the CDTL commented "Malignancies are seen in excess in cladribine treated patients and a major source of concern."[4] This pattern of increased risk of malignancy was present in the resubmission (Table 4). However there was no evidence of a specific malignancy type being overrepresented (Table 5) and the rate did not seem to increase over time.[14]

Table 2 Malignancy occurrence in defined safety cohorts

		Cladribine dose	
Monotherapy Oral cohort	**Placebo N=641, PY=2275.3**	**3.5 mg/kg N=923, PY=3754.0**	**5.25 mg/kg N=632, PY=2610.4**
Number of subjects with ≥ 1 malignant tumor	3	10	6
Adj-AE per 100 PY (95% CI) [a]	0.13 (0.043, 0.41)	0.27 (0.14, 0.50)	0.23 (0.10, 0.52)
Diff. Adj-AE per 100 PY relative to placebo (95% CI) [b]	-	0.14 (−0.14, 0.38)	0.10 (−0.18, 0.39)
Risk ratio (95% CI) [a]	-	2.03 (0.56, 7.37)	1.76 (0.44, 7.02)

		Cladribine dose	
Oral Placebo-controlled Double-blind cohort	**Placebo N=641, PY=999.1**	**3.5 mg/kg N=662, PY=1088.6**	**5.25 mg/kg N=632, PY=1071.8**
Number of subjects with ≥ 1 malignant tumor	0	5	2
Adj-AE per 100 PY (95% CI) [a]	0 (0, 0.37)	0.46 (0.19, 1.11)	0.19 (0.047, 0.75)
Diff. Adj-AE per 100 PY relative to placebo (95% CI) [b]	-	0.46 (0.076, 1.07)	0.19 (−0.20, 0.68)
Risk ratio (95% CI) [a]	-	NE	NE

Placebo-controlled Double-blind cohort	**Placebo N=745, PY=1134.7**	**Cladribine N=1458, PY=2400.2**
Number of subjects with ≥ 1 malignant tumor	1	8
Adj-AE per 100 PY (95% CI) [a]	0.088 (0.012, 0.63)	0.33 (0.17, 0.67)
Diff. Adj-AE per 100 PY relative to placebo (95% CI) [b]	-	0.25 (−0.18, 0.59)
Risk ratio (95% CI) [a]	-	3.79 (0.47, 30.27)

The specific malignancy's seen in the subjects as discussed at the midcycle are shown below.

Table 3 Malignancies in all Cladribine treated cohort

	Placebo (N=802)		Cladribine (N=1976)	
	n	(Adj-AE per 100PY)	n	(Adj-AE per 100PY)
Number of Subjects with at least one Malignant tumors treatment-emergent AE	4		34	
Malignant tumors	4	(0.15)	34	(0.36)
Basal Cell Carcinoma	2	(0.08)	5	(0.05)
Bile Duct Adenocarcinoma	0		1	(0.01)
Bladder Transitional Carcinoma	0		1	(0.01)
Bowen's Disease	0		1	(0.01)
Breast Cancer	0		2	(0.02)
Breast Cancer Stage Ii	0		1	(0.01)
Cervix Carcinoma	0		2	(0.02)
Cervix Carcinoma Stage 0	2	(0.08)	1	(0.01)
Choriocarcinoma	0		1	(0.01)
Colon Cancer Stage 0	0		1	(0.01)
Malignant Melanoma	0		2	(0.02)
Nodular Melanoma	0		1	(0.01)
Nonkeratinising Carcinoma Of Nasopharynx	0		1	(0.01)
Ovarian Cancer	0		2	(0.02)
Pancreatic Carcinoma Metastatic	0		1	(0.01)
Papillary Thyroid Cancer	0		3	(0.03)
Rectal Adenocarcinoma	0		1	(0.01)
Rectal Cancer	0		2	(0.02)
Rectosigmoid Cancer Metastatic	0		1	(0.01)
Renal Cell Carcinoma	0		1	(0.01)
Skin Cancer	0		1	(0.01)
Squamous Cell Carcinoma	0		1	(0.01)
Squamous Cell Carcinoma of Skin	0		1	(0.01)

From NDA 22561 Midcycle Meeting[14]

The clinical reviewer identifies that along with an increased risk malignancy, there is an increase in serious malignancy with the use of Mavenclad. The placebo associated malignancies were treatable with surgical excision which is not true for the Mavenclad associated malignancies. [15] The Agency plans that the risk of malignancy will be addressed as a boxed warning stating that Mavenclad can increase the risk of malignancy.[3] The boxed warning for Mavenclad will also indicate that standard cancer screening guidelines should be followed in patients treated with Mavenclad. Lastly, Mavenclad will be contraindicated in patients with current malignancies.[3]

Compared to other MS drugs with a risk for malignancy, the DNP safety team identifies the malignancy risk for Mavenclad as similar to Ocrevus which has a warning for malignancy and Lemtrada in which malignancy is included among many risks for which patients and providers are to be informed of as part of the REMS.[15]

5.3 EMBRYOFETAL TOXICITY

Toxicology studies demonstrated that cladribine is teratogenic in mouse, rabbit and rat leading to significant skeletal abnormalities and lethality.[16] During the pivotal CLARITY trial females were tested prior to treatment to ensure they were not pregnant and during treatment they were required to use adequate contraception. However, twenty-five pregnancies were reported in twenty-four females. Of these pregnancies six resulted in full-term normal live births; three in Mavenclad exposed women and three in women who had received placebo. The pregnancies of all Mavenclad exposed women are shown in Table 2. The Applicant reported no postmortem examinations were available on aborted fetuses. The Applicant states no congenital malformations have been reported after the use of cladribine in any formulation.

Table 4 Pregnancy Outcome[2]

All Exposed Cohort - Pregnancy Outcomes (Female Trial Subjects)		
	Placebo Number of Pregnancies (%), (N=21 (100 %))	Mavenclad Number of Pregnancies (%), (N=46 (100 %))
Pregnancy outcome		
Life birth	9 (43)	18 (39)
Induced abortion**	4 (19)	14 (30)
Spontaneous abortion	5 (24)	9 (20)
Medically indicated abortion	2 (9)	5 (11)
Unknown	1 (5)	0

**As per decision of the trial subjects

Data set for ISS with cut-off date was 15 May 2017; ISS Listing 3.1.1 and information from the Global Drug Patient (GPS) Database

The Agency plans to require a boxed warning for the risk of teratogenicity including that it is contraindicated in women of reproductive potential or their male partners if they are not using effective birth control. This will also include the need to exclude pregnancy in females of reproductive potential prior to starting Mavenclad, and the need for effective contraception during and for 6 months after treatment in females of reproductive potential or their male partners. Lastly, there will be a warning to stop the drug if the patient becomes pregnant.[3]

5.4 LYMPHOPENIA

Lymphopenia is a necessary and expected effect of Mavenclad, although severe lymphopenia is to be avoided. During the trials severe lymphopenia was at times reported as an adverse event. In addition, during the studies scheduled monitoring identified absolute lymphocyte counts of grade 3 or 4 lymphopenia at higher levels in Mavenclad than placebo treated patients. Table 3 demonstrates the

increased risk of severe lymphopenia in the cohort of oral placebo controlled double blind trials and the development of absolute lymphocyte counts of grade 3 or 4.[14]

Table 5 Severe Lymphopenia

Severe lymphopenia reported as AE*	Placebo	Mavenclad 3.5mg/kg (n=662)
No. of Patients with adverse events of special interest (AESIs) of severe lymphopenia (%)	0	12 (1.8)
Adj-AE per 100 PY	0	1.11
95% CI	0.00; 0.37	0.63; 1.96
*Note: As defined in the protocols and due to the mechanism of action of Mavenclad, lymphopenia was not routinely to be reported as AE.		
Severe (Grade ≥3) lymphopenia from reported laboratory values		
ALC* at least one grade 3	3 (0.5)	162 (24.5)
ALC at least one grade 4	0	4 (0.6)

During the clinical trials lymphopenia was monitored and the Agency proposed labeling will include a routine monitoring schedule (Appended Table 3) and a Warnings and Precautions for lymphopenia and herpes prophylaxis if the ANC is ≤ 200.[3]

5.5 INFECTIONS

The occurrence of infections is an expected adverse event related to Mavenclad's mechanism of action and associated lymphopenia. In all studies of Mavenclad there were 4 deaths related to infections: tuberculosis, hepatitis B, meningoencephalitis herpetic and pneumonia.[14] The association of severe infections with treatment with Mavenclad is complicated by the association of infections with MS, both related to a causal role in occurrence and relapses.[17] An overall increased risk of severe infections was not noted between Mavenclad treated and placebo treated patients in the clinical trials. To mitigate the risk of severe infections the Agency proposed labeling will address this with the following recommendations: Screening for latent infections, including tuberculosis and hepatitis, is required prior to initiation of therapy in year 1 and year 2. A delay in initiation of Mavenclad is recommended until the infection has been adequately treated. Mavenclad will be contraindicated in patients with infections with human immunodeficiency virus (HIV), active tuberculosis or active hepatitis.[3] Initiation of Mavenclad in patients currently receiving immunosuppressive or myelosuppressive therapy is not recommended.

5.5.1 Progressive Multifocal Leukoencephalopathy

Progressive Multifocal Leukoencephalopathy (PML) is a risk seen with many MS drugs associated with significant immunosuppression. The applicant reports that "In clinical trials of both oral and parenteral cladribine in MS, no cases of PML were reported during a total observation period of more than 9500 patient years in 1976 patients. Cases of PML have been reported for parenteral cladribine in patients treated with non MS indications.[18]

The Agency proposed label includes warnings and precautions for the risk of PML including noting its occurrence in patients treated with cladribine for oncologic indications. A recommendation to obtain a baseline MRI to evaluate for PML within 3 months prior to initiation of Mavenclad and to evaluate and withhold in the setting of signs or symptoms of PML will be included in the Warnings and Precautions section of the label.[3]

5.6 LIVER INJURY

The clinical reviewer identified that following her review of the source papers "of these adverse events, 5[f] of 10 cladribine subjects and 5[g] of 5 placebo subjects were confounded or had etiologies not consistent with drug-induced liver injury." This led to the assessment that 5 of 1555 (0.3%) cladribine subjects in the Monotherapy Oral Cohort had Hepatic disorder adverse events (serious or causing treatment discontinuation) consistent with drug-induced liver injury, compared to 0 of 641 placebo subjects. There were no Hy's law cases.[19] The Agency proposes that the risk of liver injury be in the Warnings and Precautions section. Recommendations for laboratory monitoring will also be included in the label.[3]

6 Expected Postmarket Use

Cladribine is currently recommended by the American Academy of Neurology as a DMT that prescribers may offer patients, therefore its use, should it be approved, is likely to be significant in patients with active MS who have failed first line therapies or have aggressive disease.[1] The label will state that "because of its safety profile Mavenclad should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.[3]" Although prescribing is likely to be by neurologists and MS specialists, the use by primary care physicians who provide primary care to a significant number of MS patients, particularly those in rural areas, is recognized.[20] The prescribers of MS drugs for patients who have failed two previous MS drugs, should be familiar with how to mitigate the risks of Mavenclad and the mitigation of these risks since they are similar to those for other MS drugs with similar risk profiles (see Appended Table 1). Additionally the need for providers to manage these risks is present in the MS literature.[21] As Mavenclad is an oral formulation, the drug will likely be available through both inpatient and outpatient pharmacies. The use of Mavenclad off label for

[f] Source: Pages 324-326 Summary of Clinical Safety and narratives. Cladribine subjects: CLARITY Subject (b) (6) (overdose of overdose of zopiclone and hydroxyzine); CLARITY Subject (b) (6) (chronic cholecystitis); CLARITY Subject (b) (6) (hepatosplenomegaly with fatal tuberculosis); CLARITY EXT Subject (b) (6) (benign hemangioma of the liver); and CLARITY EXT Subject (b) (6) (acute fatal hepatitis B).

[g] Source: Pages 326-327 Summary of Clinical Safety and narratives. Placebo subjects: CLARITY Subject (b) (6) (hepatic cyst); CLARITY Subject (b) (6) (hepatic dysfunction associated with fatal hemorrhagic stroke); CLARITY Subject (b) (6) (chronic hepatitis C); and ORACLE Subject (b) (6) and ORACLE Subject (b) (6) both had concomitantly elevated creatine kinase, AST, and ALT (consistent with muscle as a source of transaminase elevation).

autoimmune disorders, due to its oral availability, is expected to occur but with the number of immunosuppressives available, the use in these populations is difficult to predict.[22]

7 Risk Management Activities Proposed by the Applicant

The applicant has not proposed any additional risk management beyond routine labeling, routine pharmacovigilance, and pharmacovigilance studies currently underway in the US and other locations to evaluate the safety of Mavenclad.

The additional pharmacovigilance studies proposed by the applicant include a registry: " To assess the frequency of serious adverse drug reactions, including malignancies and serious infections, to assess the time to resolution of lymphopenia among patients with persistent lymphopenia, to quantify and characterize the risk of AE in the 'Blood and Lymphatic System Disorders 'and 'Neoplasms Benign, Malignant, and Unspecified 'System Organ Classes(SOCs), and to assess pregnancy outcomes in this population."[2]

In addition, Post-Authorization Safety Studies are planned in Europe to: "determine the occurrence of major congenital abnormalities (MCA), adverse pregnancy outcomes, and alterations in fetal growth, developmental and functional disabilities in pregnant women with MS exposed to Mavenclad and in pregnancies fathered by male patients with MS exposed to Mavenclad. These study outcomes will be compared with those of pregnant women with MS not exposed to any DMD (disease modifying drug) and with women whose pregnancy is fathered by a male patient with MS not exposed to any DMD, respectively."[2]

The final determination has not been made at the time of this review, however, the safety clinical reviewer has recommended a pregnancy registry, a pregnancy outcomes study, and an observational study evaluating malignancies in the postmarketing setting.[19]

8 Discussion of Need for a REMS

The clinical reviewers recommends approval of Mavenclad on the basis of the efficacy and safety information currently available.[15] Multiple sclerosis is a serious disease with progressive disability and mortality and, while current treatments exist, additional effective treatments are still required. The efficacy of Mavenclad has been demonstrated in a single clinical efficacy study and showed both statistical and clinical efficacy. Although Mavenclad is not FDA approved it is already in use in other countries and an IV formulation of cladribine is available in the US with an indication for treatment of hairy cell leukemia. The use of intravenous cladribine for the treatment of MS is currently recommended by the American Academy of Neurology even in the absence of FDA approval.[1] Mavenclad carries significant risks of embryo-fetal toxicity and malignancy which are to labelled with boxed warnings, as well as a warning for lymphopenia, severe and opportunistic infections, and hepatic injury. The risks of Mavenclad do not pose unique REMS considerations compared with the risks of

other DMTs for MS which do not have REMS to address similar risks of similar magnitude. DRISK is not recommending a REMS for the management of the risks of Mavenclad therapy.

9 Conclusion & Recommendations

Based on the clinical review; the benefit-profile is favorable therefore, a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with Mavenclad use are well documented and healthcare providers who treat patients with MS who have failed two previous indicated treatments should be familiar with the risk of embryo-fetal toxicity, lymphopenia, malignancy, infections, and hepatic injury. Prescribers should consult labeling to understand the benefits and the risks, be aware of the importance of mitigating those risks with appropriate patient selection and counseling, laboratory monitoring, effective contraception, routine cancer surveillance and pretreatment screening, vaccination and prophylaxis for infections.

At the time of this review, evaluation of safety information and labeling was ongoing. Should DNP have any concerns or questions or if new safety information becomes available that changes the benefit-risk profile, please send a consult to DRISK and this recommendation can be reevaluated.

10 Appendices

10.1 References

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10.2 APPENDED MATERIAL

Appended Table 1 FDA Approved Disease Modifying Treatments for Relapsing Remitting Multiple Sclerosis

Adverse events that are also found with Mavenclad use are underlined

Product Name FDA Approval Date	Indication	Dosing Administration	Important Safety and Tolerability Issues	Risk Management Approach REMS/Boxed Warning/ Medication Guide
Alemtuzumab 2001	LEMTRADA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile,	12mg IV daily X 5 days year 1 +/- daily x 3 days year 2	**Boxed Warning:** **Fatal autoimmune conditions: immune thrombocytopenia and anti-glomerular basement membrane disease** **Serious and life-threatening infusion reactions** **Stroke and Cerivocephalic Arterial Dissection May**	**REMS:** To inform patients of risks of autoimmune conditions, infusion reactions and **malignancies** and need for monitoring. To inform health care providers about autoimmune conditions, infusion

	the use of LEMTRADA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS		**increase risk of malignancies**	reactions and malignancies and need for monitoring
Dimethyl Fumarate 2013	TECFIDERA is indicated for the treatment of patients with relapsing forms of multiple sclerosis	120 mg twice a day orally. After 7 days, 240 mg twice a day orally.	Warnings and Precautions Anaphylaxis and Angioedema. Progressive multifocal leukoencephalopathy Lymphopenia Liver Injury Flushing	Warnings and Precautions: No REMS No Boxed Warning

Fingolimod 2010	Fingolimod is indicated for the treatment of relapsing forms of multiple sclerosis (MS) in patients 10 years of age and older	Dosage In adults and pediatric patients 10 years of age and older weighing more than 40 kg, the recommended dosage of Fingolimod is 0.5 mg orally once-daily. In pediatric patients 10 years of age and older weighing less than or equal to 40 kg, the recommended dosage of Fingolimod is 0.25 mg orally once daily. First-Dose Monitoring Monitoring After Reinitiation of Therapy Following Discontinuation	Warnings and Precautions Bradyarrhythmia and Atrioventricular Blocks Infections: Progressive Multifocal Leukoencephalopathy Macular Edema Posterior Reversible Encephalopathy Syndrome Respiratory Effects Liver Injury Fetal Risk Increased Blood Pressure Cutaneous Malignancies Immune System Effects Following GILENYA Discontinuation Hypersensitivity Reactions	Released from Communication Plan REMS 2016 Warnings and Precautions: Currently No REMS No Boxed Warnings

Mitoxantrone 1987	Mitoxantrone Injection, USP is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone Injection, USP is not indicated in the treatment of patients with primary progressive multiple sclerosis.	12mg/m^2 IV infusion every 3 months	**Boxed Warning: Congestive heart failure (CHF), potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy.** **Secondary Acute Myeloid Leukemia.**	**Boxed Warning** for Congestive Heart Failure. Secondary Acute Myeloid Leukemia

Natalizumab 2006	TYSABRI is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. TYSABRI increases the risk of PML. When initiating and continuing treatment with TYSABRI, physicians should consider whether the expected benefit of TYSABRI is sufficient to offset this risk. See important information regarding the risk of PML with TYSABRI.	300mg IV every 4 weeks	**Boxed Warning:** **Progressive Multifocal Leukoencephalopathy (PML)** Warnings and Precautions: Herpes Infections Hepatotoxicity Hypersensitivity/Antibody Formation Immunosuppression/Infections Laboratory Test Abnormalities Immunizations	**REMS:** To inform prescribers, infusion center healthcare providers, and patients about the risk of progressive multifocal leukoencephalopathy (PML) associated with TYSABRI including the increased risk of PML with longer treatment duration, prior immunosuppressant use and the presence of anti-JCV antibodies. To warn against concurrent use with antineoplastic, immunosuppressant, or immunomodulating agents, and in patients who are immunocompromised. To promote early diagnosis of PML and timely discontinuation of TYSABRI in the event of suspected PML.

Ocrelizumab 2017	OCREVUS is a CD20-directed cytolytic antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis	Hepatitis B virus screening is required before the first dose Administer OCREVUS by intravenous infusion. Start dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion Subsequent doses: 600 mg intravenous infusion every 6 months	Warnings and Precautions: Infusion reactions Permanently discontinue OCREVUS if a life-threatening or disabling infusion reaction occurs	Warnings and Precautions: No REMS No Boxed Warning
Teriflunomide 2012	Teriflunomide is a pyrimidine synthesis inhibitor indicated for the treatment of patients with relapsing forms of multiple sclerosis	7 mg or 14 mg orally once daily	**Boxed Warning: Hepatoxicity** **Risk of Teratogenicity**	**Boxed Warning** for Hepatoxicity & **Teratogenicity**

Appended Table 2 Safety Database Trials and Cohorts

Study	Indication	Type of control/blinding/ design	Cohort All Exposed	Cohort Mono-therapy Oral	Cohort Placebo Controlled Double-Blind	Cohort Oral Placebo Controlled Double-Blind	Total Number of subjects	
							Enrolled	Treated
CLARITY NCT00213135	RRMS	Randomized, placebo-controlled, double-blind, oral cladribine, MS DMD allowed as rescue medication	✓	✓	✓	✓	1326	1319
CLARITY EXT NCT00641537	RRMS	Randomized, placebo-controlled, double-blind, oral cladribine, MS DMD allowed as rescue medication. Extension study of CLARITY	✓	✓			867	806
ONWARD NCT00436826	RRMS/SPMS with active disease	Randomized, placebo-controlled, double-blind, oral cladribine, INF- as active background therapy for all subjects	✓				214	214
ORACLE MS NCT00725985	Early MS	Randomized, placebo-controlled, double-blind, oral cladribine, MS DMD allowed as rescue medication	✓	✓	✓ Only double-blind (ITP) phase	✓ Only double-blind (ITP) phase	617	616
PREMIERE NCT01013350	RRMS/SPMS with active disease/Early MS	Ongoing, prospective observational long-term safety registry of subjects who have participated to one of the 4 oral cladribine clinical trials or the phase I pantoprazole drug-drug interaction (DDI, No 27967]	✓ (only subjects from CLARITY, CLARITY EXT, ONWARD, ORACLE)	✓ (only subjects from CLARITY, CLARITY EXT, ONWARD, ORACLE)			1162	N/A Observational trial patients not given cladribine during trial

		study.						
Scripps-A	CPMS	Phase II: open label proof-of-concept, i.v. cladribine	✓				7	7
Scripps-B	CPMS	Phase II: Randomized, placebo-controlled, doubleblind, s.c. cladribine, and crossover re-treatment phase	✓		✓ (only first sequence			
Scripps-C	RRMS	Phase II: 1.5 yr. Randomized, placebo-controlled, double-blind, parallel group, s.c. cladribine, open-label retreatment long term followup phase	✓		✓ (only first sequence)		49	49
MS-Scripps	CPMS	Phase II: 2-yr. double-blind, placebo-controlled, randomised, cross-over, single center, i.v. cladribine, open-label re-treatment long term follow-up	✓		✓ (only first sequence)		49	49
MS-001	CPMS	Phase III: Randomized, placebo-controlled, double blind, parallel group, sc cladribine, long term followup	✓		✓ (only DB phase)		159	159
All Studies	Early MS/RRMS/SPMS with Active Disease/ CPMS						2432	2424

From Tables 1 & 2 ISS Statistical Analysis Plan[2]

Appended Table 3 Laboratory Monitoring

Obtain complete blood count (CBC) with differential including lymphocyte count

- before initiating MAVENCLAD in year 1,
- before initiating MAVENCLAD in year 2,
- in each treatment year at 1 month (before starting the second week of MAVENCLAD treatment within a treatment cycle), 2 months, and 6 months. See Warnings and Precautions (5.3) for instructions based on the patient's lymphocyte counts and clinical status (e.g., infections). Hold MAVENCLAD therapy if the lymphocyte count is below 200 cells per microliter,
- annually and as clinically indicated

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/s/

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