

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022561Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 22561 (resubmission)

Review # 4

Drug Name/Dosage Form	Mavenclad (cladribine) tablets
Strength	10 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	EMD Serono, Inc
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	Ben Zhang	Su Tran
Drug Product/Labeling	Rao Kambhampati	Wendy Wilson-Lee
Process	Kejun Cheng	Nallaperumal Chidambaram
Facility	Kejun Cheng	Zhihao Peter Qiu
Biopharmaceutics	Mei Ou	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia A. Woody	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

Amendments Pertinent to Product Quality

SUBMISSIONS REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-061, Resubmission after CR	5/31/2018	All
SD-066, response to IR	11/9/2018	Process
SD-068, Container labeling	12/6/2018	Labeling

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Cladribine	Adequate	1/9/2019	Reviewed by Ben Zhang
	III	(b) (4)		N/A ¹	N/A ¹	
	III	(b) (4)		N/A ¹	N/A ¹	

¹ Adequate information in application or no changes to information since previous reviews.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20229	Janssen Pharmaceuticals Leustatin (cladribine injection) 10 mg/mL for intravenous infusion. Indicated for treatment of active hairy cell leukemia.
NDA	(b) (4)	(b) (4)
IND	(b) (4)	(b) (4)
IND	74634	EMD Serono Development of cladribine tablets for treatment of multiple sclerosis.

2. CONSULTS: N/A

Executive Summary

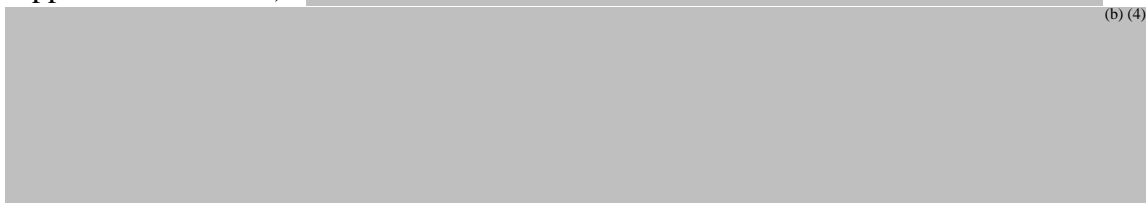
I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 222561 for Mavenclad® (cladribine) tablets. From a quality perspective, the application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. Summary of Quality Assessments

A. Product Overview

Cladribine was first marketed within the US by Janssen Pharmaceuticals as Leustatin® Injection 10 mg/mL for IV infusion to treat active Hairy Cell Leukemia (NDA 20229, approved 2/26/1993). (b) (4)



The applicant, EMD Serono (EMD) assumed sponsorship of (b) (4) and continued clinical development of cladribine, as a tablet formulation, under IND 74634. EMD submitted NDA 22561 in 2009 and resubmitted after refuse to file in May 2010. The Agency issued a complete response letter (CRL) on 2/28/2011 citing inadequate information to support safety for the proposed indication. The CRL also cited a minor quality deficiency (dissolution). The current resubmission provides the applicant's response to the deficiencies cited in the CRL. It is noted that the applicant included a full CMC update in the resubmission. Per prior agreement, the resubmission includes a detailed list of changes from the original NDA in Module 1.¹

Proposed Indication(s) including Intended Patient Population	Treatment of patients with relapsing forms of multiple sclerosis. Mavenclad has not been studied in patients under 40 kg body weight.
Duration of Treatment	Two treatment courses, one year apart.
Maximum Daily Dose	The maximum daily dose is 20 mg. The recommended cumulative dose is 3.5 mg/kg over 2 years, administered as 1 treatment course of 1.75 mg per kg per year.
Alternative Methods of Administration	None

¹ \\cdsesub1\evsprod\nda022561\0060\m1\us\12-cover-letter\table-of-changes-quality.pdf

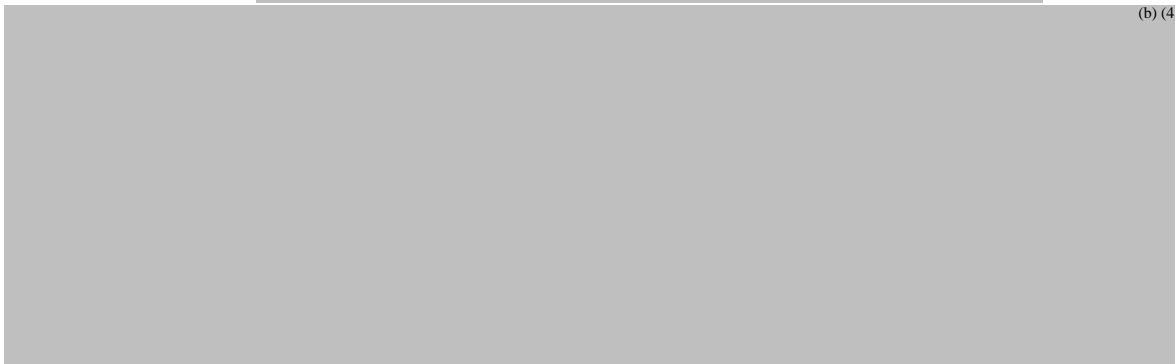
B. Quality Assessment Overview

Drug Substance

The bulk active pharmaceutical ingredient (API), cladribine, is a well characterized, weakly basic, small molecule that is slightly water-soluble (0.5 mg/mL). (b) (4)
(b) (4). Information regarding the characterization, manufacture, and control of the API is incorporated by cross-reference to drug master file (DMF) (b) (4). The DMF was reviewed and deemed adequate during the review of the original NDA. Subsequent changes to the DMF were reviewed and the DMF remains adequate to support approval of the NDA. Information submitted by the applicant directly to the NDA includes an updated drug substance specification that includes addition of controls for elemental impurities (per ICH Q3D), residual solvents (per ICH Q3C) and controls for non-related potential genotoxic impurities (PGIs) used as reagents early synthetic steps (per ICH M7). The application is also updated to include assessment of structurally related PGIs. Based on the information provided, structurally-related impurities are considered to pose no additional genotoxic risk and non-related 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 resubmission does not include any changes to the target tablet composition; however, the applicant proposes a minor adjustment (b) (4)



(b) (4). The applicant's control of process parameters and in-process controls provide adequate mitigation of product quality risks and the applicant has validated the process at commercial scale.

The product specification was revised per Agency request in the 2/28/2011, CRL to tighten the dissolution acceptance criterion (b) (4)
(b) (4) to NLT (b) (4) % dissolved in 15 minutes ($Q = (b) (4)$). Acceptance criteria for assay, total impurities, and water content were tightened based on

additional manufacturing experience. Additional minor changes are primarily editorial in nature.

Mavenclad tablets are packaged in (b) (4) blisters (b) (4) in a child-resistant carton. The blister (b) (4) proposed in the original NDA submission, (b) (4) was replaced with an equivalent (b) (4). There is no change to the product contact surface and change is considered minor.

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.

Facilities

All facilities that will be involved in commercial manufacture and testing of cladribine and Mavenclad (cladribine) tablets are currently acceptable.

Environmental Assessment

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.

C. Special Product Quality Labeling Recommendations

Cladribine is a cytotoxic compound. The product labeling will include a safety warning and instructions for appropriate handling, use, and disposal.

D. Final Risk Assessment

When the original NDA was reviewed and recommended for approval from a quality perspective, formal risk assessment was not part of the review process. Given the limited changes in the resubmission, risk assessment is not deemed necessary.



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LABELING REVIEW
NDA 022561 (Resubmission)

[IQA Review Guide Reference](#)

I. Package Insert

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Mavenclad [®] (cladribine)
Dosage form, route of administration	Tablets/Oral
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Cladribine 10 mg tablets are white, round, biconvex tablets, engraved with “C” on one side and “10” on the other side of the tablet.

2. Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Not applicable

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(4))
Available dosage forms	10 mg
Strengths: in metric system	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Cladribine 10 mg tablets are white, round, biconvex tablets, engraved with “C” on one side and “10” on the other side of the tablet.

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))
Proprietary name and established name	Mavenclad [®] (cladribine)
Dosage form and route of administration	Tablet/oral
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not applicable
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Yes

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Yes
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer’s Assessment of Package Insert: *Adequate*

The Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

The drug product is provided in the following presentations:

- NDC 44087-400-11 Box of 1 tablet: One (b) (4) day pack containing one tablet (b) (4)
- NDC 44087-400-12 Box of 2 tablets: One (b) (4) day pack containing two tablets (b) (4)
- NDC 44087-400-04 Box of 4 tablets: Four (b) (4) day packs each containing one tablet (b) (4)
- NDC 44087-400-05 Box of 5 tablets: Five (b) (4) day packs each containing one tablet (b) (4)
- NDC 44087-400-06 Box of 6 tablets: One (b) (4) day pack containing two tablets in (b) (4) Four (b) (4) day packs each containing one tablet (b) (4)
- NDC 44087-400-07 Box of 7 tablets: Two (b) (4) day packs each containing two tablets (b) (4) Three (b) (4) day packs each containing one tablet (b) (4)
- NDC 44087-400-08 Box of 8 tablets: Three (b) (4) day packs each containing two tablets (b) (4) Two (b) (4) day packs each containing one tablet (b) (4)
- NDC 44087-400-09 Box of 9 tablets: Four (b) (4) day packs each containing two tablets (b) (4) One (b) (4) day pack containing one tablet (b) (4)
- NDC 44087-400-10 Box of 10 tablets: Five (b) (4) day packs each containing two tablets (b) (4)

Sample Blister Card Container Labels:



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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Yes	Yes
Dosage strength	Yes	Yes
Net contents	Yes	Yes
“Rx only” displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	No	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	No	Yes
Bar code (21CFR 201.25)	No	Yes
Name of manufacturer/distributor	No	Yes
And others, if space is available		

Reviewer’s Assessment of Labels: *Adequate after modification to the storage statement is made.*

The labels comply with all regulatory requirements from a CMC perspective after the deficiency is fulfilled.

List of Deficiencies:

- 1) *The storage statement should be changed to Store at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].*

Overall Assessment and Recommendation: Adequate after recommended change is made.

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 2/1/19

Secondary Reviewer Name and Date: Wendy Wilson-Lee, Ph.D. 2/1/19



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BIOPHARMACEUTICS**NDA: 022561-ORIG-1-RESUB-61 [505(b)(1)]****Drug Product Name / Strength:** Mavenclad™ (Cladribine) Tablet, 10 mg**Route of Administration:** Oral**Applicant Name:** Merck Serono, Inc.**Proposed Indication:** Mavenclad™ is a nucleoside metabolic inhibitor indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS)**Submission Date:** 05/30/2018**Primary Reviewer:** Mei Ou, Ph.D.**Secondary Reviewer:** Ta-Chen Wu, Ph.D.**REVIEW SUMMARY**

The NDA 022561 for the proposed Mavenclad™ (Cladribine) Tablet, 10 mg, an immediate release tablet for oral administration, was originally submitted on 09/30/2009 and received an Refuse-to-File (RTF) letter on 11/25/2009^{1,2,3}. This NDA was resubmitted on 05/27/2010. The FDA issued a COMPLETE RESPONSE (CR) letter to the resubmission on 02/28/2011 because of the clinical issues⁴. The Division of Biopharmaceutics recommended tightening of the dissolution acceptance criterion for the proposed drug product (non-CR deficiency).

The proposed drug product is a Biopharmaceutical Classification System (BCS) III drug (high solubility, low permeability). The proposed in vitro dissolution method (including dissolution method validation) as a quality control (QC) test were previously reviewed and deemed acceptable^{5,6,7}. With the current submission, the Applicant accepted the recommended dissolution acceptance criterion and revised the related sections in NDA accordingly. The additional information provided and the overall dissolution information support the in vitro dissolution method as a QC test and revised dissolution acceptance criterion for the proposed drug product. The Applicant's response is acceptable.

¹ Refuse-to-File (RTF) Letter for NDA 022561 original submission dated 11/25/2009,

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af801b01cd&_afRedirect=2741976237644103

² Type A, Refuse-to-File Meeting dated 01/26/2010, Meeting Minutes dated 03/19/2010

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af801c841b&_afRedirect=2742332102965560

³ Clinical Pharmacology and Biopharmaceutics Review for NDA 022561 Refuse-to-File Meeting dated 03/05/2010:

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af801c524f&_afRedirect=2742057605827639

⁴ COMPLETE RESPONSE (CR) Letter for NDA 022561 resubmission on 02/28/2011:

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af802191ef&_afRedirect=2134470349301021

⁵ Clinical Pharmacology/Biopharmaceutics Review for NDA 022561 resubmission dated 11/23/2010:

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af80204722&_afRedirect=2135855910018894

⁶ Biopharmaceutics Review for NDA 022561 resubmission dated 11/03/2010:

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af801ff682&_afRedirect=2135173945605639

⁷ Drug Product Review for NDA 022561 resubmission dated 10/28/2010:

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af801fdc74&_afRedirect=2135247507891205

Recommendation:

From the Biopharmaceutics perspective, NDA 022561-ORIG-1-RESUB-61 for the proposed Mavenclad™ (Cladribine) Tablet, 10 mg, is recommended for **APPROVAL**.

The FDA approved dissolution method and acceptance criterion, as presented below, are to be implemented for the proposed Mavenclad™ (Cladribine) Tablet, 10 mg:

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Medium and Volume	Phosphate Buffer pH 6.8 (de-aerated), 900 mL
Temperature	37°C±0.5°C
Sampling Time	5, 10, 15, 20, 30 and 45 minutes
Acceptance Criterion	Q= (b)(4)% in 15 minutes

BIOPHARMACEUTICS REVIEW

Per the Clinical Pharmacology, Biopharmaceutics and Chemistry Reviews for the resubmission of this NDA: (a) the composition of the Phase II/III clinical trial formulations are similar to the to-be-marketed/commercial formulation, while the excipient change was not more than (b)(4)%, qualified as a Level 2 change, per SUPAC-IR guidance; (b) both clinical trial formulation and commercial formulation showed similar and very rapid dissolution profiles in multi-media (e.g. water, 0.1 N HCl, pH 4.5, 6.5 and 7.5 phosphate buffers, > (b)(4)% dissolution in 15 minutes); (c) in vivo bridging (bioequivalence study) and in vitro bridging (comparative dissolution) between the clinical and the commercial formulations were not required.

In current submission, there are no changes in (i) the qualitative and quantitative composition of the proposed drug product, (ii) manufacturing site, and (iii) manufacturing process since the previous 2010 submission, therefore, additional bridging studies are not needed. Biopharmaceutics review focuses on the evaluation of: (a) the response to the Biopharmaceutics comments in CR letter, (b) the additional dissolution information of the proposed drug product.

1. Response to the Biopharmaceutics comments in CR letter on 02/28/2011

The Biopharmaceutics comment in CR letter:

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 ($Q = (b)(4)$).

The Applicant's response to the above comment:

Based on the very rapid dissolution of cladribine 10 mg tablets, the Sponsor has tightened the dissolution specification to NLT (b)(4)% of the labeled amount of

cladribine dissolved in 15 minutes ($Q = \frac{(b)}{(4)}$). Please refer to the updated Module 3 Section P.5.1 Specification(s).

2. Additional Dissolution Information

The previously accepted dissolution method and the currently revised acceptance criterion are given in the following table:

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Medium and Volume	Phosphate Buffer pH 6.8 (de-aerated), 900 mL
Temperature	37°C±0.5°C
Sampling Time	5, 10, 15, 20, 30 and 45 minutes
Acceptance Criterion	$Q = \frac{(b)}{(4)}\%$ in 15 minutes

Per the Applicant, the commercial formulation of drug product, the manufacturing process restarted in 2015, the manufacturing site, and the dissolution QC method remain the same.



(b) (4)



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NDA 22-561

(Review #3)

 (b) (4)
(Cladribine)
Tablet
10 mg

EMO Serono, Inc.

Division of Neurology Drug Products

Donghao (Robert) Lu, Ph.D.

Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability.....	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Substance and Drug Product.....	6
B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Establishment Evaluation	9

Chemistry Review Data Sheet

1. **NDA 22-561**
2. **REVIEW NUMBER:** 3
3. **REVIEW DATE:** 24 November 2010
4. **REVIEWER:** Donghao (Robert) Lu, Ph.D.
5. **PREVIOUS DOCUMENTS:**

PREVIOUS DOCUMENTS	DOCUMENT DATE
NDA 22-561 (first submission) (refusal to file – eCTD lifecycle)	29-SEPT-09

6. **SUBMISSION(S) BEING REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-561 (Re- submission) (eCTD lifecycle)	27-APR-10
NDA 22-561 (Amendment 0046, CMC response)	28-OCT-10

7. **NAME & ADDRESS OF APPLICANT:**

NAME:	EMD Serono, Inc.
ADDRESS:	One Technology Place Rockland, MA 02370 USA
REPRESENTATIVE:	Peter DiRoma, VP Global Regulatory Affairs
TELEPHONE:	781-681-2887

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	(b) (4)
NON-PROPRIETARY NAME (USAN)	Cladribine
CODE NAME/ NUMBER (ONDC ONLY)	4912 Cladribine (b) (4) RWJ-26251-000 (Johnson & Johnson) EMD 280922 (Merck)
CHEMISTRY TYPE / SUBMISSION PRIORITY	6P

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Synthetic chlorinated analogue of the naturally occurring nucleoside deoxyadenosine

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: R_x OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN, Ph.Eur, USP): Cladribine

Chemical name (USP): 2-chloro-2'-deoxy-β-D-adenosine

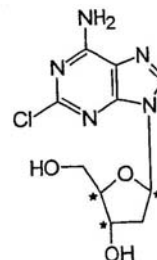
Other Name: 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine

(CAS) Registry Num: 4291-63-8

Structural Formula:

Mol. Formula: C₁₀H₁₂ClN₅O₃

Mol. Wt.: 285.69



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	II	Merck Serono	Cladribine drug substance	3	Adequate	

Note: The container closure system of Cladribine tablets is composed of a blister (b) (4). All the labeling information will be printed on the child-resistant tablet holder. The manufacturer of the finished product will perform an identification test (b) (4) and verify that the material received meets the purchase specification agreed with the supplier. Specification sheets (b) (4) were provided. The sponsor stated that the components meet the requirements of the Code of Federal Regulations – Food and Drugs, Title 21 and the European Directive 2002/72/EC.

The container closure system is adequately used for solid oral drug products – see CMC Review MaPP for review guidelines.

¹ Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Chemistry Assessment Section

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	22-NOV-10	E. Johnson (OC)
Methods Validation	No validation request	2-OCT-10	Donghao Lu, Ph.D.
ODS DMETS	Acceptable	6-AUG-10	Carol Holquist, RPh
EA	Acceptable	11-SEPT-10	Donghao Lu, Ph.D.
Micro Consultation	N/A		

The Chemistry Review for NDA 22-561

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product, Cladribine 10 mg immediate-release tablets, is recommended as APPROVAL from a CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of Drug Substance and Drug Product

1. Drug Substance

The drug substance is Cladribine. The general information on the chemical names, chemical structure, molecular formula and molecular weight can be seen on page 4 above. Cladribine is the drug substance described in DMF (b) (4) provided by Merck Serono Inc. (b) (4)

(b) (4). The impurity profile

Chemistry Assessment Section

including residual solvents was established and the possible impurities from the process were listed (see the following drug substance section). (b) (4)

(b) (4). The drug substance was physically and chemically stable based on the stability studies and it has a retest period of (b) (4) months.

2. Drug Product

The drug product is Cladribine 10 mg immediate-release tablets. It is intended for oral administration. The tablets are white round, biconvex tablets, engraved with “C” on one side and “10” on the other side of the tablets. Each tablet contains cladribine-2-hydroxypropyl- β -cyclodextrin complex (b) (4) in a proportion representative of 10 mg cladribine. It also contains sorbitol and magnesium stearate. The manufacturing process for Cladribine 10 mg tablets consists of the following

(b) (4) packing. The tablets are packed in a blister (b) (4) and sealed (b) (4)

(b) (4). All the labeling information will be printed on the tablet holder. The results from the stability studies indicated that the product is stable. Based on the stability results, a shelf life of 36 months is granted, when the product is stored at not more than 25°C.

B. Description of How the Drug Product is Intended to be Used

Cladribine 10 mg tablet drug product contains cladribine, a synthetic chlorinated analogue of the naturally occurring nucleoside deoxyadenosine. It is indicated for the treatment of relapsing remitting multiple sclerosis. Cladribine 10 mg tablets are given orally and are administered in treatment courses. A treatment course consists of a single oral daily dose of 10 or 20 mg over the first 4 or 5 days (b) (4), depending on the patient’s weight. For the treatment initiation, 2 consecutive courses at the beginning of a (b) (4) period are given. Initiation with 4 consecutive courses is recommended to be reserved for patients with more active disease. For the re-treatment, 2 consecutive courses at the beginning of a subsequent (b) (4) period are given. The product should be taken at least 3 hours before or after other oral medicines. The product can be taken before or after a meal. Cladribine 10 mg tablets are supplied in (b) (4) child-resistant (b) (4) (b) (4) blister packs. The product should be stored at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°- 86°F). The products have an expiration period (shelf life) of 36 months.

Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, EMO Serono, Inc. has submitted sufficient and appropriate information to be granted the APPROVAL status on the drug product.

III. Administrative**A. Reviewer's Signature**

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block



CHEMISTRY REVIEW



Chemistry Assessment Section

Establishment Evaluation (Acceptable)

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT					
Application:	NDA 22561/000	Sponsor:	EMD SERONO		
Org. Code:	120		1 TECHNOLOGY PL		
Priority:	3		ROCKLAND, MA 02370		
Stamp Date:	30-SEP-2009	Brand Name:	CLADRIBINE		
PDUFA Date:	28-NOV-2010	Estab. Name:			
Action Goal:		Generic Name:			
District Goal:	29-JAN-2010	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; CLADRIBINE; 10MG		
FDA Contacts:	T. BOUIE	Project Manager	301-796-1649		
	M. HEIMANN	Team Leader	301-796-1678		
Overall Recommendation:	ACCEPTABLE	on 22-NOV-2010	by E. JOHNSON	(HFD-320)	301-796-3334
	WITHHOLD	on 17-MAR-2010	by JOHNSONE		
Establishment:	(b) (4)				
DMF No:					
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE RELEASE TESTER				
Profile:	NON-STERILE BULK BY CHEMICAL SYNTHESIS	OAI Status:	NONE		
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	01-JUN-2010				
Decision:	ACCEPTABLE				
Reason:	BASED ON PROFILE				
Establishment:	CFN: 9610140	FEI: 3002806906			
	MERCK KGAA 64293 DARMSTADT, , GERMANY				
DMF No:					
Responsibilities:	FINISHED DOSAGE PACKAGER				
Profile:	TABLETS, PROMPT RELEASE	OAI Status:	NONE		
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	27-JUL-2010				
Decision:	ACCEPTABLE				
Reason:	DISTRICT RECOMMENDATION				
November 24, 2010 10:59 AM					
FDA Confidential - Internal Distribution Only					
Page 1 of 2					

Chemistry Assessment Section

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment:  (b) (4)

DMF No: 

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-NOV-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

DONGHAO R LU
11/24/2010

RAMESH K SOOD
11/24/2010

NDA 22-561

(Review #2)

 (b) (4)
(Cladribine)
Tablet
10 mg

EMO Serono, Inc.

Division of Neurology Drug Products

Donghao (Robert) Lu, Ph.D.

Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability.....	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Substance and Drug Product.....	6
B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Responses to the CMC Comments	9

Chemistry Review Data Sheet

1. **NDA 22-561**
2. **REVIEW NUMBER:** 2
3. **REVIEW DATE:** 3 November 2010
4. **REVIEWER:** Donghao (Robert) Lu, Ph.D.
5. **PREVIOUS DOCUMENTS:**

PREVIOUS DOCUMENTS	DOCUMENT DATE
NDA 22-561 (first submission) (refusal to file – eCTD lifecycle)	29-SEPT-09

6. **SUBMISSION(S) BEING REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-561 (Re- submission) (eCTD lifecycle)	27-APR-10
NDA 22-561 (Amendment 0046, CMC response)	28-OCT-10

7. **NAME & ADDRESS OF APPLICANT:**

NAME:	EMD Serono, Inc.
ADDRESS:	One Technology Place Rockland, MA 02370 USA
REPRESENTATIVE:	Peter DiRoma, VP Global Regulatory Affairs
TELEPHONE:	781-681-2887

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	(b) (4)
NON-PROPRIETARY NAME (USAN)	Cladribine
CODE NAME/ NUMBER (ONDC ONLY)	4912 Cladribine (b) (4) RWJ-26251-000 (Johnson & Johnson) EMD 280922 (Merck)
CHEMISTRY TYPE / SUBMISSION PRIORITY	6P

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Synthetic chlorinated analogue of the naturally occurring nucleoside deoxyadenosine

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: R_x OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN, Ph.Eur, USP): Cladribine

Chemical name (USP): 2-chloro-2'-deoxy-β-D-adenosine

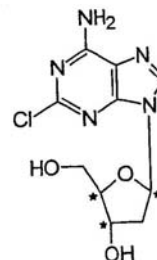
Other Name: 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine

(CAS) Registry Num: 4291-63-8

Structural Formula:

Mol. Formula: C₁₀H₁₂ClN₅O₃

Mol. Wt.: 285.69



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	II	Merck Serono	Cladribine drug substance	3	Adequate	

Note: The container closure system of Cladribine tablets is composed of a blister inserted into a child-resistant tablet holder (b) (4). All the labeling information will be printed on the child-resistant tablet holder. The manufacturer of the finished product will perform an identification test (b) (4) and verify that the material received meets the purchase specification agreed with the supplier. Specification sheets (b) (4) were provided. The sponsor stated that the components meet the requirements of the Code of Federal Regulations – Food and Drugs, Title 21 and the European Directive 2002/72/EC.

The container closure system is adequately used for solid oral drug products – see CMC Review MaPP for review guidelines.

¹ Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Chemistry Assessment Section

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	No validation request	2-OCT-10	Donghao Lu, Ph.D.
ODS DMETS	Acceptable	6-AUG-10	Carol Holquist, RPh
EA	Acceptable	11-SEPT-10	Donghao Lu, Ph.D.
Micro Consultation	N/A		

The Chemistry Review for NDA 22-561

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product, Cladribine 10 mg immediate-release tablets, is recommended as APPROVABLE from a CMC perspective, pending the Office of Compliance's recommendation. A final memorandum will be submitted when the recommendation is received.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of Drug Substance and Drug Product

1. Drug Substance

The drug substance is Cladribine. The general information on the chemical names, chemical structure, molecular formula and molecular weight can be seen on page 4 above. Cladribine is the drug substance described in DMF (b)(4) provided by Merck Serono Inc. (b)(4)

Chemistry Assessment Section



(b) (4)

(b) (4) The drug substance was physically and chemically stable based on the stability studies and it has a retest period of (b) (4) months.

2. Drug Product

The drug product is Cladribine 10 mg immediate-release tablets. It is intended for oral administration. The tablets are white round, biconvex tablets, engraved with “C” on one side and “10” on the other side of the tablets. Each tablet contains cladribine-2-hydroxypropyl- β -cyclodextrin complex (b) (4) in a proportion representative of 10 mg cladribine. It also contains sorbitol and magnesium stearate.



(b) (4)

(b) (4) The tablets are packed in a blister
(b) (4) and sealed

(b) (4)

(b) (4)

(b) (4) All the labeling information will be printed on the tablet holder. The results from the stability studies indicated that the product is stable. Based on the stability results, a shelf life of 36 months is granted, when the product is stored at not more than 25°C.

B. Description of How the Drug Product is Intended to be Used

Cladribine 10 mg tablet drug product contains cladribine, a synthetic chlorinated analogue of the naturally occurring nucleoside deoxyadenosine. It is indicated for the treatment of relapsing remitting multiple sclerosis. Cladribine 10 mg tablets are given orally and are administered in treatment courses. A treatment course consists of a single oral daily dose of 10 or 20 mg over the first 4 or 5 days (b) (4), depending on the patient’s weight. For the treatment initiation, 2 consecutive courses at the beginning of a first (b) (4) period are given. Initiation with 4 consecutive courses is recommended to be reserved for patients with more active disease. For the re-treatment, 2 consecutive courses at the beginning of a subsequent (b) (4) period are given. The product should be taken at least 3 hours before or after other oral medicines. The product can be taken before or after a meal. Cladribine 10 mg tablets are supplied in pre-packaged, child-resistant (b) (4) (b) (4) blister packs. The product should be stored at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°- 86°F). The products have an expiration period (shelf life) of 36 months.

Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, EMO Serono, Inc. has submitted sufficient and appropriate information to be granted the approvable status on the drug product. There were several CMC concerns on the original submission. The sponsor's responses to these concerns were adequate as described in following sections. The only pending issue, i.e. Office of Compliance's recommendation on facility inspections, will be addressed in the final memorandum.

III. Administrative**A. Reviewer's Signature**

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

Chemistry Assessment Section

Responses to the CMC Comments

Comment 1. To ensure the quality of the excipients from various sources, you need to implement a practice that upon receipt of the inactive components at the drug product manufacturing site from the qualified vendors, the excipients are tested at a minimum for identification and released.

Sponsor's response: The drug product manufacturer has a specific SOP which relates to the testing of excipients from their vendors. The manufacturer performs full USP release testing of all inactive excipients until at least three lots of each excipient are evaluated. At that time, a reduced testing plan may be adopted via an update to the specification of the excipient. Per procedure, this reduced testing plan must include identification testing. At this stage, the company has not adopted reduced testing on any of the excipients so full USP release testing is being performed. An English translation of the relevant SOP of the manufacturer is presented in Appendix 1. **CMC evaluation:** Adequate.

Comment 2. In validation summary for the determination of identity, content uniformity and assay in Cladribine 10 mg tablets by HPLC, you tested solution stability for up to 29 days. Your results of $\leq$ (b) (4) % change from initial indicated the solution was not stable at some time point. You need to determine the use time of the solution and list it in your method to limit the storage time for the test solutions.

Sponsor's response: During method validation testing, the sample solution stability was evaluated for the following prepared solutions when stored at room temperature:

Standard Solution: tested at 0, 1, 2, 7, 14, 21, and 29 days

API Solution: tested at 0, 1, 2, and 7 days

Cladribine Complex Solution: tested at 0, 1, 2, and 7 days

Cladribine Tablet Solution: tested at 0, 1, 2, 8, 15, 22, and 28 days

The study results are presented on the next page. The results displayed in the table demonstrate that the values at the various stability test points do not differ by more than 2% from the initial values for all samples tested. The samples can therefore be considered stable for up to 29 days (reference standard), 7 days (active ingredient and complex) and 28 days (tablets) respectively. **CMC evaluation:** Adequate.

Chemistry Assessment Section

Table 1:

Solution	% Recovery										
	Day 0	Day 1	Day 2	Day 7	Day 8	Day 14	Day 15	Day 21	Day 22	Day 28	Day 29
Standard 1	(b) (4)										
Standard 2											
API 1											
API 2											
API 3											
Complex 1											
Complex 2											
Complex 3											
Tablet 1											
Tablet 2											
Tablet 3											

Comment 3. Provide a sample for the (b) (4) tablet holder.

CMC evaluation: A sample for the (b) (4) tablet holder was received. The holder is considered to be adequately designed.

Comment 4. Submit the method validation package. The package should also include the information for the samples which will be provided upon request to FDA, related Certificates of Analysis and Material Safety Data Sheet (MSDS).

Sponsor's response: The information is provided. **CMC evaluation:** Adequate. Based on the information submitted in this NDA, it is not necessary to send any of the methods to FDA laboratories for validation.

Comment 5. On product labels, the product name should be displayed as "< Trade Name > tablets, 10 mg", instead of (b) (4).

Sponsor's response: All cladribine product labels will be revised to display as, "<Trade Name> tablets 10 mg". An example carton and tablet holder label is provided (see below). **CMC evaluation:** The sponsor adequately addressed our comment. However, the name on the labels is still not a conventional representation. The name is generally represented as "Trade Name (established name) tablets, strength". This will be addressed in the clinical division's labeling meetings.

2 Pages Draft Labeling have been Withheld In Full as B4
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/s/

DONGHAO R LU
11/08/2010

RAMESH K SOOD
11/08/2010

NDA 22-561

 (b) (4)
(Cladribine)
Tablet
10 mg

EMO Serono, Inc.

Division of Neurology Drug Products

Donghao (Robert) Lu, Ph.D.

Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability.....	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Substance and Drug Product.....	6
B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S. DRUG SUBSTANCE.....	9
P. DRUG PRODUCT	14
A. APPENDICES	42
R. REGIONAL INFORMATION	42
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	43
A. Labeling & Package Insert	43
B. Environmental Assessment Or Claim Of Categorical Exclusion	47
III. Establishment Evaluation Report.....	48
IV. List Of Deficiencies And Responses	51

Chemistry Review Data Sheet

1. **NDA 22-561**
2. **REVIEW NUMBER:** 1
3. **REVIEW DATE:** 5 October 2010
4. **REVIEWER:** Donghao (Robert) Lu, Ph.D.
5. **PREVIOUS DOCUMENTS:**

PREVIOUS DOCUMENTS	DOCUMENT DATE
NDA 22-561 (first submission) (refusal to file – eCTD lifecycle)	29-SEPT-09

6. **SUBMISSION(S) BEING REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-561 (Re- submission) (eCTD lifecycle)	27-APRIL-10

7. **NAME & ADDRESS OF APPLICANT:**

NAME:	EMD Serono, Inc.
ADDRESS:	One Technology Place Rockland, MA 02370 USA
REPRESENTATIVE:	Peter DiRoma, VP Global Regulatory Affairs
TELEPHONE:	781-681-2887

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	(b) (4)
NON-PROPRIETARY NAME (USAN)	Cladribine
CODE NAME/ NUMBER (ONDC ONLY)	4912 Cladribine (b) (4) RWJ-26251-000 (Johnson & Johnson) EMD 280922 (Merck)
CHEMISTRY TYPE / SUBMISSION PRIORITY	6P

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Synthetic chlorinated analogue of the naturally occurring nucleoside deoxyadenosine

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: R_x OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN, Ph.Eur, USP): Cladribine

Chemical name (USP): 2-chloro-2'-deoxy-β-D-adenosine

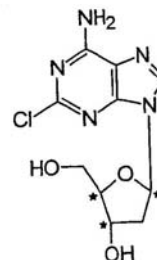
Other Name: 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine

(CAS) Registry Num: 4291-63-8

Structural Formula:

Mol. Formula: C₁₀H₁₂ClN₅O₃

Mol. Wt.: 285.69



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	II	Merck Serono	Cladribine drug substance	3	Adequate	

Note: The container closure system of Cladribine tablets is composed of a blister (b) (4)
 (b) (4)
 (b) (4) All the labeling information will be printed on the child-resistant tablet holder. The manufacturer of the finished product will perform an identification test (b) (4) (b) (4) and verify that the material received meets the purchase specification agreed with the supplier. Specification sheets (b) (4) were provided. The sponsor stated that the components meet the requirements of the Code of Federal Regulations – Food and Drugs, Title 21 and the European Directive 2002/72/EC.

The container closure system is adequately used for solid oral drug products – see CMC Review MaPP for review guidelines.

¹ Action codes for DMF Table:
 1 – DMF Reviewed.

- Other codes indicate why the DMF was not reviewed, as follows:
- 2 –Type 1 DMF
 - 3 – Reviewed previously and no revision since last review
 - 4 – Sufficient information in application
 - 5 – Authority to reference not granted
 - 6 – DMF not available
 - 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Chemistry Assessment Section

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	Pending		
ODS DMETS	Acceptable	6-AUG-10	Carol Holquist, RPh
EA	Acceptable	11-SEPT-10	Donghao Lu, Ph.D.
Micro Consultation	N/A		

The Chemistry Review for NDA 22-561

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product, Cladribine 10 mg immediate-release tablets, is recommended as APPROVABLE from a CMC perspective, pending the evaluation on sponsor's responses to our CMC comments and Office of Compliance's recommendation. A final memorandum will be submitted when these pending information and recommendation are received.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of Drug Substance and Drug Product

1. Drug Substance

The drug substance is Cladribine. The general information on the chemical names, chemical structure, molecular formula and molecular weight can be seen on page 4 above. Cladribine is the drug substance described in DMF (b)(4) provided by Merck

Chemistry Assessment Section

Serono Inc. (b) (4)
(b) (4)
(b) (4) The impurity profile including residual solvents was established and the possible impurities from the process were listed (see the following drug substance section). (b) (4)
(b) (4)
(b) (4) The drug substance was physically and chemically stable based on the stability studies and it has a retest period of (b) (4) months.

2. Drug Product

The drug product is Cladribine 10 mg immediate-release tablets. It is intended for oral administration. The tablets are white round, biconvex tablets, engraved with "C" on one side and "10" on the other side of the tablets. Each tablet contains cladribine-2-hydroxypropyl- β -cyclodextrin complex (b) (4) in a proportion representative of 10 mg cladribine. It also contains sorbitol and magnesium stearate. The manufacturing process for Cladribine 10 mg tablets consists of the following (b) (4)
(b) (4). The tablets are packed in a blister (b) (4)
(b) (4) and sealed (b) (4)
(b) (4) All the labeling information will be printed on the tablet holder. The results from the stability studies indicated that the product is stable. Based on the stability results, a shelf life of 36 months is granted, when the product is stored at not more than 25°C.

B. Description of How the Drug Product is Intended to be Used

Cladribine 10 mg tablet drug product contains cladribine, a synthetic chlorinated analogue of the naturally occurring nucleoside deoxyadenosine. It is indicated for the treatment of relapsing remitting multiple sclerosis. Cladribine 10 mg tablets are given orally and are administered in treatment courses. A treatment course consists of a single oral daily dose of 10 or 20 mg over the first 4 or 5 days (b) (4), depending on the patient's weight. For the treatment initiation, 2 consecutive courses at the beginning of a first (b) (4) period are given. Initiation with 4 consecutive courses is recommended to be reserved for patients with more active disease. For the re-treatment, 2 consecutive courses at the beginning of a (b) (4) period are given. The product should be taken at least 3 hours before or after other oral medicines. The product can be taken before or after a meal. Cladribine 10 mg tablets are supplied in (b) (4) child-resistant (b) (4) (b) (4) blister packs. The product should be stored at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°- 86°F). The products have an expiration period (shelf life) of 36 months.

Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, EMO Serono, Inc. has submitted sufficient and appropriate information to be granted the approvable status on the drug product. However, there were several CMC concerns that were sent to the sponsor on October 18, 2010 (see the list of comments at the end of this document). Their responses and the CMC evaluations for these responses will be described in the final memorandum. Office of Compliance's recommendation on facility inspections will also be provided in the final memorandum.

III. Administrative**A. Reviewer's Signature**

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

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Chemistry Assessment Section

APPENDICES

The appendix section (see M2 QOS section) included the information on the adventitious agent safety evaluation. No materials of human or animal origin are included in the drug substance or used in the synthesis of the drug substance. None of the excipients used for Cladribine tablets are from human or animal origin. Transmissible Spongiform Encephalopathy (TSE) - free declaration of the excipients was provided. There is no novel excipient used in the formulation of Cladribine 10 mg tablets. The microbial limits of the drug substance and drug product are controlled through their individual specifications. There is no potential contamination with other nonviral adventitious agents. **Evaluation:** Adequate.

REGIONAL INFORMATION**R.1 Executed Batch Records**

In this section, Executed Production Records (EPRs) for representative batches used in Phase III clinical, bioavailability, bioequivalence, or primary stability studies and supporting production information must be provided (21 CFR 314.50(d)(1)(ii)(b)). For NDA submissions, an EPR for a batch manufactured on at least a pilot scale should be submitted.

A number of drug product batches in several different formulations were used during the development of Cladribine products. The executed production records for some of these products were provided. **Evaluation:** Adequate.

R.2 Comparability Protocols

There was no comparability protocol proposed for Cladribine tablets. **Evaluation:** Adequate. Comparability protocols are optional.

R.3 Methods Validation Package

The information for the analytical methods used in the manufacture and testing of Cladribine tablets was provided in the submission. However, the information on method validation package was not provided. The package should also include the samples which will be provided upon request to FDA, related Certificates of Analysis and Material Safety Data Sheet (MSDS). **Evaluation:** A methods validation package must be submitted in the application (21 CFR 314.50(e)(2)(i) and 314.94(a)(10)). See the comment to sponsor below.

CMC comment: Submit the method validation package. The package should also include the information for the samples which will be provided upon request to FDA, related Certificates of Analysis and Material Safety Data Sheet (MSDS).

Chemistry Assessment Section

II. Review Of CTD -- Module 1: Prescribing Information**A. Labeling****A.1 Trade name**

The ODS DMETS trade name consult has not completed their review and recommendation.

A.2 Label and Package Insert

Evaluation: Adequate (Note: CMC reviewer reviews the “description” and “how supplied” sections.).

DESCRIPTION

(b) (4)

Chemistry Assessment Section

(b) (4)

Cladribine is stable at basic and neutral pH (b) (4). The ionization behavior of the molecule over the pH range 0 to 12 is characterized by a single pKa of approximately 1.21.

[Product] tablets contain the following inactive ingredients: hydroxypropyl betadex, magnesium stearate, sorbitol powder.

HOW SUPPLIED/STORAGE & HANDLING

16.1 How Supplied

[Product] tablets, 10 mg, are uncoated, white, round, biconvex, (b) (4) engraved with a "C" on one side and "10" on the other side.

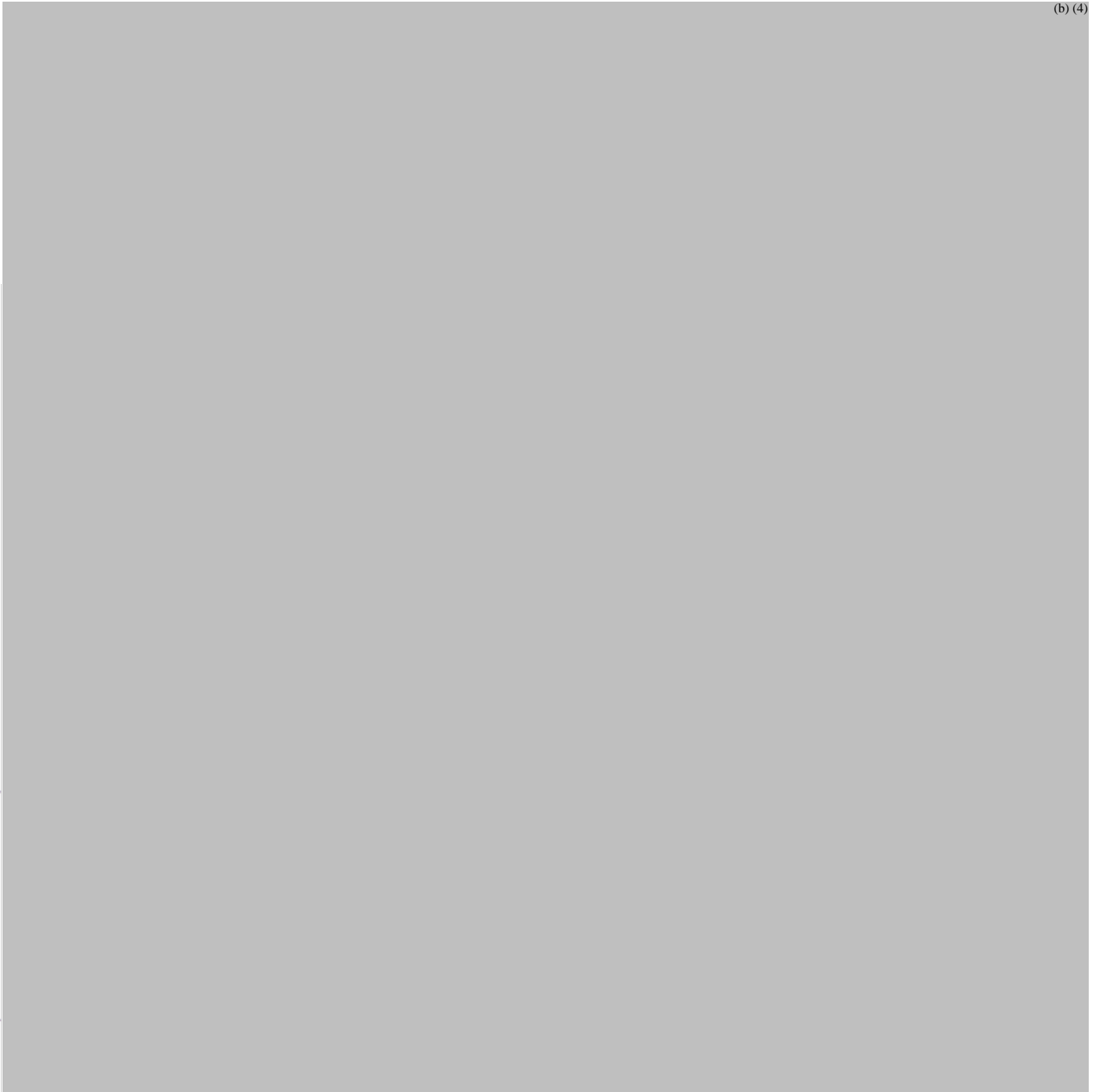
(b) (4)

16.2 Storage and Handling

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store in original container.

(b) (4)

Chemistry Assessment Section

A.3 Label

Chemistry Assessment Section

(b) (4)

Evaluation: The labels are designed adequately. However, one comment will be sent: On product labels, the product name should be displayed as “< Trade Name > tablets, 10 mg”, instead of  ^{(b) (4)}.

Chemistry Assessment Section

B. Environmental Assessment Or Claim Of Categorical Exclusion

The categorical exclusion was requested. Statements were provided that “As per the requirements, the Environmental Introduction Concentration (EIC) entering the aquatic environment from patient use is calculated without including consideration of metabolism or environmental depletion mechanisms that occur in the waste water treatment process. The EIC from patient use is based on the highest annual quantity of the active moiety expected to be produced for use during the next years and the quantity used in all dosage forms and strengths. The EIC from patient use of cladribine, based on the production estimate of (b) (4) kg for the USA, is (b) (4) ppb. Because the EIC is below 1 ppb, the data are in compliance with the exclusion criteria and the cladribine application qualifies for a categorical exclusion. To our knowledge, no extraordinary circumstances exist that require the submission of an EA.” **Evaluation:** Adequate.

III. Establishment Evaluation Report

Pending as 10/27/2010

Chemistry Assessment Section

IV. Critical Review Issues (from IQA and addressed in this review)**Drug Substance**

No critical issues were identified during the initial assessment. As noted above, however, the applicant proposes use of EP, rather than USP, analytical methods for drug substance. The reviewer should consult MaPP 5310.7 *Acceptability of Standards from Alternative Compendia*.

Note: The drug substance DMF is currently checked out to Jean Tang (DPE) for a supplement review. The reviewer assigned to this NDA should coordinate with her to ensure that the DMF is reviewed in a timely manner to support both applications.

Drug Product

With respect to the drug product formulation:

- It is recommended that the ONDQA Biopharmaceutics team be consulted regarding the appropriateness of the documentation provided to support the change in formulation from the clinical tablets to the proposed commercial tablets. Two issues are noted:
 - The quantitative change from the clinical tablets to the commercial formulation is within the limits for a SUPAC Level 2. The applicant has provided multimedia dissolution profiles to support the proposed formulation change from the clinical tablets to the commercial formulation. Justification for this is based on the applicant's classification of cladribine as a high solubility, low permeability drug (BCS Class 3). For a Class 3 drug, the required documentation is that for a SUPAC Level 2, Case B change, i.e., comparative dissolution profiles. The applicant has previously been advised that if cladribine does not meet the criteria for Case B a bioequivalence study would be needed. The appropriateness of the BCS classification, and the applicant's conclusion that a bioequivalence study is not required, should be evaluated by the Biopharmaceutics reviewer.
 - The proposed formulation change (b) (4) which may have effects on the intestinal tract. The applicant states in Module 3.2.P.2.1.6.1 that (b) (4) (b) (4) is well below the dose where an effect on the gastrointestinal tract is expected. This statement should be assessed by the Biopharmaceutics reviewer.
- It is noted that the labeling of one product containing β -HPCD, i.e., Sporanox® (itraconazole) Oral Solution, contains a warning related observation of pancreatic adenocarcinomas in a rat carcinogenicity study. The nonclinical reviewer should be consulted to confirm the acceptability of β -HPCD in the proposed product.

Chemistry Assessment Section

- The drug product is an immediate release tablet. The primary issues with respect to manufacture and control of the product are related to formation and characterization of the lyophilized cladribine/ β -HPCD complex. Therefore, it is recommended that the information supporting characterization of the cyclodextrin complex and the impact of manufacturing process parameters on the quality of the resulting product be examined closely.

Additional issues

- Administrative: A claim for categorical exclusion from environmental assessment for cladribine release tablets is included in Module 1 of the application.
- Establishment Evaluation: A full list of manufacturing sites and contract testing facilities is appended to the revised Form 356h (13-Oct-2009 amendment). Refer to Attachment 1. All sites have been entered into EES, and were submitted for facility evaluation on 14-Oct-2009.
- Labeling/Established Name: The active ingredient is not a salt. Thus, there are no issues related to consistency between the established name “cladribine tablets” and labeled potency.
- Methods Validation: Although the application includes descriptions of the proposed analytical methods and supporting validation data; the required methods validation package is not included in Module 3.2.R. It is recommended that the applicant be reminded to submit the MV package in the 74 Day letter.

Chemistry Assessment Section

List Of CMC Comments

1. To ensure the quality of the excipients from various sources, you need to implement a practice that upon receipt of the inactive components at the drug product manufacturing site from the qualified vendors, the excipients are tested at a minimum for identification and released.
2. In validation summary for the determination of identity, content uniformity and assay in Cladribine 10 mg tablets by HPLC, you tested solution stability for up to 29 days. Your results of $\leq$ (b) (4) % change from initial indicated the solution was not stable at some time point. You need to determine the use time of the solution and list it in your method to limit the storage time for the test solutions.
3. Provide a sample for the (b) (4) tablet holder.
4. Submit the method validation package. The package should also include the information for the samples which will be provided upon request to FDA, related Certificates of Analysis and Material Safety Data Sheet (MSDS).
5. On product labels, the product name should be displayed as “< Trade Name > tablets, 10 mg”, instead of (b) (4).

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/s/

DONGHAO R LU
10/28/2010

RAMESH K SOOD
10/28/2010