CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022561Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022561

COMPLETE RESPONSE

EMD Serono, Inc.
Attention: Dr. DiRoma
Vice President
One Technology Place
Rockland, MA 02370

Dear Dr. DiRoma:

Please refer to your New Drug Application (NDA) dated May 27, 2010, received May 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (cladribine) Tablets.

We acknowledge receipt of your amendment(s) dated May 28, 2010, June 24, 2010, June 28, 2010, July 2, 2010, July 20, 2010, July 21, 2010 (2), July 30, 2010, August 16, 2010, August 18, 2010, September 1, 2010, September 2, 2010, September 8, 2010 (2), September 10, 2010, September 13, 2010, September 15, 2010 (2), September 17, 20101 (2), September 22, 2010, September 23, 2010, September 29, 2010, September 30, 2010 (2), October 1, 2010, October 4, 2010, October 12, 2010, October 13, 2010 (3), October 18, 2010, October 28, 2010, November 1, 2010, November 5, 2010, November 9, 2010, November 10, 2010, and December 1, 2010.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

Although we have concluded that cladribine is effective as a treatment for patients with relapsing remitting multiple sclerosis (RRMS), safety concerns associated with its use preclude its approval at this time.

Substantial evidence of cladribine's effectiveness was provided by the CLARITY study. This study was an adequate and well-controlled clinical study of oral cladribine in patients with RRMS that was rigorously designed and executed. 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. We believe that the data, taken as a whole, meet the standard for substantial evidence of effectiveness, as provided by one adequate and well controlled clinical trial and confirmatory evidence.

Reference ID: 4413345

These benefits of cladribine, however, are outweighed by its risks. The presence of a disproportionate number of malignancies in cladribine-treated subjects represents an unacceptable risk.

Cladribine clearly appears to be associated with an increased risk of malignancy. In the CLARITY trial, there were four cases of malignancy in cladribine-treated subjects and none in placebo-treated subjects. When considering the entire safety database, in completed studies of cladribine and ongoing controlled studies of cladribine, there were 33 cases of malignancy in cladribine-treated subjects and two in placebo-treated subjects. These malignancies are found in a wide variety of anatomic sites. Analysis of a subset of these patients revealed 8.2 cases of malignancy per 1000 cladribine-treated subjects (13 cases in 1579 subjects) in all oral cladribine trials worldwide and no cases in placebo. In trials of oral cladribine in the U.S. the incidence was even higher with 18.3 cases of malignancy per 1000 subjects in cladribine treated subjects (3 cases in 164 subjects) and no cases in placebo. Ongoing reporting of malignancy cases submitted throughout the review period appears to be consistent with these rates. We analyzed whether increasing cumulative cladribine dose or increasing duration of clinical monitoring played a role in the development of malignancy but found no evidence of such relationship. We also investigated the latency from time of first cladribine dose to time of malignancy diagnosis and found no evidence that any cases occurred an implausibly short time following exposure to cladribine.

This increased risk of malignancy seen in cladribine-treated subjects as compared to placebo-treated subjects is unacceptable. You must provide an improved understanding of this risk, either through additional analyses or by conducting additional studies, before we could consider approving this application.

We note that while you have agreed that the association between malignancies and cladribine represents a potential significant safety concern, you have provided several arguments that seek to address this concern. We have reviewed your arguments and do not agree with your conclusions.

You have compared the rate of malignancy in cladribine-treated subjects to an expected general population rate, calculated using epidemiologic data. Comparisons to epidemiologic data are problematic, because rates of malignancy based on epidemiologic data vary greatly according to many factors, including location, age, and gender. We are concerned that comparing malignancy rates in cladribine-treated subjects to rates based on epidemiologic data, as opposed to randomized controls, may not adequately account for important differences between groups. We request additional information on the methods used in calculating the standardized incidence ratios (SIRs) described on pages 289-290 of the Integrated Summary of Safety.

You have discussed that many malignancy cases in cladribine-treated subjects were cases of cancer that rarely metastasize and are almost always curable by surgical resection (e.g., basal cell carcinoma). We remain concerned, because an increased risk of malignancy in cladribine-treated subjects compared to placebo-treated subjects persists after excluding these cases.

You have discussed that pre-existing risk factors have been documented in cladribine-treated subjects with reported cases of malignancy. We remain concerned, as pre-existing risk factors are likely to exist in some placebo-treated subjects, as well. We request clarification on whether risk factors for malignancy were documented in all study subjects, and whether an imbalance in pre-existing risk factors has been documented in cladribine-treated subjects as compared to placebo-treated subjects.

You have discussed that the analyses of the long-term data are potentially biased due to confounding by time since randomization. Although we agree that there is considerably more long-term experience under treatment, compared to placebo, conditions, we note that there is still a worrisome signal for malignancy in CLARITY. Although the maximum duration of observation in CLARITY is 2 years, we believe that this is a sufficient duration of exposure to cladribine to consider any malignancies occurring then to be biologically plausible. Further, the signal seen in the long-term extension contributes to our concern, given our lack of a detailed understanding of what rate of malignancies should be expected over that duration of time.

You have discussed conducting a long-term prospective follow-up safety registry (PREMIERE) to assess the risk of malignancies, as well as serious infections, lymphopenia, and other adverse events of special interest in subjects with MS who have participated in clinical trials of oral cladribine. We remain concerned, as it is unclear how this registry will serve to mitigate the risk of malignancy. We request additional information on the information to be collected and the planned methods for analysis, including details on how the expected rates of adverse events will be determined.

We have the following additional comments that will need to be addressed, assuming you can successfully respond to the previous concerns related to malignancies:

1. Cladribine causes a prompt and sustained decrease in absolute lymphocyte count occurring shortly after exposure to cladribine. In the CLARITY study, a majority of subjects continued to have significant lymphopenia at the time of last assessment. Ongoing lymphopenia is of potential importance with regard to the development of infections and malignancies, and may influence plans for repeat dosing. A clear understanding of lymphopenia in cladribine-treated subjects is essential when considering its safety profile.

   For this reason, you must ascertain the time to resolution of lymphopenia in cladribine-treated subjects in CLARITY in order to better inform our decision about the ultimate approvability of this application, and to provide appropriate guidance on the necessary duration of hematologic monitoring.

2. Your plans for long-term dosing of cladribine are vague. Your submission and proposed labeling provide no specific discussion of how dosing should be approached after the initial cycles of treatment. You should clarify, and justify, the intended maximum dosing duration of cladribine in clinical use.

3. There are several additional safety issues of concern that require the submission of additional information. These requests for additional information include:

   - Since patients with a history of taking disease-modifying drugs for multiple sclerosis may have longer durations of immunosuppression than the general patient population, we request analyses of malignancy risk and changes in hematologic laboratory measurements for this subgroup of patients.

   - Since most cases of malignancy in cladribine-treated subjects occurred in subjects over age 40, we request analyses of malignancy risk stratified by age.

   - If cladribine is taken with another agent that affects lymphocytes, additive adverse effects leading to lymphopenia may occur. We request additional information, including which specific medications may lead to these additive effects on lymphocytes, in order to provide guidance on cladribine's use.

Several other safety concerns also require the submission of additional information. Please see the appendix to this letter for a complete list of our requests for additional information to be submitted with any resubmission of this application.

PRODUCT QUALITY

1. The proposed dissolution specification of NLT (b)(4)% of the labeled amount of cladribine dissolved in 15 minutes (Q(b)(4)) is not acceptable, as cladribine dissolution is very rapid with more than (b)(4)% dissolution within 15 minutes. You must tighten the dissolution specification to NLT (b)(4)% of labeled amount of cladribine dissolved in 15 minutes (Q(b)(4)).

LABELING

Given our significant concerns about cladribine-induced malignancies, we have not included draft labeling with this letter. However, we have the following comments related to carton and container labeling.

Please submit draft carton and container labeling revised as follows:

A. CARTON LABELING AND TABLET HOLDER LABELING (all quantities)

(b) (6)

B. CARTON LABELING (all quantities)

C. BLISTER LABEL (all quantities)

(b) (6)

D. TABLET HOLDER LABELING (all quantities)

(b) (6)

E. PACKAGING DESIGN (all quantities)

(b) (6)

We reserve comment on the remainder of your proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission or use formats we have previously requested when applicable.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Hamet Touré, Regulatory Project Manager at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Russell Katz, M. D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPENDIX

The following general instructions apply to the safety requests below:

- All categorical analyses should have analysis criteria explicitly stated with the actual laboratory cutoff values that were used.

- Please refer to the meeting minutes from the pre-NDA meeting between EMD Serono and FDA on May 8, 2009 for instructions from the Division on the requested content of subject narratives.

- Prior to performing requested analyses that include information from ongoing trials, please discuss with the Division the cut-off date for these analyses.

I. Hematologic Toxicity and Hematologic Laboratory Measurements

I.1. In Table 100 of the EMD Serono ISS, it is unclear what thresholds were used for classifying Grade 1-4 decreases in White Blood Cell Counts. The central laboratory reference range lower limit of normal in the CLARITY Trial for WBC count was 2.0 x 10^9/L.[1] Thus, a WBC count of 2.0 x 10^9/L is a threshold value for Toxicity Grades 1, 2, and 3 (see table below).

Laboratory Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes (WBC) Decreased	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9/L	<3000 - 2000/mm^3 <3.0 – 2.0 x 10^9/L	<2000 - 1000/mm^3 <2.0 – 1.0 x 10^9/L	<1000/mm^3 <1.0 x 10^9/L

We request a revised version of Table 99 in the EMD Serono ISS with the actual numerical laboratory cut-off values for the lower limits of normal and upper limits of normal used to calculate each toxicity grade with or within the table.

1 Page 313 of the EMD Serono ISS.

Table 99: NCI Toxicity Grading Scheme (CTCAE Version 3.0) for Key Laboratory Parameters

Laboratory Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
Hemoglobin Decreased	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L
Leukocytes (WBC) Decreased	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9/L	<3000 - 2000/mm^3 <3.0 – 2.0 x 10^9/L	<2000 - 1000/mm^3 <2.0 – 1.0 x 10^9/L	<1000/mm^3 <1.0 x 10^9/L
CD4+ T-lymphocytes	< LLN – 500/mm^3 <LLN – 0.5 x 10^9/L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9/L	<200 – 50/mm^3 <0.2 – 0.05 x 10^9/L	< 50/mm^3 <0.05 x 10^9/L
Neutrophils (ANC) Decreased	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9/L	<1500 - 1000/mm^3 <1.5 – 1.0 x 10^9/L	<1000 - 500/mm^3 <1.0 – 0.5 x 10^9/L	<500/mm^3 <0.5 x 10^9/L
Platelets Decreased	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9/L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9/L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9/L	<25,000/mm^3 <25.0 x 10^9/L
Lymphocytes Decreased	<LLN – 800/mm^3 <LLN – 0.8 x 10^9/L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9/L	<500 - 200/mm^3 <0.5 – 0.2 x 10^9/L	<200/mm^3 < 0.2 x 10^9/L
Chemistry				
ALP Increased	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
ALT Increased	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST Increased	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Bilirubin Increased	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
CK Increased	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
(Serum) Creatinine Increased	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN

Abbreviations: ALP = alkaline phosphatase, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, CK = creatinine phosphokinase, LLN = lower limit of normal, ULN= upper limit of normal, WBC = white blood cells

I.2. Analyses reported in Table 108 of the EMD Serono Integrated Summary of Safety are described as including only subjects whose Grade 3 or 4 lymphopenia resolved during the 96 weeks of the studies; however, the upper range of time to resolution for all cladribine subjects is 202.6 weeks. Please clarify this apparent discrepancy.

I.3. We request additional information on the course of subjects with persistent hematologic laboratory abnormalities after treatment with oral cladribine (beyond 96 weeks post-initial therapy).

I.3.1. Regarding completed EMD Serono trials of oral cladribine, we request additional information on subjects with persistent hematologic laboratory abnormalities after treatment with oral cladribine (beyond 96 weeks post-initial therapy).

- I.3.1.1. For subjects with persistent hematologic laboratory abnormalities after treatment with oral cladribine (beyond 96 weeks post-initial therapy) in EMD Serono trials, describe the follow-up procedure that was performed. Summarize the adverse events that were reported in these subjects beyond 96 weeks post-initial therapy.
- I.3.1.2. Summarize the proportion of these subjects with persistent hematologic laboratory abnormalities in the following time intervals post-initial therapy: 1) >96 weeks to 2.5 years; >2.5 to 3 years; >3.5 to 4 years; and > 4 years.
- I.3.1.3. For the time intervals listed in Item I.3.1.2, summarize the proportion of subjects with persistent hematologic abnormalities who did not have subsequent follow-up.

1.3.2 Summarize your plans for characterizing the long term course of subjects with persistent hematologic laboratory abnormalities after treatment with oral cladribine (beyond 96 weeks post-initial therapy) in ongoing or future studies assessing patients treated with oral cladribine.

I.4. According to Section 1C of the Final Report of the Long Term Clinical Follow-Up Study of Multiple Sclerosis Subjects Treated with Cladribine, most MS subjects from the two main Scripps MS Cladribine treatment trials were examined at yearly intervals for 5 years after the completion of the MS Cladribine treatment protocols. In addition, all of the laboratory data dating back approximately 10 years is available in electronic format in Excel spreadsheets. We request the following:

- Datasets that include all known hematologic laboratory data for subjects who participated in the Scripps studies, including data from post-study yearly evaluations and data from the long term clinical follow-up study by Dr. Sipe.
- Figures displaying changes in hematologic laboratory measurements in Scripps subjects over time.
- If a Scripps subject had a known cause for a persistent hematologic abnormality other than treatment with cladribine, please provide a table documenting the sequence of laboratory measurements and suspected cause of hematologic abnormalities with the dates that they occurred.

I.5. Regarding the analyses of adverse events and serious adverse events of hemorrhage in CLARITY subjects using the MedDRA Hemorrhage SMQ, we request the following:

- For subjects with an adverse event in the Hemorrhage SMQ, provide the median, range, and interquartile range of the minimum platelet count measured between 30 days prior and 5 days after the start of the adverse event for each subject group.

- For subjects with a serious adverse event in the Hemorrhage SMQ, provide the median, range, and interquartile range of the minimum platelet count measured between 30 days prior and 5 days after the start of the serious adverse event for each subject group.
- For subjects with an adverse event in the Hemorrhage SMQ, provide the median, range, and interquartile range of the platelet count measured closest to the start date of the AE, from dates ranging 30 days prior to the AE start date to the actual AE start date.
- For subjects with a serious adverse event in the Hemorrhage SMQ, provide the median, range, and interquartile range of the platelet count measured closest to the start date of the SAE, from dates ranging 30 days prior to the SAE start date to the actual SAE start date.

For each of the analyses requested in Question I.5, provide: 1) the number of subjects with AEs or SAEs 2) the number and percentage of subjects with AEs or SAEs who had platelet measurements available for analysis; and 3) the mean and range of the number of days from the platelet measurement analyzed and the start of the AE or SAE.

I.6. In the EMD Serono ISS, some reference ranges for hematologic laboratory parameters differ from reference ranges used by other sources. We request reanalysis of White Blood Cell counts using the reference range 4.3 to 10.0 x $10^9/L^2$ and of CD4 lymphocyte count using the reference range 500-1500 cells/ uL.[3] Using these reference ranges, we request revised analyses in the format of the following tables:

- Table 100 from the EMD Serono ISS
- Table 32_1.1 from EMD Serono ISS Appendix C3

We request that these tables include clear notation of the laboratory cut-off values used.

I.7. We request analyses of hematologic laboratory measurements, during weeks 0-96 of the controlled phase of completed studies, stratified by history of prior use of disease-modifying drugs (DMDs) for multiple sclerosis.

- DMDs analyzed should include: interferon beta-1a, interferon beta-1b, glatiramer acetate, mitoxantrone, natalizumab, and fingolimod.
- We request analyses for the following subgroups stratified by history of using disease-modifying drugs (DMDs) for multiple sclerosis prior to study entry: 1) no DMD use; 2) any DMD use; 3) use of 1 DMD; and 4) use of 2 or more DMDs
- For each subject group, we request tables similar in format to: 1) Table 100 from the EMD Serono ISS; and 2) Table 32_1.1 from EMD Serono ISS Appendix C3.
- For analyses of White Blood Cell counts and CD4 lymphocyte counts, we request that you include analyses using both the reference ranges used in the 5/27/2010 submission and the reference ranges requested in Question I.6.
- We request that these tables include clear notation of the laboratory cut-off values used.

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2 (Ref: Daniel D. Federman, M.D., Elizabeth G. Nabel, MD, eds. 2010. ACP Medicine. New York, NY. BCDecker Inc. ISBN 0-9703902-9-7. ISSN 1548-9345. STAT!Ref Online Electronic Medical Library. http://online.statref.com/document.aspx?fxid=48&docid=905. 11/5/2010 3:04:39 PM CDT).
3 Johns Hopkins Point of Care Information Technology. HIV Guide. Accessed at http://www.hopkinsaids. edu/management/laboratory_testing/cd4_cell_count html?contentInstanceId=8279 on November 4, 2010.

I.8. We request analyses of hematologic laboratory measurements during weeks 0-96 of the controlled phase of completed studies stratified by location.

- We request analyses for the following subgroups: 1) U.S. subjects; and 2) non-U.S. subjects.
- For each subject group, we request tables similar in format to: 1) Table 100 from the EMD Serono ISS; and 2) Table 32_1.1 from EMD Serono ISS Appendix C3.
- For analyses of White Blood Cell counts and CD4 lymphocyte counts, we request that you include analyses using both the reference ranges used in the 5/27/2010 submission and the reference ranges requested in Question I.6.
- We request that these tables include clear notation of the laboratory cut-off values used.

II. Other Laboratory Measurements

General

II. 1. We request that you submit a table of the threshold laboratory values used as criteria for analyses in EMD Serono ISS Table 115 and for analyses in CLARITY Trial report Table 25643-199.

Table 25643- 199: Chemistry Laboratory Test Shifts from Baseline to Week 96 by Treatment Group - Safety Population

		Cladribine 5.25 mg/kg (n=454) Week 96				Cladribine 3.5 mg/kg (n=430) Week 96				Placebo (n=435) Week 96			
Laboratory Test (unit)	Baseline Classification	Low	Normal	High	Missing	Low	Normal	High	Missing	Low	Normal	High	Missing
Sodium (mmol/L)	Low	0	1	0	0	1	6	0	0	0	2	0	0
	Normal	2	394	2	41	5	372	4	28	6	380	4	33
	High	0	4	0	0	0	2	1	0	0	3	0	0
	Missing	0	10	0	0	0	9	0	2	0	7	0	0
Potassium (mmol/L)	Low	0	0	0	0	0	1	0	0	1	0	0	0
	Normal	1	389	4	46	0	378	6	32	2	383	2	37
	High	0	3	0	0	0	1	0	0	0	2	0	1
	Missing	1	10	0	0	0	10	0	2	0	7	0	0
Calcium (mmol/L)	Low	3	6	0	0	2	8	0	0	1	8	0	3
	Normal	10	367	2	43	10	348	8	29	9	353	7	33
	High	0	8	3	1	0	9	3	1	1	10	3	0
	Missing	0	11	0	0	0	9	1	2	0	7	0	0
Protein (g/L)	Low	0	4	0	0	0	1	0	0	0	3	0	1
	Normal	0	389	1	43	0	384	0	28	1	381	0	34
	High	0	6	0	0	0	6	0	0	0	7	0	1
	Missing	0	11	0	0	0	9	0	2	0	7	0	0
Creatinine (umol/L)	Low	2	6	0	1	0	13	0	0	2	4	0	3
	Normal	0	385	4	43	2	372	1	29	1	381	3	32
	High	0	0	1	1	0	1	0	1	0	1	0	1
	Missing	0	11	0	0	0	9	0	2	0	7	0	0
Bilirubin (umol/L)	Low	0	1	0	0	0	0	0	0	0	0	0	0
	Normal	3	364	4	50	8	351	4	29	3	360	10	34
	High	0	11	9	0	0	10	14	2	0	8	8	4
	Missing	0	11	1	0	0	9	0	3	0	8	0	0
Albumin (g/L)	Low	0	0	0	0	0	0	0	0	0	0	0	0

Table 115: Chemistry Maximum Toxicity Grade During Weeks 0 - 96 of the Controlled Phase by Cladribine Tablets Equivalent Cumulative Dose Range (Population: Subjects Receiving Study Drug During Weeks 0 - 96 of the Controlled Phase of the Completed Studies)

Chemistry Test	Maximum Toxicity Grade	0 mg/kg (n=514) n (%)	All Cladribine Subjects (n=1073) n (%)	Cladribine >0-2.63 mg/kg (n=103) n (%)	Cladribine >2.63-4.38 mg/kg (n=471) n (%)	Cladribine >4.38-6.13 mg/kg (n=478) n (%)	Cladribine >6.13 mg/kg (n=21) n (%)
AST (u/L)	0	442 (86.0)	929 (86.6)	85 (82.5)	412 (87.5)	413 (86.4)	19 (90.5)
	1	59 (11.5)	117 (10.9)	11 (10.7)	48 (10.2)	56 (11.7)	2 (9.5)
	2	9 (1.8)	11 (1.0)	0 (0.0)	9 (1.9)	2 (0.4)	0 (0.0)
	3	1 (0.2)	3 (0.3)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	3 (0.6)	13 (1.2)	7 (6.8)	0 (0.0)	6 (1.3)	0 (0.0)
ALT (u/L)	0	390 (75.9)	813 (75.8)	80 (77.7)	357 (75.8)	359 (75.1)	17 (81.0)
	1	97 (18.9)	209 (19.5)	14 (13.6)	95 (20.2)	96 (20.1)	4 (19.0)
	2	19 (3.7)	30 (2.8)	2 (1.9)	13 (2.8)	15 (3.1)	0 (0.0)
	3	5 (1.0)	8 (0.7)	0 (0.0)	6 (1.3)	2 (0.4)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	3 (0.6)	13 (1.2)	7 (6.8)	0 (0.0)	6 (1.3)	0 (0.0)
Alkaline Phosphatase (u/L)	0	465 (90.5)	960 (89.5)	91 (88.3)	424 (90.0)	426 (89.1)	19 (90.5)
	1	44 (8.6)	99 (9.2)	5 (4.9)	47 (10.0)	46 (9.6)	1 (4.8)
	2	2 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	3 (0.6)	13 (1.2)	7 (6.8)	0 (0.0)	6 (1.3)	0 (0.0)

II.2. We request shift tables that display the number of CLARITY Trial subjects with abnormal urinalysis parameters (protein, ketones, glucose, blood, and pH) at baseline and post-treatment. (Similar in format to CLARITY Trial report Table 25643-199.)

Elevated creatine phosphokinase

II.3. We request analyses of baseline and follow-up creatine phosphokinase (CPK) increases by CTCAE grade in completed and ongoing trials for cladribine-treated and placebo-treated subjects.

II.4. We request narratives for Grade 3 and Grade 4 elevations in creatine phosphokinase (CPK). In addition to the requested content for narratives in general, these narrative should include:

- All known CPK measurements for each subject
- Whether a history of exercise preceded the CPK elevation
- Whether the initial elevated CPK measurement was performed as part of routine testing, or whether it was prompted by an event
- Whether related laboratory tests were performed including aldolase, lactate dehydrogenase, lactate, AST, and ALT; if yes, we request these results

- Results of any chemistry laboratory results performed while the CPK level was elevated (including serum creatinine and blood urea nitrogen), along with reference ranges.
- Results of any urine myoglobin testing performed

Increased creatinine

II.5. We request a narrative for CLARITY Subject (b) (6), who had a Grade 4 increase in creatinine. According to the ISS dataset, at Week 9 his creatinine level is listed as 1294 µmol/L (14.6 mg/dL) (normal range 80-133 µmol/L) and his potassium level is listed as 10.2 mmol/L (10.2 meq/L) (normal range 3.5-5.3 mmol/L). No baseline creatinine is available in the ISS dataset. The only other creatinine measurement available in the ISS dataset was a measurement of 76 µmol/L at Week 48. We request an explanation for this subject's changes in creatinine level.

III. Malignancy

III.1. Malignancy Cases in Placebo-Controlled Trials

For subgroups stratified by location (U.S. versus non-U.S. sites) and by route of administration (oral vs. parenteral), we request tables with the number of reported malignancies, number of subjects, incidence proportions, subject-years of exposure, and incidence rates for cases of malignancy in completed and ongoing trials for placebo-treated and cladribine-treated subjects.

In addition to stratification by location and by route of administration, we request analyses be further stratified by the following parameters:

- III.1.1. Cumulative dose category (oral dose equivalent >0-2.63 mg/kg, >2.63-4.38 mg/kg, >4.38-6.13 mg/kg, >6.13 mg/kg, and all cladribine doses combined)
- III.1.2. Duration of follow-up (≤48 weeks, >48 to 96 weeks, >96 to 144 weeks, >144 weeks, and all subjects combined)
- III.1.3. Gender (male, female, and all subjects combined)
- III.1.4. Age (<40 years versus ≥40 years at the time of initial treatment, and all subjects combined)
- III.1.5. History of using disease-modifying drugs (DMDs) for multiple sclerosis prior to study entry (no DMD use, any DMD use, known use of 1 DMD, and known use of 2 or more DMDs). For subject groups analyzed for Question III.1.5, we also request tables summarizing: 1) which DMDs had been used by each subject group; 2) the median and range of subject age at study entry; 3) proportion of female subjects; 4) median and range of EDSS scores at study entry; median number of reported adverse events per subject; and 6) the countries of origin for each subject group.

For each of the subject groups analyzed in Question III.1., we request the following information:
-The mean and median cumulative doses, as well as the cumulative dose range, for subjects in each group.

- The mean and median duration of exposure for subjects in each group.
- A list of the number of subjects that each study contributed to each group.

Please provide a summary of methods used for the tables requested in Question III.1.

III.1.6. We request that you confirm whether information on the following risk factors for malignancy were recorded in all study subjects in any of the cladribine trials with data reported:

- Previous malignancy
- History of medication use leading to increased malignancy risk
- Environmental risks
- Smoking
- Family history of malignancy

We request tables summarizing data for any of the risk factors that were recorded in all study subjects.

III.2. Comparisons of Malignancy Rates to Epidemiologic Data

We request a detailed description of the methods used to calculate the number of expected cases for the standardized incidence ratios (SIRs) described on pages 289-290 of the EMD Serono ISS, including:

- Which age, gender, and location-specific rates were applied to specific subject groups (with references to specific sections of the *Incidence of Cancer in Five Continents, Vol. IX*)
- According to the EMD Serono ISS on pp. 289-290, "When no information was available for a country, incidence rates from another country or combination of countries were used." We request a list of countries with unavailable information, how many subjects were located in each of these countries, the total number of subjects located in all of these countries, and data from which country or countries were used in place of the unavailable data.
- How these various rates were combined to calculate the number of expected cases
- Discussion of the strengths and weaknesses of comparing the data from the *Incidence of Cancer in Five Continents, Vol. IX* to data from the cladribine clinical trials.

IV. Myelodysplasia

We request to be notified within 15 days of any reported case of myelodysplasia in a subject who has taken cladribine.

V. Infection

V.1. We request a proposal on what should be done to minimize morbidity and mortality from infection. This proposal should include recommendations regarding hepatitis screening, tuberculosis screening, varicella vaccination, and hepatitis B vaccination. The proposal should

discuss which patient populations who should receive the vaccinations, as well as the recommended time frame for administering any vaccination(s). If you do not propose that vaccinations be administered, we request a justification for this recommendation.

V.2. We request additional information about (1) (b) (6) a 26 year old male from the Ukraine who was diagnosed with tuberculosis of the right upper lung (MFR Control No. 7014989; initial report submitted 02 Sep 2010) and (2) (b) (6) a 45 year old female from Lebanon who was found to have conversion to a positive PPD. We request the following information:

- Update on status of each subject
- Past PPD results and dates
- Laboratory results, including all available hematologic laboratory measurements at baseline and after treatment
- If the subjects' treatment assignments have been unblinded, we request this information.

VI. Cardiac Arrhythmias

We request additional information regarding the treatment-emergent cardiac arrhythmias and conduction disorders adverse events occurring during weeks 0-96 of the controlled phase, which are summarized in Table 96 of the EMD Serono ISS. We request a dataset with the following information for the adverse events listed in Table 96:

- Unique Subject ID (identical to ISS dataset ADAEC variable SUBJID)
- Oral cumulative dose at AE onset (numeric, identical to ISS dataset ADAEC variable TRTORCUM)
- Days from first dose to AE onset (identical to ISS dataset ADAEC variable AESTUDDY)
- MedDRA Primary Preferred Term
- Adverse Event Reported Term
- Serious Adverse Event (yes or no, identical to ISS dataset ADAEC variable AESAEYN)
- Study number
- Subject number
- Days from most recent study dose prior to AE onset to date of AE onset

VII. Coronary Artery Disorders HLGT

We request narratives for all adverse events categorized in the Coronary Artery Disorders High Level Group Term in completed placebo-controlled trials. We request that these narratives include all available vital sign measurements for these subjects prior to and during each adverse event.

VIII. Cardiac Failure

VIII.1. We request analyses of treatment-emergent adverse events from ongoing and completed placebo-controlled trials using the following MedDRA SMQs (narrow versions):

- Cardiac failure
- Haemodynamic oedema, effusions, and fluid overload
- Cardiomyopathy

For each of the MedDRA SMQs listed above, we request analyses of: 1) all adverse events; 2) adverse events that occurred within 60 days of initial treatment; 3) all adverse events designated as serious adverse events or that resulted in discontinuation of treatment; and 4) adverse events designated as serious adverse events or that resulted in discontinuation of treatment that occurred within 60 days of initial treatment.

We request the number of cases, the number of subjects, incidence proportions, subject-time of exposure in subject-years, and incidence rates for cladribine-treated and placebo-treated study subjects.

- Please specify what cut-off date was used.
- For each of the 12 sets of analyses above, we request a table of all adverse event cases with the following information:

- Trial
- Subject Number
- Sex
- Country
- Preferred term for the adverse event
- Treatment group
- Cumulative cladribine dose at adverse event onset
- Latency
- Whether the event was a Serious Adverse Event
- Whether the event caused discontinuation of treatment
- For SAEs and discontinuations, a link to the narrative

VIII.2. We request a summary and references for all published cases of cardiac failure that occurred within 6 months of starting treatment with cladribine.

IX. Vital Signs

IX.1. We request clarification on how the timing of vital sign measurement related to the time of dosing in the CLARITY Trial.

IX.2. Similar in format to the analyses included in Table 121 from the EMD Serono ISS, we request the following analyses of subjects with outlier values for vital signs during weeks 0-96 of the controlled phase by cladribine tablets equivalent cumulative dose range: 1) subjects with at least 1 pulse rate measurement of less than 60 bpm; and 2) subjects with at least 1 pulse rate measurement decreased by ≥20 bpm.

IX.3. We request additional information regarding adverse events from completed controlled trials coded to the following Preferred Terms: 1) Dizziness; 2) Dizziness postural;

3) Presyncope; and 4) Syncope. We request a dataset with the following information for these adverse events:

- Unique Subject ID (identical to ISS dataset ADAEC variable SUBJID)
- Oral cumulative dose at AE onset (numeric, identical to ISS dataset ADAEC variable TRTORCUM)
- Days from first dose to AE onset (identical to ISS dataset ADAEC variable AESTUDDY)
- MedDRA Primary Preferred Term
- Adverse Event Reported Term
- Serious Adverse Event (yes or no, identical to ISS dataset ADAEC variable AESAEYN)
- Study number
- Subject number
- Days from most recent study dose prior to AE onset to date of AE onset

X. Hypersensitivity

X.1. We request a narrative that includes the details of the SAEs of angioedema and urticaria, which led to treatment discontinuation, for Subject (b) (6) in the ONWARD Study.

X.2. We request additional information regarding CLARITY Subject (b) (6) (19 year old female who had a severe cutaneous reaction):

- Please confirm whether a skin biopsy was performed.
- Please confirm whether this subject experienced any desquamation; if yes, please describe, including the approximate percentage of body surface area and location(s) affected.
- We request any available photos of this subject's skin reaction

XI. Hearing Loss

We request narratives regarding the following adverse events in the HLT Hearing Losses:

Table 4. Adverse events in the HLT Hearing Losses in completed controlled trials

CLARITY Subject ID	Age	Treatment Assignment	Preferred Term
(b) (6)	34	Cladribine 3.5 mg/kg	Deafness
	40	Cladribine 5.25 mg/kg	Deafness bilateral
	39	Cladribine 3.5 mg/kg	Deafness neurosensory
	45	0 mg/kg	Deafness unilateral
	29	Cladribine 5.25 mg/kg	Hearing impaired
	40	Cladribine 5.25 mg/kg	Hypoacusis

XII. Neurologic Toxicity

According to the Leustatin prescribing information, "severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens" for treatment of Hairy Cell Leukemia. We request a summary of the published literature of neurological toxicity reported after treatment of Hairy Cell Leukemia with standard dosing regimens of intravenous cladribine.

XIII. Seizure

We request additional information regarding subjects who had seizure adverse events (Table 5).

Table 5. Information Requests for subjects with Seizure Adverse Events in Completed and Ongoing Cladribine Studies and Trials

Study/ Subject No.	Total Cladribine Dose[1]	Latency[2]	Age Sex Country	SAE Preferred Term	Comments/Requests
CLARITY/ (b) (6)	3.5 mg/kg	1 year, 8 months	47 F USA	Convulsion	We request information on the duration of the convulsion. *(Narrative located on pages 1360-1 of the CLARITY trial report.)*
MS-Scripps/ (b) (6)	7.0 mg/kg	8 months	28 F	Post-Traumatic Epilepsy	We request a narrative for this adverse event.
CLARITY Extension/ (b) (6)	blinded	3 days	26 F Czech Republic	Epilepsy	We request a narrative for this adverse event.
CLARITY Extension/ (b) (6)	blinded	1 year	44 F Bulgaria	Epilepsy	We request a narrative for this adverse event.

[1]Oral cladribine equivalent cumulative dose
[2] Time from first day of treatment to diagnosis

XIV. Drug-Drug Interactions

Your proposed labeling contains the following language: (b) (4)
(b) (4)

(b) (4)

If the drug is to be marketed, information for patients and prescribers will need to include information that specifies which drugs may increase the frequency of reductions in lymphocyte count. We need clarification from you on how this list would be compiled.

XV. Registry Studies

XV.1. We request additional information about the planned RECORD MS registry.

XV.2. We request an update on the subjects enrolled and the data collected in the PREMIERE registry. Please discuss the cut-off date with the Division prior to compiling this information.

XV.3. We request a detailed list of all information that is to be collected as part of the PREMIERE registry.

XVI. Other Requests for Individual Subject Follow-Up

XVI.1. Regarding the reported thyroid adenoma in a 61 year old female from the Czech Republic who participated in the CLARITY Extension Trial (Subject number (b) (6); mfr. Control no. 7030335), we request follow-up, including the pathology results for the lobectomy of the right thyroid lobe performed on (b) (6). This case was initially reported on December 14, 2010.

XVI.2. We request the following additional information regarding Case 7023305, a 21 year old male subject from Poland in the ORACLE MS trial with elevated amylase and lipase levels (information submitted 22 Nov 2010):

- Blood triglyceride measurements
- Blood lactate measurements
- Results of any imaging tests
- Follow-up of amylase and lipase levels
- Provide an assessment of this case; discuss whether this is a case of pancreatitis.

XVI.3. We request the treatment assignment (CLARITY and CLARITY Extension) for the case of basal cell cancer in a 40 year old female in the CLARITY Extension Trial (Mfr. Control No. 7026942), which was submitted to IND 074634 on 11/22/10.

XVI.4. Regarding SSL, the 37 year old female from India who died of cardiopulmonary arrest in the ORACLE-MS Trial (Mfr. Control No. 7019448), we request:

- Copies of any available ECGs with readings
- Any available information on ECG results for this subject
- Any available information on prior arrhythmias or vital sign abnormalities in this subject
- Information on any history of dizziness, presyncope, or syncope in this subject
- Results of prior brain imaging studies in this subject.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
02/28/2011