CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022561Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	March 25, 2019
From	Paul Lee, MD, PhD Nick Kozauer, MD Eric Bastings, MD
Subject	Summary Memorandum
NDA #	22561
Applicant	EMD Serono, Incorporated
Date of Submission	May 31, 2018
PDUFA Goal Date	March 31, 2019
Proprietary Name	Mavenclad
Established or Proper Name	Cladribine
Dosage Form(s)	10 mg oral tablet
Applicant Proposed Indication(s)/Population(s)	3.5 mg/kg over 2 years
Action or Recommended Action:	Approval
Approved/Recommended Indication(s)/Population(s) (if applicable)	Treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS. MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Cladribine is a nucleoside metabolic inhibitor that interferes with DNA repair and synthesis, proposed by the applicant for the treatment of relapsing forms of multiple sclerosis (MS). Cladribine causes significant depletion of circulating lymphocytes after administration which lasts for months. Cladribine is approved in an intravenous form with an indication for the treatment of hairy cell leukemia.

Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (secondary progressive MS with relapses), are a group of chronic and potentially disabling MS phenotypes of apparent autoimmune etiology characterized by episodes of worsening focal neurological deficits and disseminated lesions of demyelination. Symptoms include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. Over several years, many, but not all, patients with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. In some patients, disability may accrue progressively in the absence of obvious relapse events, a process termed secondary progressive disease. Secondary progressive disease that occurs with continued relapses is described as active secondary progressive disease, with the relapses being the clinical manifestation, in part, of an inflammatory demyelination that is presumed to be distinct from the pathogenesis of the progressive component of the disease. In the active secondary progressive phase of the disease, patients can accrue disability both from acute relapses and from the progressive component of the disease. Active secondary progressive disease and relapsing-remitting disease overlap in evolution. Categorization as secondary progressive disease is based on clinical judgment; there are no clinical findings or biomarkers that meaningfully define or predict the phenotypes of relapsing forms of MS. A continued progression of disability with no concurrent inflammatory activity and no clinical relapses is described a non-active secondary progressive MS.

This application is a resubmission in response to a Complete Response letter issued by the Agency on February 27, 2011. The Agency had concluded that, while the initial application had established substantial evidence of efficacy for cladribine, there was evidence that cladribine was associated with multiple different types of malignancies that precluded an approval for the indication of the treatment of relapsing forms of multiple sclerosis (MS). The Agency indicated that further characterization of this malignancy risk would be needed to support a potential approval action. This review assesses the safety findings in a resubmission that attempts to address the deficiencies raised in the 2011 Complete Response letter.

Assessment of Benefits: The original MS application provided substantial evidence of effectiveness, based on the results of a single clinical trial (CLARITY). This was a Phase 3, placebo-controlled, three-arm, randomized (1:1:1), double-blind, multi-center study that evaluated 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 patients with relapsing-remitting MS enrolled at 155 centers in 32 countries. The effect of cladribine was demonstrated by effects on relapse rate, disability progression, and various imaging markers of disease activity. These findings were consistently demonstrated with multiple analyses and are robust. The 3.5 mg/kg cumulative dose of cladribine reduced the annualized relapse rate (ARR) from a mean of 0.33 relapses per year in the placebo treatment group to 0.14, a relative reduction of risk of 58%. The 3.5 mg/kg dose of cladribine also reduced the risk of disability progression (hazard ratio 0.67; 19% progression on placebo vs. 13% on cladribine). The results for the 5.25 mg/kg cumulative dose of cladribine were nearly identical to those of the 3.5 mg/kg dose. The applicant is seeking an indication only for the 3.5 mg/kg dose because of a lack of observed dose-dependency on efficacy and safety.

Assessment of Risks: Cladribine exposure has been associated with malignancies such as malignant melanoma, ovarian cancer, or pancreatic cancer. As discussed above, the need for further characterization of the malignancy risk with cladribine led to a Complete Response action in the first review cycle, with a need to address a concern that the risk may increase over time. The resubmitted application provides an adequate longitudinal assessment of the malignancy risk (i.e., 0.27 events/100 patient-years compared to 0.13 events/100 patient-years in placebo-treated patients), and supports that the risk of malignancy remains stable over time, as demonstrated with the additional long-term follow-up presented in this application. The risk of malignancy with cladribine, however, persists for years after treatment completion.

There is also evidence from animal models that cladribine can cause significant harm to the developing fetus. Boxed warnings are needed to provide adequate warning of the serious risks of malignancy and teratogenicity.

The most common serious adverse event associated with cladribine is a reduction in lymphocyte counts (which occurs in nearly 90% of patients.) The reduced lymphocyte count can rarely (1% of patients) lead to compromised immune function and is associated with a rare (<1% of patients) risk of infections including life-threatening opportunistic infections or recrudescence of latent infections such as reactivation of tuberculosis, hepatitis, or varicella virus.

Assessment of Benefit-Risk: Multiple drugs are approved for the treatment of relapsing forms of multiple sclerosis. However, individual patient responses can vary with any of these treatments, and there remain patients who do not have an adequate response, or cannot tolerate available therapies. Therefore, there is a need for additional options for the treatment of relapsing forms of MS. Cladribine is clearly effective for the treatment of relapsing forms of MS. Based on the results of the CLARITY study, patients with relapsing forms of MS are expected to have their frequency of relapses reduced by about 60%. For every 100 patients with relapsing-remitting MS taking cladribine instead of placebo over a

period of 96 weeks, progression of disability would be prevented in 6 patients. Cladribine, however, has significant risks that can yield serious, and potentially fatal, outcomes, and approximately one patient would be expected to experience an event that may lead to permanent harm or death over the same period (96 weeks). The potential benefits of cladribine for the treatment of relapsing forms of MS clearly outweigh the risks. However, because of its significant risks, cladribine should generally be recommended for patients with relapsing forms of MS who had an inadequate response, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Because of its safety profile, cladribine is not recommended for use in patients with clinically isolated syndrome, who may not experience any future relapses.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (SPMS with relapses), are phenotypes of MS, a chronic and potentially disabling central nervous system disease of apparent autoimmune etiology characterized by episodes of worsening focal neurological deficits and disseminated lesions of demyelination. The usual age of onset of MS is 20 to 50 years. Symptoms include recurrent paroxysms of diminished sensory or motor function that can be disabling and usually resolve within one month. Over several years, many, but not all, patients with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. In some patients, disability may accrue progressively in the apparent absence of relapse events, a process termed secondary progressive disease. Secondary progressive disease that occurs with continued relapses is described as active secondary progressive disease, with the relapses being the clinical manifestation, in part, of an inflammatory demyelination that is presumed to be distinct from the pathogenesis of the progressive component of the disease. The clinical course of relapsing forms of MS varies widely. Some patients may have a relatively benign manifestation with few discrete relapse events; others may become severely disabled after only a few years. There are no reliable predictors of outcome. Active secondary progressive disease and relapsing-remitting disease overlap in evolution. Assignment of a secondary progressive disease diagnosis is based on clinical judgment; there are no clinical findings or biomarkers that meaningfully define or predict the phenotypes of relapsing forms of MS.	Relapsing forms of MS, which include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (SPMS with relapses) are serious and disabling.
Current Treatment Options	• Fourteen different drugs are approved to treat relapsing forms of MS. All approved therapies reduce relapse rates. The mechanism of action is unknown for all approved therapies. • Four approved therapies for relapsing forms of MS are administered orally on a daily basis.	Multiple drugs are approved for the treatment of relapsing forms of multiple sclerosis. However, individual patient responses can vary with any of these treatment options, and there remain patients who do not have an adequate response,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Some effective treatments for relapsing forms of MS have significant risks and are designated as second-line therapies, meaning they are generally recommended for patients who have had an inadequate treatment response or cannot tolerate one or more therapies with relatively less risk of a serious adverse outcome.	or can't tolerate available therapies.
Benefit	• A 96-week, randomized, placebo-controlled clinical trial (CLARITY study) showed a 58% reduction in the frequency of relapses in patients with relapsing-remitting MS, compared to placebo. A patient administered cladribine would expect to have more than half as many relapses on an annual basis in the 96-weeks after cladribine was initiated. • Over the 96-week period of observation, 13% of patients treated with cladribine experienced confirmed progression of disability, compared to 19% in the placebo group. Thus, the absolute reduction in risk of progression was 6%, and the relative risk reduction was 33% (hazard ratio = 0.67). Based on the mean effect size in this study, one would need to treat 17 patients for 96 weeks in order to prevent one confirmed progression, i.e., the number needed to treat (NNT) over 96 weeks is 17. Calculation of a NNT over one year is problematic, because disability does not progress at a constant rate with respect to time. • A treatment effect showing reductions in the number of new Gadolinium enhancing T1 and T2 lesions supports the primary efficacy outcome finding of a reduction in relapses.	The Agency concluded during the review of the original application that cladribine is effective in reducing the relapse rate in patients with a relapsing form of MS. The relative risk of advancement of disability is also significantly reduced at 96-weeks.
Risk and Risk Management	• The safety database for cladribine for treatment of MS includes Phase 2 and 3 studies of oral or parenteral cladribine, as well as an extension study and a long-term safety monitoring patient registry. Drug exposure is adequate for NDA resubmission. No subjects were above age 65 at the time of enrollment. The studies provide a limited amount of data on patients from the United States. • In the Phase 3 placebo-controlled study, the most common adverse events were: Upper respiratory infection (38%); Headache (25%); Lymphopenia (24%); Nausea (10%); Back pain (8%).	Cladribine can cause serious adverse reactions that can lead to disability or death, including an increased risk of malignancy and fetal harm. However, information regarding these risks can be accurately described in the prescribing information (PI). Labeling will also provide detailed monitoring recommendations to attempt to mitigate these risks to the extent possible. Therefore, in the context of the established efficacy of cladribine for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Treatment with cladribine can increase the risk of malignancy. Cladribine interferes with DNA synthesis and repair through incorporation into DNA and through inhibition of enzymes involved in DNA metabolism. Patients administered cladribine appear to be at higher risk of many different types of cancer. Some malignancies in cladribine patients were more severe [e.g., metastatic pancreatic carcinoma, malignant melanoma (2 cases), ovarian cancer] compared to malignancy cases in placebo patients, all of which were curable by surgical resection [basal cell carcinoma, cervical carcinoma in situ (2 cases)]. In controlled and extension clinical studies worldwide, malignancies occurred more frequently in cladribine-treated patients (10 events in 3,754 patient-years [0.27 events per 100 patient-years]), compared to patients on placebo (3 events in 2,275 patient-years [0.13 events per 100 patient-years]). For patients at sites in the United States who were treated with cladribine, malignancies occurred at a higher rate [2.21 events per 100 patient-years] than observed worldwide; however, the US findings are based on a limited amount of patient data. Following standard cancer screening guidelines in patients treated with cladribine will improve patient outcomes, but the risk of malignancy remains. • Cladribine causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% patients treated with cladribine experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2-3 months after the start of each treatment cycle and were lower with each additional treatment cycle. In patients treated with a cumulative dose of cladribine 3.5 mg per kg over 2 years as monotherapy, 26% and 1% had nadir absolute lymphocyte counts less than 500 and less than 200 cells per microliter, respectively. While complete blood count with differential including lymphocyte count will be obtained before and after cladribine treatment, risks from lymphopenia remain.	the treatment of relapsing forms of MS, its safety profile is adequate to support an approval action. Labeling for use in patients who had an inadequate response, or are unable to tolerate, an alternate drug indicated for the treatment of MS reflects the degree of concern that the risks associated with cladribine, particularly the risk of malignancy, will be long-lasting even with no additional exposure beyond two treatment courses. The risks of cladribine increase after the first two courses of treatment and have not been studied beyond four courses of treatment. Labeling will reflect this information and only recommend two courses of therapy. A Boxed Warning is needed to provide information about the serious risks of malignancy and fetal risk. In addition, because of these risks, treatment with cladribine should be generally reserved for patients who had an inadequate response to, or could not tolerate, an alternative MS therapy. Cladribine should not be used in patients with CIS. Post-marketing requirements are necessary to further characterize the risks of malignancy and fetal harm. Enhanced pharmacovigilance (e.g., expedited reporting, provision of specified summary

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Infections occurred in 49% of cladribine patients, compared to 44% of placebo patients in clinical studies. The most frequent serious infections in the cladribine group included pneumonia, herpes zoster, and pyelonephritis. Opportunistic infections reported with cladribine treatment included fungal infections and coccidiomycosis. Three of 1976 (0.2%) cladribine clinical study patients developed tuberculosis. Performing tuberculosis screening prior to initiation of cladribine treatment may help to reduce risks. One clinical study patient died from fulminant hepatitis B infection. Performing screening for hepatitis B and C prior to initiation of cladribine therapy may help to reduce risks. Serious herpes zoster infections occurred in 0.3% of cladribine patients. Vaccination of patients who are antibody-negative for varicella zoster virus prior to initiation of cladribine will help to reduce this risk. Administering anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter may also reduce this risk. Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with parenteral cladribine for oncologic indications. PML was not reported in clinical studies of cladribine for MS. Prescribers are advised to obtain a baseline magnetic resonance imaging (MRI) before initiating cladribine, and to withhold cladribine and perform an appropriate diagnostic evaluation at the first sign or symptom suggestive of PML. • Cladribine may cause fetal harm when administered to pregnant women. The risk of fetal harm can be reduced by excluding pregnancy before the initiation of cladribine therapy, and by using effective contraception during cladribine dosing and for at least 6 months after the last dose in each treatment year. However, pregnancies in which there is risk of fetal harm will likely occur. • Increased frequencies of hematologic toxicity and bone marrow suppression have been reported with cladribine in clinical studies. Low neutrophil counts occurred in 30% of cladribine patients, compared to	information in periodic reports) should be obtained for opportunistic infections, graft-versus-host disease with blood transfusion, liver injury, serious skin reactions, and acute cardiac failure.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	16% of placebo patients. Low hemoglobin levels occurred in 26% of cladribine patients, compared to 19% of placebo patients. Low platelet counts occurred in 11% of cladribine patients, compared to 4% of placebo patients. Serious cases of pancytopenia (some with documented bone marrow hypoplasia) requiring transfusion and granulocyte-colony stimulating factor treatment, thrombocytopenia, and neutropenia have been reported in cladribine clinical studies at dosages similar to or higher than the approved cladribine dosage. While prescribers are advised to obtain a complete blood count with differential before and after treatment, risks from hematological toxicity remain. • Cases of myelodysplastic syndrome have been reported with parenteral cladribine in multiple sclerosis and in other indications, as well as with other purine analogues. Measuring complete blood count annually and as clinically indicated after treatment with cladribine may help with detection of myelodysplastic syndrome. • In clinical studies, 0.3% of cladribine patients had liver injury (serious or causing treatment discontinuation), compared to 0 placebo patients. • In clinical studies, 11% of cladribine patients had hypersensitivity adverse events, compared to 7% of placebo patients. One patient had a serious skin reaction resembling erythema multiforme. • One patient experienced life-threatening acute cardiac failure with myocarditis after treatment with cladribine.	

2. Background

Product Information and Applicant's Proposals
Cladribine is a synthetic chlorinated purine analog of the naturally occurring nucleoside deoxyadenosine and differs in structure from the naturally occurring nucleoside deoxyadenosine only by the substitution of a chlorine for hydrogen in the 2-position of the purine ring. This chloride substitution renders cladribine resistant to deamination by adenosine deaminase. Cells with high levels of deoxycytidine kinase (DCK) and low levels of deoxynucleotidase (5'NTase) activity (*e.g.*, lymphocytes) phosphorylate cladribine to the monophosphate form (CdAMP). Subsequently, CdAMP is further phosphorylated to CdATP by other kinases. Accumulation of CdATP leads to numerous effects on the metabolism of susceptible cells. In dividing cells, CdATP causes depletion of the deoxynucleotide triphosphate pool, resulting in inhibition of DNA synthesis. In resting cells, CdATP causes defective repair of DNA strand breaks and activation of poly (ADP-ribose) polymerase, which along with depletion of nicotinamide adenine dinucleotide and adenosine triphosphate, ultimately leads to cell death. Cladribine causes a selective depletion of lymphocytes, but the effects of cladribine are not limited to lymphocytes.

The proposed indication for cladribine is the treatment of adult patients with relapsing forms of multiple sclerosis (MS). The proposed dose is 3.5 mg per kg body weight over two years, administered as one treatment course of 1.75 mg per kg per year. The applicant evaluated a 5.25 mg/kg dose but is not seeking an approval for this dose. Each treatment course consists of two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of four or five days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight.

Therapeutic Context
MS is the leading cause of acquired disability in the world. Patients with relapsing forms of MS experience paroxysms of worsening disability that improve over weeks. Over time, many patients with relapsing forms of MS accumulate disability that is permanent. In the United States, there are fourteen approved therapies for relapsing forms of MS. All currently approved therapies for relapsing forms of MS reduce the frequency of clinical relapses; many of the approved therapies for relapsing forms of MS reduce the likelihood of patients experiencing short-term disability worsening. Each approved therapy has unique benefits and risks. Given the safety and accumulated clinical experience with therapies such as the interferons, glatiramer acetate, and oral immunomodulator therapies, any newly approved therapy will likely be used after patients have had an inadequate treatment response to one or more of these therapies.

Regulatory Background and Marketing History
Intravenous cladribine (Leustatin) was approved for the treatment of hairy cell leukemia in February 1993. For this indication, intravenous cladribine is given as a single course by continuous infusion for seven consecutive days at a dose of 0.09 mg/kg/day.

The applicant originally submitted a New Drug Application (NDA) for cladribine as a treatment for multiple sclerosis (MS) to the Agency on May 28, 2010. The NDA contained efficacy and safety data from a single pivotal clinical trial (CLARITY). CLARITY was a 96-week randomized, double-blind, placebo-controlled trial that enrolled 1326 patients with relapsing-remitting MS to receive either a cumulative oral cladribine dose of 3.5 mg/kg, 5.25 mg/kg, or placebo in a 1:1:1 ratio. Treatments were administered in short courses as described above. Please refer to the reviews of the original application for a detailed discussion of the trial design. The Agency's review concluded that the submission provided substantial evidence of efficacy, but, despite the robust evidence that cladribine was effective, the Agency issued a Complete Response (CR) letter on February 27, 2011, citing concerns over a disproportionate number of malignancies in both the controlled and extension periods of the CLARITY trial. The Agency stated in the CR letter that the applicant's arguments to refute the potential association of cladribine with the malignancies were not persuasive, and that the applicant had not provided any strategy to mitigate the risk, or to prevent, malignancies in patients exposed to cladribine. The Agency concluded that "further clarification [of the malignancy risk] will be necessary before approval can be considered."

The detailed regulatory history of cladribine is summarized in the clinical review of the original submission authored by Dr. Jody Green dated December 13, 2010.

The applicant resubmitted the NDA to the Agency on May 31, 2018, responding to the Agency's CR letter with additional safety data from the CLARITY extension trial and other material to address the previous application's deficiencies cited in the CR letter. At the Agency's request, the applicant did not provide additional efficacy data for review, and therefore the clinical component of the submission was limited to safety findings.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team involved with the review of this resubmitted application. OPQ recommends approval of this resubmitted application. The original application review by OPQ had recommended acceptance with a dissent of one reviewer, Dr. Houda Mahayni, who had recommended against approval because of unacceptable dissolution specification. The OPQ review notes that the applicant included a full CMC update in the resubmission that includes a response to deficiencies noted in the previous reviews and CR letter issued by the Agency in 2011.

Drug Substance

OPQ states that cladribine is a well-characterized small molecule. The updated drug master file was deemed adequate. Other updated information was reviewed and found to be adequate. Structurally-related impurities are considered to pose no additional genotoxic risk, and non-related potential genotoxic impurities are not present at detectable levels in recently manufactured batches.

Drug Product
Mavenclad tablets contain 10 mg cladribine as a cladribine/ hydroxypropyl betadex complex (b) (4), sorbitol, and magnesium stearate. The applicant made a minor change to the manufacturing process since the initial submission. Review of the applicant's current control of process parameters and in-process controls find that the applicant's processes provide adequate mitigation of product quality risks, and that the applicant has validated the process at commercial scale. Additionally, per a request in the CR letter dated February 28, 2011, the review notes that the dissolution acceptance criterion was improved to the requested specifications based on additional manufacturing experience. The improvement of the dissolution specification satisfies the previous reviewer's concern that prompted a recommendation against approval.

OPQ concludes that based on the long-term and accelerated stability data provided in the resubmission, which includes 6 months of accelerated data and 36 months of long-term data from completed studies on the primary stability batches and 6 months of long-term and accelerated data three recent commercial scale batches, the requested 36-month expiration dating period for product stored under controlled room temperature conditions is granted. All facilities that will be involved in commercial manufacture and testing of cladribine and Mavenclad (cladribine) tablets are currently acceptable.

The OPQ review notes that the applicant submitted a claim for categorical exclusion under 21 CFR § 25.31(b). Approval of the application is expected to increase use of the active moiety; however, the expected environmental introduction concentration (EIC) is less than 1 part per trillion and there are no extraordinary circumstances. The claim is granted.

The OPQ review concludes that a formal risk assessment was not performed because of the limited changes in the resubmission, and the recommendation of approval for the initial application stands.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Melissa Banks-Muckenfuss, and Dr. Lois Freed was the team lead. Dr. Banks-Muckenfuss concludes that the application remains approvable from a pharmacology/toxicology standpoint. The nonclinical review notes that it is intended to act as a supplement to the nonclinical review authored by Dr. Melissa Banks dated February 18, 2011, which had recommended approval. The applicant submitted additional ADME studies and two combination toxicity studies to supplement the previous application. Dr. Banks-Muckenfuss's major conclusions are as follows:

- The ADME studies submitted provide additional information about the disposition of cladribine; however, the information pivotal for nonclinical assessment remains unchanged. It was determined during the first review cycle that no major human metabolites were identified *in vivo*. Please see the additional discussion of the metabolic profile of cladribine in Section 5 of this memorandum.

- In the submitted combination toxicity studies, the dose of cyclic oral cladribine administered alone (i.e., 30 mg/kg) resulted in increased mortality and adverse effects in kidney (i.e., cortical sclerosis, degenerating/regenerating tubules), testes (e.g., germinal epithelial degeneration and/or atrophy), and lymphoid tissues, as well as some evidence of alterations (pericarditis) in heart in males. In this 5-cycle study, 30 mg/kg of cladribine exceeded the maximum tolerate dose.

- The nonclinical information provided in the resubmission adds minor information to inform the overall safety profile for cladribine (supporting kidney, testes, and lymphoid tissues as target organs). The current submission does not change the previous nonclinical recommendation of approval.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Drs. Hristina Dimova (the primary reviewer), Kevin Krudys, and Angela Men (the clinical pharmacology team lead). This OCP review refers most of the key findings back to the completed OCP review dated November 24, 2010, of the NDA 22561 submission. In their original review, the OCP team had recommended approval. The current OCP review only evaluates issues the applicant addressed in this resubmitted application. The OCP team continues to recommend approval of this application.

Table 1 summarizes the conclusions of the OCP review with respect to the pharmacologic and clinical pharmacokinetic properties of cladribine.

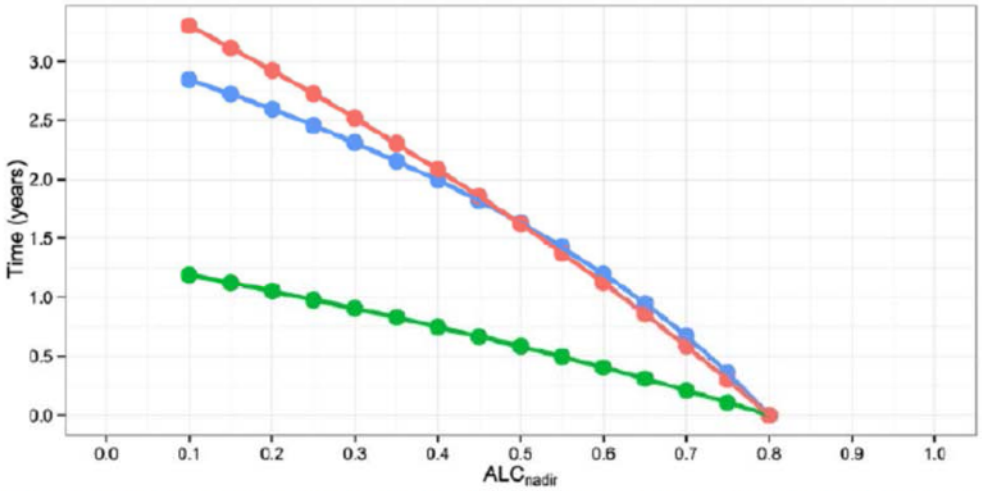
Table 1: Summary of OCP Review Findings

Pharmacology	
Mechanism of Action	The mechanism by which cladribine exerts its therapeutic effects in MS is not fully elucidated, but its predominant effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to MS.
General Information	
Bioanalysis	All PK information proposed in the label are obtained using acceptable analytical methods.
Healthy Volunteers vs. Patients	Because of the cytotoxicity of cladribine, all clinical studies were conducted in patients.
Absorption, Distribution, Metabolism, and Excretion	
Absorption	The bioavailability of cladribine is approximately 40%. Following fasted administration of cladribine, the median time to maximum concentration (Tmax) was 0.5 hours (range 0.5 to 1.5 hours). Following administration of cladribine with a high fat meal, the geometric mean Cmax decreased by 29% and AUC was unchanged. The Tmax was prolonged to 1.5 hours.
Distribution	The plasma protein binding of cladribine is 20% and is independent of plasma concentration, in vitro. Intracellular cladribine concentration in human lymphocytes was approximately 30 to 40 times extracellular, in vitro.
Metabolism	Cladribine is a prodrug that is phosphorylated to the active moiety cladribine monophosphate (Cd-AMP) by deoxycytidine kinase in lymphocytes. Cd-AMP is further phosphorylated to cladribine diphosphate (Cd-ADP) and cladribine triphosphate (Cd-ATP). The dephosphorylation and deactivation of Cd-AMP is catalyzed by cytoplasmic 5'-NTase. The metabolism of cladribine in blood has not been fully characterized. However, extensive whole blood and negligible hepatic enzyme
Elimination	Cladribine's estimated terminal half-life is approximately 24 hours. The intracellular half-lives of the cladribine phosphorylated metabolites Cd-AMP and Cd-ATP are 15 hours and 10 hours, respectively. Cladribine estimated median apparent renal clearance is 22.2 L/hr and non-renal clearance is 23.4 L/hr.

The OCP review notes that the resubmission includes a response to the specific concern of lymphopenia raised in the CR letter. In the CR letter, the Agency requested that the applicant "ascertain the time of resolution of lymphopenia in cladribine treated subjects... to provide appropriate guidance on the necessary duration of hematologic monitoring." Since the initial submission, subject exposure to cladribine and follow-up has significantly increased with the CLARITY extension study and the long-term follow-up registry for cladribine (PREMIERE). Furthermore, retreatment criteria based on lymphocyte count were studied in the oral cladribine in early MS (ORACLE MS) study. These clinical observations have been used to inform the applicant's response to the request in the CR letter. In addition, modeling and simulation was performed using data from the CLARITY, CLARITY extension, and ORACLE MS trials to support the clinical observations.

The following applicant figure, copied from the OCP review, demonstrates predicted time to Grade 1 lymphopenia from different values of nadir absolute lymphocyte counts in patients receiving cladribine.

Figure 1: Time to Return to Lymphopenia of Grade 1 from Different Absolute Lymphocyte Nadir Values



The figure shows the time to return to a lymphopenia of Grade 1 (ALC = $0.8*10^9$ cells/L) from different ALC. The solid lines show the typical subject (green), a subject with -2 SD ALC_0 (red) and a subject with +2 SD MRT (blue).
Abbreviations: ALC: absolute lymphocyte count; SD: standard deviation; MRT: mean residence time

The OCP review otherwise addressed issues raised by the applicant in this re-submission.

- In the OCP review of the initial submitted application dated November 24, 2010, there was concern for the possibility of cladribine forming complexes with other poorly soluble products *in vivo* because the cladribine tablet formulation contains hydroxypropyl betadex (b) (4). The applicant recommends separating any other oral products by three hours to prevent possible interactions with other poorly soluble products. After review of the justification for the three-hour separation, the OCP team concludes that the three-hour interval is acceptable and agrees with this separation period being stated on labeling.

- The OCP review of the initial submitted application noted that total cladribine clearance was dependent on creatinine clearance, but the applicant did not conduct studies in patients with renal impairment. In the resubmission, the applicant provides data from the CLARITY study of 173 patients with mild renal impairment and one patient with moderate renal impairment. The applicant estimates that mild renal impairment would increase cladribine exposure by 25%. Analysis of safety parameters in patients with mild renal impairment patient showed no clear association. The OCP review concludes that dose adjustment for patients with mild renal impairment (defined as creatinine clearance ≥ 60 mL/min) is not needed. Because of the limited data, the OCP review concludes that cladribine is not recommended in patients with moderate or severe renal impairment and agrees with applicant's proposed labeling language to that effect.
- The OCP review of the initial submitted application reviewed an *in vitro* study suggesting that the importance of hepatic CYP enzymes in elimination of cladribine was low but noted that because of the lack of a human mass balance study, there was insufficient understanding of the circulating drug-related material in human plasma or any major circulating metabolite. The OCP review notes that there is a more recent published *in vitro* metabolite profiling study of cladribine which showed extensive metabolism and a high percentage (>57%) of metabolites attributable to adenosine deaminase pathway processing. Therefore, the OCP review concludes that the applicant's proposed wording for elimination on labeling, which states that (b) (4) (b) (4) (b) (4) is not acceptable and proposes instead, "The metabolism of cladribine in whole blood has not been fully characterized. However, extensive whole blood and negligible hepatic enzyme metabolism was observed, *in vitro*."
- The previous submission had not adequately addressed whether cladribine could inhibit CYP3A4 and whether cladribine could induce cytochrome P450. The applicant submitted studies, deemed acceptable by the OCP review team, that demonstrated low risk of a clinically relevant inhibitory effect on CYP3A4/5 and low risk of clinically relevant induction of CYP450 1A2, 2B6, or 3A4 despite some inconsistent findings.
- The initial and resubmitted applications do not have any dedicated drug-drug interaction studies to evaluate the effect of cladribine on systemically acting hormonal contraceptives. Given the inconsistencies in the enzyme induction results, the OCP review suggests there is uncertainty whether hormonal contraceptives may have reduced effectiveness and agrees with language proposed by the applicant for a secondary barrier method of contraception during and at least six months after last dose of cladribine therapy.
- The resubmission includes supplemental studies of transporters. The new data suggested that cladribine is a weak inhibitor of BCRP and does not cause clinically significant inhibition of hOATP1B1, hOATP1B3, or hOCT1.
- The resubmission provides additional PK/PD analyses of the previously submitted clinical study with interferon beta-1a. The previous conclusion had been there was no significant PK impact of interferon beta-1a on cladribine. The safety data in the resubmission suggest a potential additive effect on lymphopenia. The OCP review agrees with the applicant's proposed language in labeling regarding a potential increased risk of lymphopenia with concomitant use of cladribine and interferon beta-1a.
- The applicant cites a case study publication demonstrating that concomitant treatment with lamivudine renders cladribine inactive by inhibition of its phosphorylation. The OCP

review agrees with proposed labeling language that recommends avoidance of concomitant use of cladribine with compounds that require intracellular phosphorylation such as lamivudine, zalcitabine, ribavirin, stavudine, or zidovudine.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The efficacy of cladribine was established based on the data provided in the original 2010 NDA.

The Cross-Discipline Team Leader Review, dated February 27, 2011, authored by Dr. Billy Dunn, citing the conclusions of the clinical review of Dr. Jody Green and the biometrics review of Dr. Sharon Yan, concluded there was sufficient evidence of efficacy in the CLARITY study analysis provided in the initial NDA submission. Dr. Russell Katz in the Agency's Action Memorandum for the initial submission dated February 27, 2011, states, "…the CLARITY study, by itself, establishes the effectiveness of cladribine in the treatment of patients with [relapsing forms of multiple sclerosis]."

8. Safety

Dr. Evelyn Mentari conducted the safety review of this resubmitted application. Dr. Sally Jo Yasuda, the safety team lead, provided a supervisory review. Drs. Mentari and Yasuda had provided a primary safety review and a supervisory review, respectively, of the initial submission of this NDA. The safety review team had recommended against approval in their reviews dated January 4, 2011. They recommend approval of this resubmission, provided that appropriate safety labeling, as summarized in their reviews, are agreed to by the applicant.

The following table, copied from Dr. Mentari's review and provided by the applicant, summarizes the extent of exposure to cladribine in the updated safety database:

Table 2: Duration of Exposure - Number of Subjects Exposed to Oral Cladribine, by Cladribine Dose and Number of Treatment Weeks (Cladribine Safety Database)

	Number of subjects exposed to cladribine										
		Number of treatment weeks [a]									
Dosage	≥ 1 dose	≥ 1	≥ 2	≥ 3	≥ 4	≥ 5	≥ 6	≥ 7	≥ 8	≥ 9	≥ 10
Any dose	1747	1746	1694	1527	1428	783	715	347	318	146	126
Cladribine monotherapy [b]											
3.5 mg/kg	728	727	685	570	522	0	0	0	0	0	0
5.25 mg/kg	437	437	437	437	418	343	302	0	0	0	0
7.0 mg/kg (3.5 mg/kg re-exposed)	195	195	195	195	195	195	184	150	139	0	0
8.75 mg/kg (5.25 mg/kg re-exposed)	195	195	195	195	195	195	193	193	176	146	126
Cladribine + IFN-β [c]											
3.5 mg/kg + IFN-β	130	130	120	70	38	0	0	0	0	0	0
5.25 mg/kg + IFN-β	11	11	11	9	9	2	0	0	0	0	0
7.0 mg/kg + IFN-β	51	51	51	51	51	48	36	4	3	0	0
8.75 mg/kg + IFN-β [d]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Source: Table FDA Q2.1.1.

IFN=interferon, NA=not applicable.

[a] A treatment week is considered complete when a subject received cladribine for ≥ 4 days per weekly administration.

[b] The summary of exposure to cladribine monotherapy includes data from the oral cladribine studies CLARITY, CLARITY EXT, and ORACLE MS.

[c] The summary of exposure to cladribine in combination with IFN-β includes data from the oral cladribine study ONWARD.

[d] As per the ONWARD study design, no subjects initially randomized to 5.25 mg/kg cladribine + IFN-β were re-exposed to cladribine in the open-label extension period.

In her safety review, Dr. Mentari states that there are 1747 patients who were exposed oral cladribine at or above 3.5 mg/kg. This figure includes 522 monotherapy patients exposed to the proposed marketing dose, that is, who had four treatment weeks at a total dose of 3.5 mg/kg given over two years (two treatment weeks separated by 1 month in the first year, and two treatment weeks in the second 48-week period). In the original submission, the median duration of follow-up was 1.8 years, leading to concerns regarding time course of resolution of lymphopenia and adequate characterization of long-term risks such as malignancies. Dr. Mentari notes in her review of the resubmission that the mean duration of observation in patients treated with cladribine 3.5 mg/kg in the monotherapy oral cohort was now 4 years.

The applicant provided updated safety pools and analyses derived from the following trials:

Table 3: Cladribine Studies and Analysis Cohorts in the Pooled Safety Dataset

Study	Indication	Type of control/ blinding/ design	All exposed	Placebo-controlled double-blind	Oral placebo-controlled double-blind	Monotherapy oral
CLARITY	RRMS	Randomized, double-blind, placebo-controlled, oral cladribine; DMD allowed as rescue medication	✓	✓	✓	✓
CLARITY EXT	RRMS	Randomized, double-blind, placebo-controlled, oral cladribine; DMD allowed as rescue medication, extension study of CLARITY	✓			✓
ONWARD	RRMS/ SPMS with active disease	Randomized, double-blind, placebo-controlled, oral cladribine; INF-β as active background therapy for all subjects	✓			
ORACLE MS	Early MS	Randomized, double-blind, placebo-controlled, oral cladribine; DMD allowed as rescue medication	✓	✓ Only double-blind (ITP) phase	✓ Only double-blind (ITP) phase	✓
PREMIERE	RRMS/ SPMS with active disease/ early MS	Prospective, observational, ongoing, long-term safety registry of subjects who participated in 1 of the 4 oral cladribine studies (CLARITY, CLARITY EXT, ONWARD, or ORACLE MS) or the Phase I pantoprazole DDI study	✓ Without subjects from Phase I study			✓ Without subjects from ONWARD and Phase I study
Scripps-A	CPMS	Phase II, open-label, proof-of-concept, iv cladribine	✓			
Scripps-B	CPMS	Phase II, randomized, double-blind, placebo-controlled, sc cladribine; cross-over retreatment phase	✓	✓ Only first sequence		
Scripps-C	RRMS	Phase II, 1.5-year, randomized, placebo-controlled, double-blind, parallel group, sc cladribine; open-label retreatment long-term follow-up phase	✓	✓ Only first sequence		
MS-Scripps	CPMS	Phase II, 2-year, double-blind, placebo-controlled, randomized, cross-over, single-center, iv cladribine; open-label retreatment long-term follow-up	✓	✓ Only first sequence		
MS-001	CPMS	Phase III, randomized, double-blind, placebo-controlled, parallel-group, sc cladribine, long-term follow-up	✓	✓ Only double-blind phase		

Source: ISS SAP, Table 2.

CPMS=chronic progressive multiple sclerosis, DDI=drug-drug interaction, DMD=disease-modifying drug, ITP=initial treatment period, INF-β=interferon beta, iv=intravenous, MS=multiple sclerosis, RRMS=relapsing-remitting multiple sclerosis, sc=subcutaneous, SPMS=secondary progressive multiple sclerosis.

a Two additional cohorts were used for specific analyses presented in this Summary of Clinical Safety (see text above the table): the CLARITY cohort (including

The safety reviewers rationalize the exclusion of a small post-authorization RECORD MS safety trial from this pool because this trial's few safety findings would not alter their conclusions. Their reviews note that the ORACLE MS, CLARITY, and CLARITY EXT trials are discussed most extensively because of their large sizes and because of their use of the proposed marketed dose of cladribine.

Regarding the resubmission's data quality, Dr. Mentari finds that there are some missing details associated with adverse events and that there are adverse events and patient discontinuations of therapy she believes are miscategorized.

The following are important safety findings that were identified by Drs. Mentari and Yasuda.

Deaths and Discontinuations

The safety reviews note four deaths in the CLARITY trial for patients on the 3.5 mg/kg dose of cladribine (0.52/100 patient-years) vs. two deaths in patients on placebo (0.27/100 patient-years). In the CLARITY trial, there were more frequent serious adverse events (SAEs) and discontinuations due to adverse events (AEs) as well as treatment emergent adverse events (TEAEs) in patients receiving cladribine compared to placebo. Dr. Yasuda indicates deaths of concern in the original review included deaths due to metastatic pancreatic carcinoma, tuberculosis, and fulminant hepatitis B, and those remain of concern in the present review as well. The clinical reviews note one additional death (ovarian cancer) in the CLARITY study that was reported in the resubmission and was apparently not known at the time of the original submission.

The following table, reproduced from Dr. Yasuda's review, summarizes deaths, discontinuations, and serious adverse event frequencies in the CLARITY trial and the exposed cohort of all patients in controlled trials with cladribine:

Table 4: Deaths, Serious Adverse Events, and Discontinuations in Cladribine Trials

CLARITY		**Placebo**	**Cladribine 3.5 mg/kg**	**Cladribine 5.25 mg/kg**
		n=433 731.7 PY	n=44 774.1 PY	n=444 783.1 PY
	Deaths	0.5% (n=2) 0.27 per 100 PY	0.9% (n=4) 0.52 per 100 PY	0.2% (n=1) 0.13 per 100 PY
	SAEs	7.4% 4.49 per 100 PY	10.0% 6.01 per 100 PY	9.5% 5.64 per 100 PY
	Discontinuations due to TEAEs	2.1% 1.23 per 100 PY	4.5% 2.65 per 100 PY	7.0% 4.13 per 100 PY
All Exposed Cohort		**Placebo**	**Cladribine**	
		n=802 2631.5 PY	n=1976 9508.9 PY	
	Deaths	0.6% 0.19 per 100 PY	1.1% 0.22 per 100 PY	
	SAEs	11.8% 3.93 per 100 PY	16.8% 3.92 per 100 PY	
	Discontinuations due to TEAEs	3.3% 1.05 per 100 PY	13.0% 2.98 per 100 PY	

Treatment-Emergent Adverse Events

The table below, reproduced from Dr. Mentari's safety review, summarizes the most common treatment-emergent adverse events that occurred in the CLARITY study:

Table 5: CLARITY Study. Treatment-Emergent Adverse Events that Occurred in at Least 5% of Cladribine 3.5 mg/kg Subjects and More Frequently Than in Placebo Subjects

	MAVENCLAD (N=440) %	Placebo (N=435) %
Upper respiratory infection	38	32
Headache	25	19
Lymphopenia	24	2
Nausea	10	9
Back pain	8	6
Arthralgia and arthritis	7	5
Insomnia	6	4
Bronchitis	5	3
Hypertension	5	3
Fever	5	3
Depression	5	3

For adverse event rows defined by more than one MedDRA Preferred Term, Preferred Terms are listed below:

- Upper respiratory infection includes Preferred Terms: ACUTE SINUSITIS, CHRONIC SINUSITIS, INFLUENZA LIKE ILLNESS, LARYNGITIS, LARYNGITIS VIRAL, NASOPHARYNGITIS, PHARYNGITIS, PHARYNGITIS BACTERIAL, PHARYNGITIS STREPTOCOCCAL, RESPIRATORY TRACT INFECTION, RESPIRATORY TRACT INFECTION VIRAL, RHINITIS, SINUSITIS, TONSILLITIS, UPPER RESPIRATORY TRACT INFECTION, UPPER RESPIRATORY TRACT INFECTION BACTERIAL, VIRAL PHARYNGITIS, VIRAL RHINITIS, VIRAL UPPER RESPIRATORY TRACT INFECTION.
- Headache includes Preferred Terms: HEADACHE, MIGRAINE, TENSION HEADACHE
- Lymphopenia includes Preferred Terms: LYMPHOPENIA, LYMPHOCYTE COUNT DECREASED
- Arthralgia and arthritis include Preferred terms: ARTHRALGIA, ARTHRITIS, OSTEOARTHRITIS, SPINAL OSTEOARTHRITIS. Most events were arthralgia.
- Bronchitis includes Preferred terms: BRONCHITIS, BRONCHITIS CHRONIC, BRONCHITIS VIRAL.
- Hypertension includes PTs: BLOOD PRESSURE INCREASED, HYPERTENSION, HYPERTENSIVE CRISIS, HYPERTENSIVE EMERGENCY, LABILE HYPERTENSION.
- Fever includes PTs: PYREXIA, HYPERTHERMIA, BODY TEMPERATURE INCREASED, HYPERPYREXIA.
- Depression includes PTs: DEPRESSION, DEPRESSED MOOD, DYSTHYMIC DISORDER.

Submission Specific Safety Issues

The following safety issues, identified during the development program, will be discussed below:

- Malignancies
- Lymphopenia
- Fetal Risk
- Infections
- Hematologic Toxicity and Bone Marrow Suppression
- Graft-versus-Host Disease with Blood Transfusions
- Hepatic Disorders
- Hypersensitivity
- Cardiac Failure
- QT Prolongation

Malignancies

Cladribine interferes with DNA synthesis and repair through incorporation into DNA and through inhibition of enzymes involved in DNA metabolism. Data from the 2010 NDA submission indicated an increased risk of malignancy associated with cladribine treatment. In the CR letter, the Agency requested data to support an improved understanding of the malignancy risk. In this resubmission, the increased risk of malignancy with cladribine treatment compared to placebo remains. However, additional data provided in this submission allows for an improved understanding of the risk.

The table below, reproduced from Dr. Yasuda's review, shows the incidence of malignancies in the placebo-controlled CLARITY study in MS, and in the monotherapy oral cohort that included controlled and uncontrolled data (CLARITY, ORACLE MS, CLARITY EXT and PREMIERE registry). In both cohorts, the risk of malignancies was greater in the 3.5 mg/kg and 5.25 mg/kg groups vs. placebo, but with no dose response. The clinical reviews further reveal that subjects who received additional treatment cycles of 3.5 mg/kg after the first 2 years had a higher incidence of malignancy AEs of 0.91 events per 100 person-years

(calculated from the start of the first dose in Year 3, 95% CI 0.43, 1.90), with a risk ratio of approximately 7 compared to placebo.

Table 6: Malignancy Risk in CLARITY and Other Cladribine-Exposed Cohorts

Study	Placebo	Cladribine dose 3.5 mg/kg	5.25 mg/kg
CLARITY	N=433 737.1 PY	N=442 774.1 PY	N=444 783.1 PY
number of subjects with malignancies	0	3	2
incidence per 100 person years (95% CI)	0 (0, 0.5)	0.39 (0.13, 1.2)	0.26 (0.06, 1.02)
Monotherapy Oral Cohort	N=641 2275.3 PY	N=923 3754.0 PY	N=632 2610.4 PY
number of subjects with malignancies	3	10	6
incidence per 100 person years (95% CI)	0.13 (0.043, 0.41)	0.27 (0.14, 0.50)	0.23 (0.10, 0.52)

In her review, Dr. Mentari notes that data provided in the resubmission, in response to a concern in the CR letter about the potential for higher malignancy rates with longer durations of patient follow-up, did not show increased rates with 4 years of observation compared to the median time on study of 1.8 years in the original submission. This lack of an increase obviates the concerns raised in the original submission's safety reviews of a potential for higher observed risk with longer follow-up.

Dr. Mentari provides several observations regarding the persistent malignancy risk.

United States versus Other Countries' Population Risks
Dr. Mentari shows that the incidence rate for malignancies for cladribine 3.5 mg/kg was higher in patients from the United States [2.21 per 100 person-years (95% CI 0.83, 5.88)] than the rate of 0.17 person-years (0.08, 0.38) in the non-United States patients, although she notes that the duration of observation in the US subjects was small (188.5 person-years), and the point estimate is unstable.

Demographic Variables
Dr. Mentari states that at baseline there were no notable imbalances in demographic characteristics between treatment groups that might provide an explanation for imbalanced risk of malignancy. The CR letter requested an analysis of malignancy risk stratified by age because most cases of malignancy in cladribine-treated subjects occurred in subjects over age 40. Dr. Mentari notes that age was identified as a risk factor for development of malignancies in the applicant's analysis, a finding that is consistent with malignancy risk in the general population. The applicant notes baseline differences in use of contraceptives and hormone replacement therapy and sex as being potentially relevant.

The applicant provided information on methods used to calculate the standardized incidence ratios, as requested in the CR letter, and has compared the rate of malignancy in the cladribine database to an expected general population using the GLOBOCAN database for comparison of the overall study population and the Surveillance, Epidemiology, and End Results (SEER) database. The applicant states that there appears to be no increased incidence relative to the

epidemiological databases and suggests that the numeric imbalance for cladribine vs placebo is due to a lower than expected placebo rate. As had been noted in the CR letter, the safety reviewers raise the concern that comparisons to epidemiologic data are problematic.

Prior MS Therapy
The CR letter requested an analysis of malignancy risk for the subgroup of patients taking MS therapies because they may have longer durations of immunosuppression than the general population. There was a slight increase in malignancy associated with prior MS therapies for both the placebo and cladribine groups.

Malignancy Summary
The Agency disagrees with the applicant's assertion in the resubmitted application that there is insufficient evidence to support a claim that cladribine causes malignancies. Dr. Yasuda provides the following rebuttals that form the basis of the Agency's conclusion that cladribine causes an increased risk of malignancies:

- The additional data provided with the application confirm the presence of an increased, but longitudinally, stable risk of malignancy.

- The interpretability of the comparison of malignancy incidence rates from the cladribine development program to external sources are limited for a number of reasons discussed in detail in Dr. Mentari's and Dr. Yasuda's safety reviews. Therefore, the comparison to a contemporaneous placebo treatment group continues to provide the most reliable risk estimate of the risk, and this comparison provides strong evidence of an increased risk.

- Impaired DNA repair, a known mechanism of cladribine, may be associated with a variety of cancers including breast, colorectal, gastric, endometrial, and ovarian cancers. Therefore, the lack of clustering of a specific malignancy type is not reassuring because a nonspecific effect on DNA repair would yield a risk of many different types of cancer consistent with what is what is seen in the cladribine safety findings.

- The lack of any observed lymphoid-malignancies is not reassuring because cladribine can also cause malignancies by mechanisms other than lymphopenia (i.e., DNA strand-breaks in the inhibition of DNA repair).

- Although many of the observed malignancies had a latency period from the initiation of treatment of less than four years, whereas the malignancies in question can have a latency of decades, this finding does not exclude the potential that cladribine could accelerate an underlying established malignant process by interfering with DNA repair.

Lymphopenia

Cladribine causes a dose-dependent decrease in lymphocyte count, as noted in the review of the initial application. The CR letter stated that the applicant must ascertain the time to resolution of lymphopenia in cladribine-treated subjects in part to provide appropriate guidance on the necessary duration of hematologic monitoring. The present submission further characterizes time to resolution and allows for recommendations for monitoring. The CR letter requested information on analysis of hematologic measurements in patients taking alternative MS therapies and this concern regarding lymphopenia is addressed in the present submission. The CR letter requested additional information on medications that may lead to additive effects on lymphocytes. The clinical reviewers state that the information included in the present submission allows for adequate discussion and recommendations in labeling.

In her review, Dr. Mentari notes that in clinical trials, 87% of patients treated with cladribine 3.5 mg/kg experienced lymphopenia, 26% had nadir lymphocyte counts less than 500 cells per microliter and 1% had nadir counts less than 200 cells per microliter. Dr. Mentari noted in her previous review that in the CLARITY trial, cladribine treated subjects had a higher incidence of abnormal CD4 lymphocyte counts (80.8%) vs placebo treated subjects (13.9%) and a larger percentage of cladribine-treated subjects (43.4%) had CD4 lymphocyte counts qualifying as Grade 3 (< 500-200 cells/mm^3) or 4 Toxicity (< 200 cells/mm^3) compared to placebo-treated subjects (1.3%).

Dr. Mentari shows that the median lymphocyte count begins decreasing by Week 2 (median 1.26 cells per microliter for cladribine 3.5 mg/kg vs 1.94 cells per microliter for placebo), with some patients having Grade 3 lymphopenia even at that time. She shows that the lowest median occurred approximately 7-9 weeks after the start of each treatment cycle and that they were lower with each treatment cycle. She notes that at the end of Year 2 in the Monotherapy Oral Cohort, 2% of patients had absolute lymphocyte counts of less than 500 cells per microliter, and that the median time to recover from Grade 3 lymphopenia to Grade 1 was 28.1 weeks.

Dr. Mentari notes that in the 3.5 mg/kg cladribine group the incidence of lymphopenia less than 500 cells per microliter was higher in subjects with use of disease modifying drugs prior to study entry compared to those with no prior use (32.1% vs 23.8%).

The CR letter requested additional information, including which specific medications may lead to these additive effects on lymphocytes, to provide guidance on cladribine's use. In the ONWARD study in which oral cladribine was administered with interferon-beta. The applicant shows on p. 43 of a document entitled "Response CRL - Clinical" in module 1 that the incidence of severe (Grade ≥ 3) lymphopenia was higher in ONWARD compared with the CLARITY study where cladribine was administered as monotherapy, as shown in the table below from the applicant's document. The applicant has included language in the prescribing information regarding an increased risk of lymphopenia with concomitant use of cladribine with interferon-beta. The findings are summarized in the following table provided by the applicant:

Table 7: Number (%) of Subjects with Severe (Grade ≥3) Lymphopenia in the ONWARD and CLARITY studies

	ONWARD Original Protocol		ONWARD Amendment 1 and 2	CLARITY	
	Clad 3.5 mg/kg + IFN-β	Clad 5.25 mg/kg + IFN-β	Clad 3.5 mg/kg + IFN-β	Clad 3.5 mg/kg	Clad 5.25 mg/kg
	N=16	N=17	N=124	N=430	N=454
Grade ≥ 3	12 (75.0)	15 (88.3)	79 (63.7)	110 (25.6)	204 (44.9)

Source: ONWARD CSR, Sections 12.1.3.3.3 and 12.2.3.3.5; CLARITY CSR, Tables 25643-209.
Clad=cladribine; IFN-β=interferon-beta.

Fetal Risk

Cladribine inhibits DNA synthesis. Cladribine is embryolethal in pregnant mice, and teratogenic in mice and rabbits. Dr. Mentari notes that there were 18 pregnancies treated with cladribine that resulted in live births. The reported birth defects occurred in a set of twins, one with omphalocele and one with patent foramen ovale, in a pregnancy that occurred approximately 2 years and 3 months after the last cladribine administration. It is not possible to determine the role of cladribine in this outcome. The safety reviewers conclude that the mechanism of action is strongly suggestive of a risk to the fetus and that cladribine should be contraindicated in pregnant women and in women of reproductive potential not using effective contraception. A boxed warning for teratogenicity is also recommended. The review recommends a pregnancy registry study as a postmarketing requirement.

Infections

In her review, Dr. Mentari notes that in the Oral Placebo-Controlled Double-Blind Cohort, TEAEs in the Infections and Infestations SOC occurred in 44% for placebo-treated patients vs 49% for cladribine-treated patients. She shows that the most frequent severe infections in cladribine-treated patients included herpes zoster and pyelonephritis, at rates of approximately 0.2 to 0.3 per 100 PY for either dose of cladribine.

Dr. Mentari notes four deaths related to infections in the All Exposed Cohort including a case of tuberculosis, fulminant hepatitis B, herpetic meningoencephalitis, and pneumonia with brain edema and herniation. Dr. Mentari also notes two additional cases of tuberculosis with successful treatment. Based on these observed infections, the safety reviewers recommend as follows:

- A Warning of tuberculosis risk of reactivation and tuberculosis screening prior to administration of cladribine
- A Warning regarding hepatitis infection risk and hepaitis screening prior to administration of cladribine
- A Warning regarding herpetic infections and anti-herpes prophylaxis

Cases of progressive multifocal leukoencephalopathy (PML) were not identified in the MS development program, but cases of PML have been noted in patients treated with parenteral

cladribine. The safety review team recommends a Warning for PML risk and baseline magnetic resonance imaging of the brain prior to treatment initiation.

Hepatic Disorders

The clinical safety review reports that the frequencies of liver laboratory parameter abnormalities, stratified by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) were similar in placebo and cladribine 3.5 mg/kg subjects in the Monotherapy Oral Cohort. Dr. Mentari notes that 5 of 1555 (0.3% cladribine subjects) in that cohort had Hepatic disorder SOC adverse events that were serious or caused treatment discontinuation consistent with drug-induced liver injury, and that were not confounded, versus 0 of 641 placebo subjects. Onset ranged from a few weeks to several months after initiation of treatment, and abnormalities resolved on treatment discontinuation. In one case the ALT was 21x upper limit of normal. There were no observed cases that fulfilled Hy's law criteria. The review team recommends labeling language to provide adequate notice of this risk.

Cardiac Failure

The clinical safety review identified 1 of 1976 (0.1%) cladribine subjects in the All Exposed Cohort who developed myocarditis and acute cardiac failure. This case was of a 20-year-old male with normal baseline cardiac function, and no reported symptoms of viral illness before this acute illness, who experienced life-threatening acute cardiac failure, pulmonary edema, and atrial fibrillation 11 days after his first dose of cladribine in ORACLE-MS, with magnetic resonance imaging findings supporting a diagnosis of myocarditis. Dr. Mentari reasonably suggests that possible mechanisms of myocarditis related to cladribine include infection or drug toxicity, and she proposes that because the structure of cladribine is closely related to adenosine, drug toxicity may occur via disruption of the cardiac adenylate cyclase pathway. Dr. Mentari also notes three published cases of acute cardiac failure have been reported with cladribine for other treatment indications for which a role for cladribine cannot be ruled out, although two were confounded and lacking detail. The safety review recommends labeling language to describe risk of acute cardiac failure in the cladribine prescribing information.

Thorough QT Study

The review of the initial cladribine submission had suggested potential need for a thorough QT study to exclude small effects, but the toxicity of cladribine limits the possibility of enrolling a thorough QT study. Dr. Melissa Banks-Muckenfuss, in her nonclinical review dated February 11, 2018, noted no statistically effects of cladribine on cardiac action potential in isolated canine Purkinje fibers. She states that in stably transfected HEK-293 cells, cladribine produced only a 13% inhibition of the hERG tail current and that an IC50 value could not be determined. In the original review by the Interdisciplinary Review Team (IRT) for QT studies dated September 26, 2010, large effects on the QTc interval at Tmax were not observed in the cardiac safety report from CLARITY. The IRT noted no cardiac AEs of concern in the clinical program. Further evaluation of the effect of cladribine will not be pursued at this time.

Safety Conclusions

Cladribine causes serious and potentially fatal adverse events. Many of the adverse events, lymphopenia, infections, hepatic injury, and cardiac failure are amenable to labeling warnings,

including placement in the Warnings and Precautions section of labeling. However, it is critical that every effort be made to ensure that patients and prescribers are well informed about the risks of treatment, that appropriate clinical and laboratory monitoring is reliably performed, and that additional information regarding the known serious risks of treatment is accrued in the postmarketing setting.

Cladribine interferes with DNA replication and repair processes, and there is a credible scientific rationale for cladribine being a teratogen. Cladribine is embryolethal in mice and teratogenic in mice and rabbits. Based on cladribine's mechanism of action and animal findings, the review team concludes that a Boxed Warning for teratogenicity is necessary for cladribine to provide adequate warning of the serious risk to the fetus. Further, the review team recommends a contraindication in pregnancy because of the observed effects of cladribine. The reviewers advise that females of reproductive potential should prevent pregnancy by use of effective contraception during cladribine dosing and for at least 6 months after the last dose in each treatment course. MS is a disease that preferentially affects women with reproductive potential. It is critical to convey to these patients and prescribers the magnitude of potential risk of harm were a pregnancy to occur.

The most prominent risk identified in the cladribine safety database, during the initial and present reviews, was of an increased risk of several different types of malignancies. The presence of a malignancy signal with cladribine is likely intrinsic to its interference in DNA synthesis and repair and is potentially enhanced further by the persistent depletion of lymphocytes that would reduce immune surveillance for malignancies.

Given the safety review team's current recommendation of approval, it is reasonable to revisit the rationale for the previously issued CR letter and recognize the progression from that decision to the present. The crux of the CR letter's basis was that there was evidence that cladribine caused multiple different types of malignancies, and that despite robust evidence of efficacy, cladribine's potential for causing cancer precluded approval.

Based on the short duration of follow-up data available for review at the time of the 2011 CR letter, there was concern that the apparent malignancy risk was potentially underestimated and would increase with longer observation time. However, with the addition of the data provided in this resubmission, it appears that the malignancy risk is stable, but not reduced, over time. This observation obviates a significant concern raised in the initial reviews of the original submission.

Dr. Yasuda in her review provides an additional important contextual assessment of the current approval with the recognition that, in the interval since cladribine's initial application, the Agency has approved several therapies for MS which confer an increased risk of malignancy compared to placebo, e.g., alemtuzumab, ocrelizumab, and fingolimod (which was approved prior to cladribine's initial review but its malignancy risk had yet to be elucidated). As discussed, the malignancy risk associated with cladribine exposure has now been more accurately characterized based on the additional data provided with the current application relative to the uncertainty that existed during the review of the original application. Although

each of these drugs has their own unique risk-benefit considerations, the malignancy risk associated with cladribine is generally within the relative risk of these approved therapies.

The review team suggests a boxed warning for malignancies is necessary to provide the appropriate awareness of this risk to patients with MS, a patient population that will be young (in their third/fourth decades of life) and who, with knowledge of this risk, could benefit from lifestyle modifications and screening to mitigate their personal cancer risks. At minimum, a boxed warning is appropriate because of the protean nature of the malignancy risk.

The malignancy risk and longevity of the treatment effect on lymphocytes dictates a different approach to the indicated population. Evidence in the resubmission suggests a synergistic effect on lymphopenia with interferon therapy. It is therefore a concern that cladribine may not be safely combined with other immune modulating therapies during its expected duration of effect. The temporary prohibition of therapies that cause lymphocyte reduction, which encompasses nearly all the approved therapy options for MS, severely constrains therapeutic options for patients in the two-year window of cladribine therapy. Therefore, cognizant of the presence of the boxed warnings for malignancy and teratogenicity, and other serious adverse events, cladribine is not a therapy that should be administered as first-line therapy to most patients with relapsing forms of MS without careful consideration of the risks and short-term limitations in treatment. There are other therapies with efficacy in relapsing forms of multiple sclerosis with apparently equivalent effects on relapse reduction but a more favorable safety profile and shorter durations of effect. Cladribine has robust effectiveness offset by significant risk. Other therapies with significant risk considerations in MS are indicated for patients who have had treatment failure to one or more therapies. For these reasons, the indications and use statement will indicate cladribine for patients who have generally failed to achieve adequate response to a prior MS therapy.

9. Advisory Committee Meeting

This application was not referred to an Advisory Committee for review because the clinical trial design was acceptable, the efficacy findings were clear, and the safety profile, despite the malignancy risk, was acceptable for the serious disease being treated. Labeling will make prescribers fully aware of the risks, allowing them to inform patients and decide whether to use the drug.

10. Pediatrics

In the original application, the applicant had requested a full waiver of pediatric studies, justifying the request based on cladribine's immunosuppressive, hematopoietic, and genotoxic effects. After internal discussion, in 2010, the Agency changed the full waiver request to a partial waiver in patients <10 years old with the studies in patients aged 10-17 years old deferred to allow time for collection and review of additional safety data in adults.

A safety review of the data in resubmitted application confirmed a presumed lifelong increased risk of malignancy. The resubmission also identified a myelodysplastic syndrome signal in adults that had been cited as a potential concern by the applicant as justification for their initial request for a full waiver of pediatric studies. With confirmation of a longitudinal risk of malignancy in adult patients, as well as new evidence of myelodysplasia risk, the Agency concludes that exposure to cladribine represents an unacceptable risk in pediatric patients. The Agency also notes that the previous partial waiver came at a time when there were no approved therapies for patients < 18 years old with MS. As such, the unmet medical need that existed then is not present now because there is an approved, effective therapy for pediatric patients with MS. The agreed labeling for cladribine will warn against pediatric use as follows:

"Safety and effectiveness in pediatric patients (b) (4) have not been established. Use of MAVENCLAD is not recommended in pediatric patients due to the risk of malignancies. [see Warnings and Precautions (5.1)]"

11. Other Relevant Regulatory Issues

Controlled Substance Staff review

Dr. Jovita Randall-Thompson provided a Controlled Substances Staff review of cladribine. Dr. Randall-Thompson concludes that there was no abuse signal found with cladribine, and that, like the intravenous form of cladribine, labeling for cladribine should not include a Section 9, Drug Abuse and Dependence.

12. Labeling

See the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

Dr. Charlotte Jones from the Division of Risk Management (DRISK) provided a review; Dr. Donella Fitzgerald was the Team Lead. The DRISK review states that the safety concerns with cladribine are documented adequately in labeling and that a REMS is not necessary to ensure safe use.

The following will be postmarketing requirements:

- Establish a worldwide Pregnancy Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to Mavenclad (cladribine) during pregnancy. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring and plans for comprehensive data analysis and yearly reporting.

Draft Protocol Submission:	08/19
Final Protocol Submission:	09/20
Annual Interim Report:	09/21
	09/22
	09/23
	09/24
	09/25
	09/26
	09/27
	09/28
	09/29
	09/30
Study Completion:	02/31
Final Report Submission:	02/32

- Conduct an observational study to assess the long-term risk of malignancy for Mavenclad (cladribine) compared to other therapies used in the treatment of adults with relapsing forms of multiple sclerosis. Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to cladribine-exposed patients; clearly define the primary comparator population. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms. For the Mavenclad-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial four-year period and follow for a minimum of 8 years from the time of enrollment.

Draft Protocol Submission:	08/19
Final Protocol Submission:	09/20
Study Completion:	02/33
Final Report Submission:	02/34

- Conduct a clinical drug-drug interaction study to evaluate the effect of cladribine on the pharmacokinetics (PK) of oral contraceptives. Include an evaluation of the effect on the components ethinyl estradiol (EE) and norelgestromin (NGMN).

  Draft Protocol Submission: 06/19
  Final Protocol Submission: 06/20
  Study Completion: 08/23
  Final Report Submission: 08/24

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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