CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202317Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	202317
Applicant Name	Ceptaris Therapeutics, Inc.
Date of Submission	2/27/13
PDUFA Goal Date	8/27/13
Proprietary Name / Established (USAN) Name	Valchor/Nitogen Mustard Gel 0.02%
Dosage Forms / Strength	0.02% Topical Gel
Proposed Indication(s)	For the treatment of Mycosis Fungoides (CTCL (b) (4)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Angelo DeClaro, M.D..
Statistical Review	Qing Xu, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Yash Chopra, PhD./ Natalie Simpson, Ph.D./Haleh Saber, Ph.D.
CMC Review/OBP Review	Gaetan Ladoucer, Ph.D./Anne Marie Russell, Ph.D./Janice Brown, M.S. /Ali Al-Hakim, Ph.D./ Sarah Pope Miksinski, Ph.D.
Microbiology Review	Stephen E. Langille, Ph.D./Bryan Riley, Ph.D.
Clinical Pharmacology Review	Rachelle Lubin, Ph.D./Julie Bullock, Pharm.D.
DDMAC	James Dvorsky
DSI	Anthony Orencia, M.D.
CDTL Reviews	Angelo DeClaro, M.D.
OSE/DMEPA	Kevin Wright, Pharm.D./Yelena Maslov, Pharm.D./Scott Dallas, R.Ph.
OSE/Epidemiology	
OSE/DRISK	Suzanne Berkman Robottom, Pharm.D./ Cythina LaCivita, Pharm.D./Claudia Manzo, Pharm.D.
Other - statistical safety	
Other – Pediatrics Maternal Health Team Other- Pharmacometrics	

Signatory Authority Review Template

1. Introduction

Cepatris submitted a 505 b2 application for Valchor (nitrogen mustard 0.02% gel). The applicant's proposed indication is for the topical treatment of (b) (4) Stage IA, IB (b) (4) mycosis fungoides type cutaneous T-cell lymphoma (CTCL) who have received at least one prior skin-directed therapy (b) (4)

This submission is a Class 2 resubmission and a response to a Complete Response letter which detailed numerous CMC deficiencies, a non-clinical deficiency, two clinical deficiencies and a regulatory deficiency.

2. Background

The Applicant has submitted a 505b 2 application for Valchor, mechlorethamine, a nitrogen mustard. Mechlorethamine as a topical gel has been used without FDA approval for nearly 50 years to treat Mycosis Fungoides (MF) at concentrations ranging from 0.01% to 0.04%.

The applicant has not provided all necessary non-clinical studies for review and will be relying on the literature and reference listed product for Valchor. Per the CMC review addendum the reference listed drug is: NDA#6695. Thus, the 505 b2 pathway is appropriate.

Topical application of mechlorethamine (nitrogen mustard) for treatment of mycosis fungoides has been used since the 1950s and is described in the literature. The National Comprehensive Cancer Network recommends the use of topical nitrogen mustard therapy for the treatment of mycosis fungoides (skin involvement). Currently topical nitrogen mustard ointments/creams are compounded at compounding pharmacies.

3. CMC/Device

The May 4, 2012 Complete Response Letter outlined 13 deficiencies, primarily involving CMC issues. This submission addressed those issues. Drs. Ladoucer, Russell, Ali-Hakim, and Pope-Miksinski reviewed this submission and all recommend approval.

From Drs. Ladoucer and Russell's primary review for this submission the following text is excerpted:
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.

I concur with the recommendations for approval.

4. Nonclinical Pharmacology/Toxicology

During the first cycle one pharmacology/toxiciology deficiency was noted. However during this review cycle, no issues that would preclude approval are present.

Dr. Simpson provided the following recommendation in her review:

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 LD, MUSTARGEN, and published literature on nitrogen mustard may be used to supplement the labeling of VALCHLOR, if necessary.

5. Clinical Pharmacology/Biopharmaceutics

No issues were identified that would preclude approval during the first review cycle.

6. Clinical Microbiology

No issues were identified that would preclude approval.

7. Clinical/Statistical-Efficacy

From the Medical Officer's original review of efficacy:

The efficacy of Valchlor was evaluated in 242 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 efficacy results from this non-inferiority clinical trial are listed below.

- *The primary endpoint was CAILS response (based on maximum of 5 index lesions per patient). Secondary endpoints include SWAT response (global response), duration of CAILS response, time to CAILS response, and time to CAILS progression. Non-inferiority to active control would be demonstrated if the lower limit of the 95% confidence interval of response rate ratio (Valchlor:control) is $\geq$ 0.75.*
- *Clinical trial 2005NMMF-201-US achieved its primary endpoint. The CAILS response rate ratio was 1.24 with 95%CI of 0.98 to 1.58. The CAILS response rate was 60% in Valchlor arm and 48% in control arm.*
- *Secondary endpoints supported the primary endpoint result.*

– The SWAT response rate ratio was 1.07 with 95%CI of 0.82 to 1.39. The SWAT response rate was 50% in the Valchlor arm, and 46% in the control arm.

– Time to CAILS response and time to SWAT response were similar between treatment arms. Median time to response (CAILS or SWAT) was 4 months for the Valchlor arm, and 3 months for the control arm.

– Duration of CAILS response and duration of SWAT response were similar between treatment arms. Median duration of response (CAILS or SWAT) was not reached.

- *The trial population consisted of 242 patients enrolled from U.S. sites. Patients were required to have central and local pathology confirmation of the diagnosis of mycosis fungoides. All patients had at least one prior therapy. There was similar distribution of demographic parameters (gender, age, race) and baseline disease characteristics (stage of disease, duration of disease, prior therapies) between treatment arms.*

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of efficacy.

8. Safety

From the initial Medical Officer's review of safety:

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.*
- *Dermatitis is a known adverse event with topical mechlorethamine therapy. In this clinical trial, 73% in Valchlor arm and 69% in control arm experienced dermatitis, or a complication from dermatitis. Grade 3-4 dermatitis was reported in 29% of patients in Valchlor arm and 19% in control arm. Treatment discontinuations due to AEs (22% in Valchlor arm, 18% in control arm) were due to skin-related AEs. 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).*

The following text is from Dr. DeClaro's current review:
Module 5 of this resubmission included 2 published references. The Applicant had previously submitted datasets and additional case report forms (NDA 202317 SDN 31 Received 7/26/2012) to support the re-analysis of duration of follow-up for adverse events….. 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 ≥ 65 years and prior history of nMSC, but not duration of MF or treatment type (Valchlor vs. control formulation).

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of safety.

During the first cycle review two clinical deficiencies were identified: one directly related to the ONDQA/CMC issues with product quality characterization which suggested a new clinical trial may be necessary and the second relating to the adequacy of safety follow-up. In this submission, the sponsor has adequately addressed the ONDQA/CMC issues thus a new clinical trial is not necessary and the sponsor has provided the requested safety data. Thus these deficiencies are resolved.

9. Advisory Committee Meeting

This product was not discussed at an advisory committee meeting.

10. Pediatrics

N/A – orphan product

11. Other Relevant Regulatory Issues

The previously identified regulatory deficiency has been resolved. There are no other outstanding issues.

The Office of Scientific Investigation did not uncover any reliability issues with regard to the clinical study conducted for the indication.

12. Labeling

All disciplines participated in labeling discussions and negotiations with the applicant.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
  Approval
- Risk Benefit Assessment- Topical nitrogen mustard has been used for over 50 years to effectively treat mycosis fungoides. The clinical trial demonstrated a response rate similar to the comparator. The most common adverse reactions associated with use of this product in the clinical trial were are dermatitis, pruritus, bacterial skin infection, skin ulceration or blistering, and hyperpigmentation. The reported adverse reactions are what would be expected when this product is marketed.
- Recommendation for Post marketing Risk Management Activities – routine surveillance and post-marketing requirement below
- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC) –

  Due to the potential for inadvertent exposure, the Applicant is requested to undertake an assessment and analysis of spontaneous reports of inadvertent exposure of anyone other than the patient for a period of 2 years from the date of approval.

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/s/

ANN T FARRELL
08/22/2013