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RESEARCH**

APPLICATION NUMBER:
202317Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	12 August 2013
From	R. Angelo de Claro, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 202317 (second review cycle)
Applicant	Ceptaris Therapeutics, Inc.
Date of Submission	27 February 2013
PDUFA Goal Date	27 August 2013
Proprietary Name / Established (USAN) names	Valchlor
Dosage forms / Strength	0.016% gel
Applicant's Proposed Indication	Treatment of (b) (4) Stage IA, IB (b) (4) mycosis fungoides type cutaneous T-cell lymphoma
Recommended:	Approval

Material Reviewed/Consulted	Reviewer
Medical Officer Review	R. Angelo de Claro, MD
Statistical Review	Yun Wang, PhD/Mark Rothmann, PhD/Rajeshwari Sridhara, PhD
Pharmacology Toxicology Review	Natalie Simpson, PhD/Haleh Saber, PhD
ONDQA-CMC and Biopharmaceutic Reviews	Anne Marie Russell, PhD /Gaetan Ladouceur, Ph.D/Janice Brown, MS/Ali Al Hakim, PhD
Microbiology Review	Stephen Langille, PhD
Clinical Pharmacology Review	Rachelle Marie Lubin, PharmD/Julie Bullock, PharmD
OSI/DG CPC	Anthony Orenca, MD
OSE/DRISK	Suzanne Robottom, PharmD/Cynthia LaCivita, PharmD
OSE/DMEPA	Kevin Wright, PharmD/Yelena Maslov, PharmD
OSE/DPV	Afrouz Nayernama, PharmD/Tracy Salaam, PharmD
Patient Labeling Team (DMPP)	Karen Dowdy, RN, BSN/Barbara Fuller, RN, MSN, CWO CN

1. Introduction

The Applicant submitted a Class 2 Resubmission on 27 February 2012 to address complete response issues with the 505(b)(2) application. FDA issued the Complete Response letter on 4 May 2012. The complete response issues included clinical, non-clinical, product quality, and regulatory issues. All of these complete response issues have been resolved with the Applicant's resubmission.

The NDA is supported by one randomized, observer-blinded, clinical trial (Protocol 2005NMMF-201-US) which was designed to determine whether the Ceptaris formulation (in a proprietary propylene glycol base) of 0.016% mechlorethamine (equivalent to 0.02% mechlorethamine HCl) was non-inferior to a pharmacy-compounded formulation of 0.02% mechlorethamine HCl in an Aquaphor base in 260 patients with Stage IA, IB, or IIA mycosis fungoides-type cutaneous T-cell lymphoma. All patients were started on once daily treatment (with the frequency adjusted for toxicity) in an outpatient setting for up to 12 months. The clinical trial was conducted under Special Protocol Assessment agreement with the FDA.

CDTL Recommendation: The recommendation of the CDTL review is Regular Approval, contingent upon labeling agreement between the Agency and the Applicant.

2. Background

Topical application of mechlorethamine (nitrogen mustard [NM]) for treatment of mycosis fungoides has been used in practice since the 1950s. This community practice of off-label use of topical nitrogen mustard has led to a recommendation by the National Comprehensive Cancer Network (NCCN) for the use of topical nitrogen mustard therapy in the treatment of limited/localized as well as generalized skin involvement of mycosis fungoides.

A tabulated summary of the clinical experience of topical mechlorethamine for the treatment of mycosis fungoides is shown in Table 1.

Table 1. Efficacy Results for Topical Mechlorethamine from Published Literature

Reference	Description	Results
Vonderheid, 1989	Design: Retrospective analysis of medical records Drug: NM 0.01-0.02%, aqueous formulation	CR rates: St IA 80% (71/89), St IB 68% (45/66), St IIA 28/46 (61%) Definition of CR: complete disappearance of clinically detectable disease for at least 2 weeks and was confirmed in most cases by skin biopsy specimens
Ramsay, 1988	Design: Retrospective analysis of medical records Drug: NM 0.017% aqueous formulation	CR Rates at 2 years: St I 76% (48/63), St II 45% (20/44) Definition of CR: clearance of all lesions
Kim, 2003	Design: Retrospective analysis of medical records Drug: NM 0.01-0.02%, aqueous formulation (prior to 1980), ointment formulation (post 1980)	Response Rates: T1 disease (N=107): 65% CR (N=70), 28% PR (N=30), 93% CR+PR T2 disease (N=88): 34% CR (N=30), 38% PR (N=33), 72% CR+PR Definition of Responses: CR was defined as complete clinical regression of all MF lesions; PR, as any response less than complete but greater than 50% clinical improvement.
de Quatrebarbes, 2005	Design: Single arm prospective clinical trial Drugs: NM 0.02% aqueous formulation and betamethasone cream	CR Rate: St IA 61% (20/33), St IB 58% (15/26), St IIA 40% (2/5) Definition of CR: CR was defined as the disappearance of all clinical lesions of MF.

The safety issues with use of topical mechlorethamine include dermatitis and secondary cancers (Kim 2003, Vonderheid 1989, Ramsay 1988). Topical mechlorethamine may result in

severe cutaneous reactions such as severe erythema, blistering, ulceration, and secondary complications such as infections. These safety issues are included in the Box Warning for the reference listed drug, Mustargen, which states “Due to the toxic properties of mechlorethamine (e.g., corrosivity, carcinogenicity, mutagenicity, teratogenicity), special handling procedures should be reviewed prior to handling and followed diligently”.

For this 505(b)(2) application, the Applicant submitted a patent certification regarding Mustargen, the Reference Listed Drug for this application.

3. CMC/Device

The following is from the executive summary of the CMC primary review for the complete response resubmission.

A. Description of the Drug Substance and Drug Product

(1) Drug Substance

Mechlorethamine hydrochloride has been commercially available for over 50 years using an old manufacturing process. However, for this NDA a new manufacturing process was established (b) (4). This new process has produced high quality drug substance in a reproducible manner.

(b) (4)

A retest period (b) (4) is supported by drug substance stability data.

(2) Drug Product

The drug product is supplied by University of Iowa Pharmaceuticals (UIP) as a nonsterile gel with a 0.016% concentration of mechlorethamine packaged in a multi-use 60 gram tube for topical administration. Inactive ingredients include: Diethylene Glycol Monoethyl Ether (diEGEE (b) (4)), Propylene Glycol, Isopropyl Alcohol, glycerin, lactic acid (b) (4), hydroxypropylcellulose (HPC (b) (4)), sodium chloride, (b) (4), Menthol, Edetate Disodium (b) (4) and Butylated Hydroxytoluene (BHT). All are compendial and none are novel.

(b) (4)

Viscosity is monitored during manufacturing. Samples are collected for assay and manufacturing continues at risk while they are analyzed offsite.

The clinical product was supplied (b) (4) in (b) (4) tubes. Comparability between the clinical (b) (4) lots and the proposed commercial UIP lots was not demonstrated in the application due to inadequate characterization of the clinical lots. Consequently, there is no adequate bridge between the clinical product administered to patients in the pivotal trial and the commercial product proposed for market.

Based on submitted stability data, an 18-month expiry period has been granted with storage at -20C. Also, an in-use period of 60 days has been granted with storage at refrigerated temperatures and daily excursions to room temperature for no more than one hour.

Recommendation and Conclusion from Primary CMC review: This is a recommendation to approve this product from a Chemistry, Manufacturing and Controls (CMC) standpoint.

Additional clarification was provided in the secondary CMC review from Ali Al Hakim.

In Chemistry Review #2, the CMC reviewer makes additional comments regarding clinical issues (information located on pages 8, 11, 12-14, 32) It is this reviewer's assessment that the CMC reviewer's comments regarding clinical issues and related discussion including e-mails are not directly relevant to the overall quality determination, since the CMC review deals with the assurance of quality of the drug product and not with a direct determination of safety and/or efficacy.

In conclusion, while I do concur with the primary reviewer's recommendation of approval, I do not concur with the primary CMC reviewer's stated outstanding deficiency raised in CMC review # 2. Based on my assessment and consistent with the primary reviewer's overall recommendation, the Applicant's response to all previous CMC deficiencies is satisfactory and there are no outstanding CMC deficiencies that remained unresolved.

Recommendation from Secondary CMC review: The NDA is recommended for approval from CMC perspective.

4. Nonclinical Pharmacology/Toxicology

The following is from the executive summary of the Pharmacology-Toxicology review for this complete response resubmission.

Conclusion and Recommendation: Recommending approval.

The proposed specifications are acceptable for the impurities. There are no pharmacology/toxicology issues to preclude approval of VALCHLOR for the proposed indication.

The labeling of nonclinical sections for VALCHLOR will be based on the label for the listed drug, MUSTARGEN, and published literature on nitrogen mustard may be used to supplement the labeling of VALCHLOR, if necessary.

5. Clinical Pharmacology/Biopharmaceutics

The following is from the executive summary of the Clinical Pharmacology review for this resubmission.

A complete response was issued to the sponsor on May 5, 2012. The sponsor resubmitted their application on February 27, 2013 (SDN 36). There were no new clinical pharmacology related data to support this resubmission.

Recommendation: The Office of Clinical Pharmacology/Division 5 considers this resubmission of NDA 202317 to be acceptable provided the Applicant and the Agency come to an agreement regarding the labeling language.

6. Clinical Microbiology

The following is from the executive summary of the product quality microbiology review for the first review cycle. There were no new microbiology data submitted in the complete response resubmission.

The drug product is formulated into a (b) (4) gel containing (b) (4) isopropanol. The drug product is manufactured under GMP conditions and is unlikely to support microbial growth. No product quality microbiology deficiencies were identified based upon the information provided.

Recommendation: NDA 202-317 is recommended for approval from the standpoint of product quality microbiology.

7. Clinical/Statistical- Efficacy

The Applicant seeks the approval for Valchor, mechlorethamine 0.016% (equivalent to 0.02% mechlorethamine HCl) in a propylene glycol gel (PG), for the second-line treatment of stage I (b) (4) MF for adults (> 18 years). This NDA was based on a single clinical trial, 2005NMMF-201-US (Study-201), a randomized, single-blinded (observer-blinded), active-controlled clinical trial of topical mechlorethamine in patients with early stage mycosis fungoides. The primary objective of the study was to evaluate the efficacy of topical application of VALCHLOR as compared to mechlorethamine HCl 0.02% in an Aquaphor ointment (COMPARATOR) in subjects with stage I or IIA MF.

Patients were evaluated for a response on a monthly basis for the first 6 months and then every 2 months for the last 6 months using the Composite Assessment of Index Lesion Severity (CAILS) score). The CAILS score is obtained by adding the severity score of each of the

following categories for up to 5 index lesions: erythema, scaling, plaque elevation, and surface area. Severity was graded from 0 (none) to 8 (severe) for erythema and scaling; 0 to 3 for plaque elevation; and 0 to 9 for surface area. A response was defined as greater than or equal to 50% reduction in baseline CAILS score which was confirmed at the next visit at least 4 weeks later. Non-inferiority was considered to have been demonstrated if the lower bound of the 95% confidence interval (CI) around the ratio of response rates (VALCHLOR/COMPARATOR) was greater than or equal to 0.75.

Patients were also evaluated using the Severity Weighted Assessment Tool (SWAT). The SWAT score is derived by measuring each involved area as a percentage of total body surface area (%BSA) and multiplying it by a severity weighting factor (1=patch, 2=plaque, 3=tumor or ulcer). A response was defined as greater than or equal to 50% reduction in baseline SWAT score which was confirmed at the next visit at least 4 weeks later.

Statistical Issues and Methodologies: A critical statistical and clinical issue was the major protocol violation involving randomization that occurred at a single site (New York University [NYU]), where patients were assigned to treatment arm based on disease stage, and not by the randomization codes. All 18 patients from NYU were excluded from the efficacy analysis of the primary and secondary efficacy endpoints.

Using the likelihood based methods of Miettinen and Nurminen, an estimate of ratio of CAILS response rates along with its 95% confidence limit was calculated for the intent-to-treat population excluding data from the NYU clinical trial site. If the lower 95% confidence limit is greater than 0.75, then it will be concluded that by using the ratio of response rates, the 0.02% NM in the PG formulation is non-inferior to the AP formulation.

The secondary endpoint, SWAT response was analyzed using the same method as for CAILS response. Time to CAILS response, duration of CAILS response, and time to CAILS progression were summarized by Kaplan-Meier method.

The following is an executive summary of the efficacy review issues identified by the Clinical and Statistical Teams. Refer to Table 2 for the key efficacy findings.

Table 2. Efficacy Results for Clinical Trial 2005NMMF-201-US

Response Rates	VALCHLOR N=119	COMPARATOR N=123
CAILS Overall Response (CR+PR), % (N)	60%	48%
Complete Response (CR)	14%	11%
Partial Response (PR)	45%	37%
SWAT Overall Response (CR+PR), %(N)	50%	46%
Complete Response (CR)	7%	3%
Partial Response (PR)	43%	43%

Statistical and Clinical Reviewers’ Conclusions:

- a. The observed CAILS response rates ratio (VALCHLOR/COMPARATOR) was 1.24 with lower 95% confidence limit of 0.98, which was greater than the pre-specified non-inferiority threshold of 0.75.
- b. The SWAT analysis results were consistent with CAILS results in supporting non-inferiority of VALCHLOR to COMPARATOR.

8. Safety

The following is an executive summary of the findings of the Safety Review Team. The safety of Valchlor was evaluated in 255 patients with early stage mycosis fungoides in one randomized, active-control, observer-blinded clinical trial (Clinical Trial 2005NMMF-201-US). A summary of the key safety results from this clinical trial are listed below.

- Topical mechlorethamine was applied once daily. The duration of treatment was similar between treatment arms with a median of approximately 52 weeks. Fifty-five percent of patients required suspension of treatment or reduction of dose frequency during the clinical trial.
- The most common adverse event was dermatitis, a known adverse event with topical mechlorethamine therapy. Dermatitis was reported in 57% of patients in the Valchlor arm and 58% in the control arm. Moderately-severe or severe dermatitis was reported in 23% of patients in Valchlor arm and 17% in control arm. Most cases of dermatitis resolved, however 9% in Valchlor arm and 13% in control arm had residual dermatitis at the end of the clinical trial.
- Eleven of 255 (4%) patients developed non-melanoma skin cancer (nMSC) during the course of the clinical trial or during long-term follow-up. Eight patients developed nMSC during treatment with topical mechlorethamine. Risk factors associated with development of nMSC include age \geq 65 years and prior history of nMSC, but not duration of MF or treatment type (Valchlor vs. control formulation).

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held for this application.

10. Pediatrics

Valchlor is exempt from the pediatric study requirements in 21 CFR 314.55 because Valchlor has orphan status. FDA granted Orphan Drug designation on 12 August 2004 for Valchlor for the treatment of mycosis fungoides. Valchlor has not been evaluated in pediatric patients.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Exclusivity or Patent Issues of Concern:** None

DHP received clearance from for action from a 505(b)(2) perspective on 23 July 2013. Beth Duvall notified DHP that the application was discussed at the 505(b)(2) clearance meeting on 22 July 2013, and that clearance had been granted.

- **Financial Disclosures:** Adequate and complete.
- **Other GCP Issues:** None
- **Office of Scientific Investigation (OSI) Audits: The following is an executive summary of the findings arising from DSI visits to the following sites:**

1. Madeleine Duvic, M.D. /Study Protocol 2005NMMF-201-US/Site #002 at Houston, TX.

A total of 65 subjects were screened, 61 subjects were randomized and completed the study. An audit of 18 randomized subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms (CRFs), study drug accountability logs, study monitoring visits and correspondence. Informed consent documents and Applicant generated correspondence were also inspected.

2. Matthew B. Zook, M.D., Ph.D./Study Protocol 2005NMMF-201-US/Site #002 at Rockledge, PA. A total of 28 subjects were screened, 15 subjects were randomized, and 11 subjects completed the study. An audit of 15 randomized subjects' records was conducted.

3. Bruce Strober, M.D., Ph.D./ Study Protocol 2005NMMF-201-US/Site #007 at New York, NY (Previous address during conduct of this study); Farmington, CT (present address). A total of 24 subjects were screened, 18 were randomized and 6 subjects completed the study. [Note: 4 subjects were voluntarily withdrawn, 4 subjects were withdrawn]

OSI Medical Officer Comments: Per OSI consult and discussions with the Division of Hematology Products (DHP), there was an Applicant-acknowledged incorrect randomization of 16 patients at the New York University (NYU) Site. The study coordinator at this clinical investigation site (Site #007) did not follow the randomization code. DHP wanted to verify the accuracy of the Applicant's assessment during the clinical audit. This error in randomization was acknowledged in the NDA submission to the Agency in Section 10.2 Protocol Deviations of the Clinical Study Report. This was also discussed during the Applicant's orientation face-to-face meeting with DHP on October 6, 2011. As acknowledged by the Applicant and submitted in its NDA, this problem occurred exclusively at Site #007 and not systematically throughout the study.

The above finding was corroborated during two Office of Regulatory Affairs (ORA) field visits: (a) January 17-20, 2012 with the senior clinical research coordinator for Study Protocol

2005NMMF-201-US at Site #007 and (b) February 22, 2012, with Dr. Bruce Strober, the original principal investigator for this study (b) (4) Reference ID: 3106796, Page -6 NDA 202317 nitrogen mustard (b) (4) Clinical Inspection Summary. Per ORA field staff, the original study research nurse, who was the only study-unblinded member of this clinical trial investigation, did not follow proper procedures for randomization.

The study-unblinded research nurse was involved in randomizing and dispensing of the test article. This original study research nurse assigned the PG formulation to all patients in stratum one with Stage 1A disease and AP formulation to all patients in stratum two with Stage 1B and IIA disease. This was discovered by another study-unblinded clinical research coordinator, who took over research responsibilities from the original research nurse, and reported the error to the originally study-blinded clinical site principal investigator, who then informed the Applicant. As part of the clinical site's preventive action plan per ORA, the Applicant was notified and the NYU Dermatopharmacology Unit of the Department of Dermatology transferred all drug dispensation responsibilities to the NYU investigative pharmacy. In summary, ORA confirmed that the error in randomization, noted by the Applicant in their NDA submission and during the ORA clinical audit with Dr. Strober, was an isolated incident at Site #007 with respect to Study Protocol 2005NMMF-201-US.

OSI Overall Assessment of Findings and Recommendations

Three clinical investigator sites were inspected in support of this application for Study Protocol 2005NMMF-201-US. No regulatory violations were noted or issued. Based upon review of 8 inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication. OSI defers to DHP regarding the decision to include or exclude these known, incorrectly randomized patients, as identified in the NDA submission, in their final analyses and deliberations.

- **Other discipline consults:** None
- **Any other outstanding regulatory issues:** None

12. Labeling

- **Proprietary name:** On 26 June 2013, DMEPA concluded that Valchlor™ was acceptable and the DMEPA review and proprietary name granted letter are in DARRTS.
- **OSE/DRISK.** The Applicant submitted voluntarily a proposed REMS consisting of a Medication Guide (b) (4) The following is from the conclusion of the DRISK team

DRISK and DHP agree that a REMS is not required for mechlorethamine gel at this time. Please convey to the sponsor that they can disseminate the proposed DHCP letter outside of a REMS if they choose.

If new safety information becomes available or use includes a new patient population, the risk-benefit of this drug should be re-evaluated.

- **OSE/DPV.** OSE/DPV recommended an enhanced pharmacovigilance plan for secondary exposure adverse events. Refer to Section 13 for the agreed-upon post-marketing plan with the Applicant.

In order to best assess postmarketing reports of secondary exposure, we are requesting that Ceptaris, the sponsor of this topical formulation of mechlorethamine, perform enhanced pharmacovigilance (PV) for a period of up to 2 years after this notification. The primary enhancements to the current routine PV paradigm for these products in this proposal are the following commitments:

Submit expedited reporting of both serious and non-serious outcomes for all initial and follow-up adverse drug experiences as Postmarketing 15-day “Alert Reports” indicative of secondary exposure in individuals other than the prescribed patient.

Submit a summary, evaluation, and line listing of all secondary exposure events from postmarketing sources, including consumer reports, solicited reports, and foreign reports in the PADER/PBRER.

- **OSE/DMEPA.** The DMEPA review for container labels, carton and insert labeling was put into DARRTS on 23 July 2013. Their recommendations for changes to the carton and container were sent to the Applicant.
- **Patient Labeling Team.** A patient labeling consult was requested. The patient labeling group participated in the labeling discussions. Refer to the Patient Labeling review in DARRTS.
- **OPDP/DDMAC.** DDMAC consult was requested. DDMAC attended labeling meetings and provided input. Refer to DDMAC review in DARRTS.
- **Prescriber Labeling:** At the time of completion of the CDTL review, labeling negotiations are ongoing between the Agency and the Applicant. The remaining labeling issues include clarification of the wording for the indication, dosage and administration, adverse reactions, and a new Applicant proposal for description of the time-course for safety and efficacy findings in the labeling.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** Regular Approval, contingent upon labeling agreement between the Agency and the Applicant
- **Risk Benefit Assessment:** The CDTL finds a favorable benefit-risk profile for Valchlor for the indication: [REDACTED] (b) (4). This recommendation is based from the efficacy and safety results of the single randomized clinical trial (2005NMMF-201-US) included in the application.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

DHP and DRISK concluded that a REMS is not required for approval.

Recommendation for MedGuide: DHP decided that a MedGuide will be included with the labeling to ensure patients receive written advice about the risks of Valchlor.

- **Recommendation for other Postmarketing Requirements and Commitments**

Agreement was reached between the Agency and the Applicant for an enhanced pharmacovigilance plan as a post-marketing requirement (PMR). The Applicant submitted the PMR language on 7 August 2013.

NDA #/Product Name: 202317 Valchlor

PMR Description: An assessment and analysis of spontaneous reports of inadvertent exposure of anyone other than the patient who has been exposed to Valchlor (Mechlorethamine Hydrochloride) Gel 0.016%. Specialized follow-up should be obtained on these cases to collect additional information on the events. This **enhanced pharmacovigilance** should continue for a period of 2 years from the date of approval. The following components should be assessed and analyzed in a final report:

- Expedited reports of both serious and non-serious outcomes for all initial and follow-up adverse drug experiences resulting from secondary exposure to the skin, mucous membranes, and eyes of individuals other than the patients being treated submitted as Postmarketing 15-day “Alert Reports”;

- A summary and line listing of all secondary exposure events from postmarketing sources, including consumer reports, solicited reports, and foreign reports submitted in each PADER/PBRER; and
- Documentation of attempts to contact all reporters of events, and obtain findings about the events, including but not limited to - the circumstances leading to the exposure, ultimate highest severity of the exposure, and resolution status.

Submit the protocol for FDA review and concurrence before commencing the process and before the “Final protocol date below”

PMR Schedule Milestones:	Final Protocol / Plan Submission:	<u>10/2013</u>
	Study Completion:	<u>10/2015</u>
	Final Report Submission:	<u>12/2015</u>

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/s/

ROMEO A DE CLARO
08/12/2013