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RESEARCH**

APPLICATION NUMBER:
202317Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number: 202,317
Supporting document/s: 36
Sponsor's letter date: February 27, 2013
CDER stamp date: February 27, 2013
Product: VALCHLOR (mechlorethamine HCl) Gel 0.0.2%
Indication: For the topical treatment of (b) (4)
(b) (4) Stage IA, IB (b) (4) mycosis
fungoides type cutaneous T-cell lymphoma
(CTCL)
Sponsor: Ceptaris Therapeutics, Inc.
Review Division: Division of Hematology Oncology Toxicology
(for Division of Hematology Products)
Reviewer: Natalie E. Simpson, Ph.D.
Supervisor/Team Leader: Haleh Saber, Ph.D.
Division Director: John Leighton, Ph.D., DABT
Ann Farrell, M.D. (DHP)
Project Manager: Tyree Newman

Template Version: September 1, 2010

Background and Regulatory History

VALCHLOR (mechlorethamine), also known as nitrogen mustard, is a 0.02% topical gel to be used for the treatment of cutaneous manifestations of CTCL. Mechlorethamine is a nitrogen analog of sulfur mustard. The Applicant submitted this 505 (b)(2) NDA in July of 2011, relying on the nonclinical data from the listed drug (LD) MUSTARGEN label. Published articles have been also submitted, e.g. in support of the use of the drug for the proposed indication and on toxicities associated with the drug.

The Applicant was issued a Complete Response letter (CRL) by the Agency on May 4, 2012. The specific nonclinical concern was that the levels (b)(4) exceeded the threshold defined by ICH Q3B (R2) (b)(4) and these impurities could not be qualified by clinical experience, as proposed, due to insufficient characterization of clinical trial lots and insufficient information on the amount of impurities patients were exposed to.

Current NDA Submission

On February, 27, 2013, NDA 202,317 was resubmitted by the Applicant with data demonstrating that the impurities in the five recently manufactured commercial lots of drug product are below the threshold described in ICH Q3B (R2) (b)(4) (See attachment, Table 1). The proposed drug product specifications (b)(4) for individual impurities (See attachment, Table 2) is acceptable for the total daily use of (b)(4) nitrogen mustard per ICH Q3B (R2) guidance. (b)(4)

Therefore, the Applicant's response to CRL item 14 - revision and justification of impurities specification - is acceptable.

A shelf-life study (b)(4) and a 12-week in-use study to simulate patient daily exposure to VALCHLOR, by which one of the commercial lots was kept at 2 to 8°C with removal to room temperature for 1hr/day, demonstrated that impurity levels continued to meet specification standards throughout the shelf-life and daily use of the drug product (See attachment, Table 3).

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

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immediately following this page

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/s/

NATALIE E SIMPSON
04/19/2013

HALEH SABER
04/19/2013

MEMORANDUM

Date: April 26, 2012
From: Haleh Saber, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
NDA: 202317
Drug: VALCHLOR (mechlorethamine)
Indication: For the topical treatment of (b)(4) Stage IA, IB
(b)(4) mycosis fungoides type cutaneous T-cell lymphoma (CTCL)
Applicant: Ceptaris Therapeutics, Inc. (originally Yaupon Therapeutics, Inc.)

Introduction and Regulatory Background

VALCHLOR (mechlorethamine), also known as nitrogen mustard, is a 0.02% topical gel to be used for the treatment of cutaneous manifestations of CTCL. Mechlorethamine is a nitrogen analog of sulfur mustard. The Applicant submitted this 505 (b)(2) NDA in July of 2011, relying on the nonclinical data from the reference listed drug (RLD) MUSTARGEN label. Published articles have been also submitted, e.g. in support of the use of the drug for the proposed indication and on toxicities associated with the drug.

Several interactions took place between the Agency and the Applicant, starting in 2004. Interactions included discussions on nonclinical development of the drug. In a CMC meeting held on February 2, 2010, the Applicant was asked to characterize the impurity profile of their drug product. The following items were among discussion points communicated to the Applicant:

- a. In addition to the proposed release and stability specifications for the drug product (appearance, pH, viscosity, assay and minimum fill), establish:
 - i. a homogeneity specification to ensure uniform strength of the product in the as-marketed packages.
 - ii. individual known, individual unknown, and total impurities specifications, (including related substances and degradants) to ensure purity.
 - iii. a (b)(4) specification.
 - iv. a (b)(4) specification (b)(4)
- b. Develop an accurate analysis method and obtain reference standards for all impurities.
- c. Establish the degradation pathway of your drug product and identify and report as per ICH all impurities, including degradants, in production and stability programs.
- d. Report impurities based on the amount of the active pharmaceutical ingredient (b)(4) The meeting package reports (b)(4) impurities that have been observed, using a LC/MS method, in batches produced (b)(4) These impurities were reported (b)(4)

- (b) (4) When calculated as a percentage of the active pharmaceutical ingredient, these levels of impurity exceed ICH identification thresholds.”
- e. Conduct a temperature study to characterize the degradation profile under labeled use of the to-be-marketed product. The study data should be sufficiently robust to provide clear evidence to support the proposed expiry and evaluate worst case scenarios. (b) (4)
 - f. As part of the stress evaluation of the drug product, conduct freeze/thaw studies.
 - g. Provide extractables/leachables data from studies conducted on the to-be-marketed products to demonstrate acceptable compatibility profiles for the container/closure systems.
 - h. As per your proposed dosing and administration instructions (e.g., “thin film”) provide quantitative values of daily topical exposure of the API and all impurities which exceed ICH thresholds.

During this meeting, FDA further advised the Applicant to provide tabulated information of impurities, their levels, and justification (based on non-clinical or clinical data) for those exceeding ICH levels.

Current Submission

This is a 505(b)(2) NDA application. Information from the MUSTARGEN label could be used for labeling of VALCHLOR. The articles submitted may be also useful in providing additional information for the label if needed. Of note, due to the deficiencies, the labeling review has not been initiated.

(b) (4)
See the table attached for the list of impurities and the proposed specifications. (b) (4)

[REDACTED] (b) (4)

No data are available on exposure to the impurities in clinical trials as data were not prospectively collected. [REDACTED] (b) (4)

[REDACTED] Hence, a justification based on clinical data is not feasible. The Applicant may use other measures to justify the level of the impurities or reduce the impurities to stay within the threshold defined by ICH Q3B (R2). The latter could be achieved by:

- 1- reducing the specifications [REDACTED] (b) (4)
- 2- [REDACTED] (b) (4)

Recommendation: The Applicant should either lower the specifications for the impurities in the drug product [REDACTED] (b) (4) as defined by ICH Q3B (R2) or adequately justify the proposed specifications. [REDACTED] (b) (4)

[REDACTED]

Due to the deficiencies, the labeling review has not been initiated. It is expected that most nonclinical information provided in the label for MUSTARGEN could be used to label VALCHLOR. The Applicant has also submitted published articles in support of the nonclinical sections of the label. The articles have not been reviewed at this time.

ATTACHEMENT: Table of Impurities

ATTACHMENT
Table of Impurities



(b) (4)

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/s/

HALEH SABER
04/26/2012

JOHN K LEIGHTON
04/27/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202317 **Applicant:** Yaupon Therapeutics **Stamp Date:** 7/27/2011

Drug Name: Nitrogen Mustard **NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		Appears to be acceptable.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Route of administration is different. However, this is acceptable for this 505(b)(2).
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable. Non-clinical information is from published articles.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Revisions are needed. Dose/exposure multiples may not be relevant because route of administration in animals were not the same as in humans
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	This is a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? - YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

ALEXANDER H PUTMAN
09/01/2011

HALEH SABER
09/02/2011