

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202317Orig1s000

CHEMISTRY REVIEW(S)

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

Application: NDA 202317/000	Sponsor: CEPTARIS THERAP
OT Code: 161	101 LINDENWOOD DR STE 400
Priority: 5	MALVERN, PA 19355
Stamp Date: 27-JUL-2011	Brand Name: NITROGEN MUSTARD
PDUFA Date: 27-MAY-2012	Estab. Name:
Action Goal:	Generic Name: NITROGEN MUSTARD
District Goal: 28-NOV-2011	Product Number; Dosage Form; Ingredient; Strengths 001; GEL; MECHLORETHAMINE HYDROCHLORIDE; .02%

FDA Contacts: T. LAMBERT	Project Manager	3017964246
J. BROWN	Team Leader	3017961652

Overall Recommendation:	ACCEPTABLE	on 16-NOV-2011	by D. SMITH	(HFD-323)	3017969643
	PENDING	on 04-AUG-2011	by EES_PROD		
	PENDING	on 04-AUG-2011	by EES_PROD		

Establishment:	CFN:	FEI:	(b) (4)
	(b) (4)		
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
Pr	CONTROL TESTING LABORATORY		
	OAI Status:	NONE	
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	04-AUG-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN:	FEI:	(b) (4)
	(b) (4)		
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	(b) (4)		
Profile:	(b) (4)		
OAI Status:	NONE		
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	04-AUG-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

Establishment: CFN: 1933181 FEI: 1000305235
UNIVERSITY OF IOWA PHARMACEUTICAL
IOWA CITY, , UNITED STATES 522425000

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-AUG-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: 1918751 FEI: 1918751
UNIVERSITY OF IOWA PHARMACEUTICALS (UIP)
IOWA CITY, , UNITED STATES 522421112

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-NOV-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

SHANNON J CREWS
09/03/2013

ONDQA Division Director's Memo
NDA 202-317, Valchlor (mechlorethamine HCl 0.02% gel for topical use)
Date: 16-AUG-2013
Author: Sarah Pope Miksinski, Director (Acting)/DNDQA2/ONDQA

Reference is made to the primary Chemistry, Manufacturing and Controls (CMC) review dated 16-JUL-2013. Reference is also made to the secondary CMC review dated 08-AUG-2013. Both primary and secondary reviews recommend approval from a CMC standpoint, and both primary and secondary reviewers confirm that there are no outstanding CMC deficiencies that would preclude approval.

I concur with the primary and secondary reviewers' recommendations of approval. Additionally, I concur that there are no outstanding CMC deficiencies for this NDA.

There is no change to the previous ONDQA recommendation: all CMC review issues have been resolved, and ONDQA recommends approval of this NDA.

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/s/

SARAH P MIKSINSKI
08/20/2013

NDA 202317

ValchlorTM
mechlorethamine HCl 0.02%* gel for topical use
(*equivalent to mechlorethamine 0.016% per new salt naming/strength policy)

Ceptaris Therapeutics, Inc.
(formerly Yaupon, Inc.)

Anne Marie Russell, Ph.D.
CMC Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II
for
Division of Hematology Products (DHP)

CMC Assessment Section

CMC memo

At the time of review completion (CMC review #2 dated 1-Aug-2013), the carton and container labeling had not been finalized since some non-CMC comments were outstanding.

This memo documents the final versions of the carton and container labels. They were submitted by email to the OND Project Manager Tyree Newman on 26-July-2013. They are acceptable from a CMC standpoint.

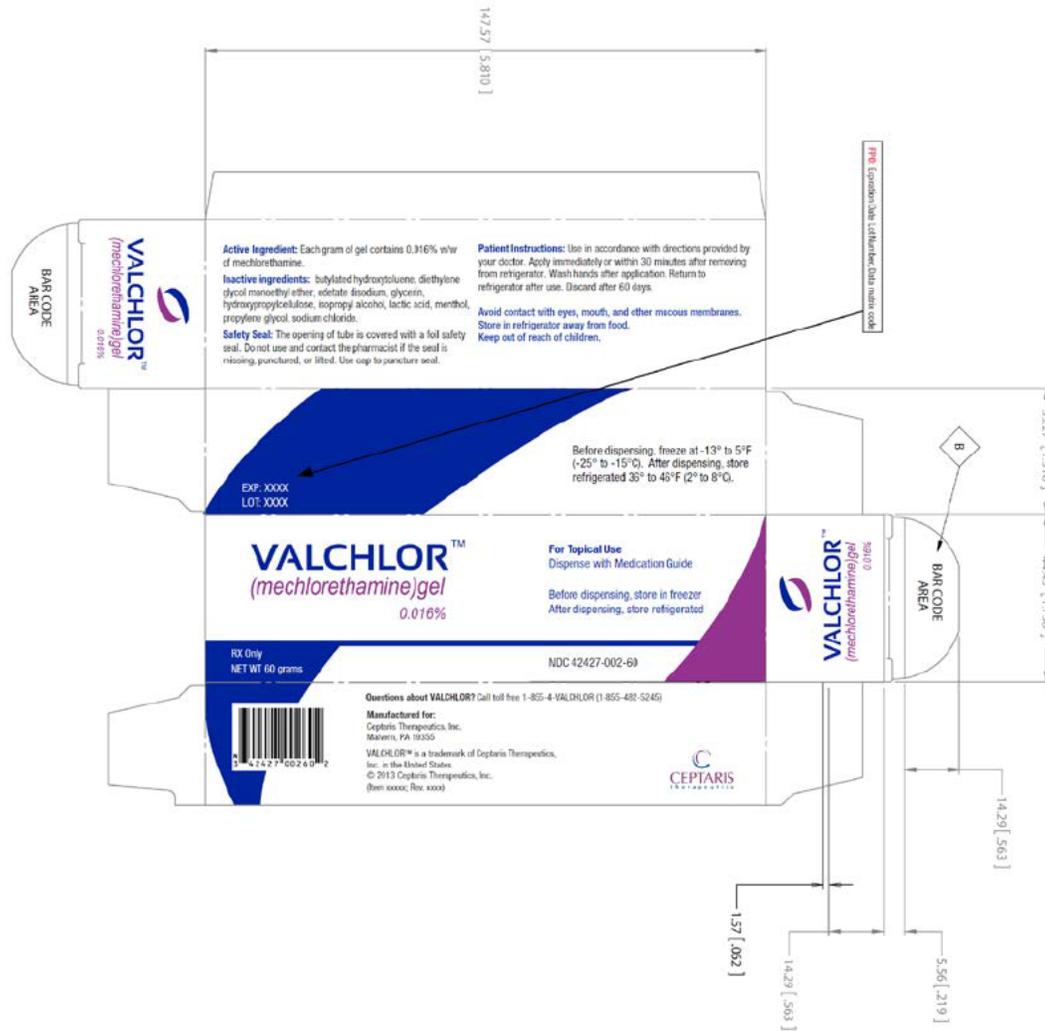
Immediate container labels:

A copy of the container label is provided below. The name and strength revisions, as agreed are included. This is acceptable:



CMC Assessment Section

A copy of the carton label provided below. The name and strength revisions, as agreed are included. This is acceptable:



Evaluation: Final carton and container as submitted are acceptable.

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/s/

ANNE M RUSSELL
08/19/2013

ALI H AL HAKIM
08/19/2013

Secondary Review

NDA 202317

Valchlor™

Mechlorethamine HCl 0.02% gel for topical use

Although CMC review # 2 recommends an approval action for this NDA, the reviewer raises some additional concerns regarding clinical batches and related clinical issues. These concerns are outlined below.

In Chemistry Review #1, the reviewer stated that *“Due to insufficient characterization, comparability between the clinical trial and commercial products has not been demonstrated. Sufficiently characterize clinical trial and commercial products to demonstrate comparability.”* In Chemistry Review # 2, the CMC reviewer evaluated the response to the above deficiency and concluded that the response is inadequate.

In the NDA, the applicant provided the following table which compares the clinical batches with the proposed commercial batches.



(b) (4)



(b) (4)

It is essential to mention here that the topical drug product route of administration, without

any significant systematic exposure, has less risk compared to other drug products including Injection, Inhalation, Oral, etc.

The proposed commercial drug product batches, which are intended to be used widely by the patient population, were stored (b) (4)

Additionally, the above clinical batches in table 3 (b) (4) represents the range of impurity for 7 clinical lots) which were used in the original clinical trial demonstrated their efficacy and safety, as reported by the clinical reviewer, **Dr. R. Angelo de Claro, M.D, in his review dated June 25, 2013 who stated "trials demonstrated adequate clinical efficacy and safety profile"**.

Therefore, I do not concur with the CMC reviewer's comment that: *"The applicant did not provide any data on the clinical trial product"*.

My assessment is that the applicant did provide data as shown in table 3. It is my assessment that the clinical trial lots were adequately tested for assay and impurities (b) (4)

the assay for these batches remained within the proposed NDA drug product specification (b) (4)

(b) (4) The commercial drug product batches have individual specified impurities controlled at the qualification threshold and individual unspecified impurities at the identification threshold (ICH Q3A). The commercial product remains within these limits throughout the shelf life. In addition, **the non clinical reviewer, Dr. Natalie E. Simpson, reported in her review dated April 19, 2013 that "the proposed specifications are acceptable for the impurities. There are no pharmacology/toxicology issues to preclude approval of VALCHLOR for the proposed indication"**.

Therefore, I do not concur with the CMC reviewer's comment that *"The characterization of the clinical trial product remains inadequate in this application"*.

The proposed commercial drug product batches that are intended to be used by the patient population are stored (b) (4)

The commercial batches are of higher quality [REDACTED] (b) (4)

Therefore, I do not concur with the CMC reviewer's comment that "*Inadequate characterization between the clinical trial product and the commercial product can not be established*".

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. The NDA is recommended for approval from CMC perspective.

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/s/

ALI H AL HAKIM
08/08/2013

NDA 202317

ValchlorTM

mechlorethamine HCl 0.02%* gel for topical use

(*equivalent to mechlorethamine 0.016% per new salt naming/strength policy)

**Ceptaris Therapeutics, Inc.
(formerly Yaupon, Inc.)**

**Gaetan Ladouceur, Ph.D.
Anne Marie Russell, Ph.D.
CMC Review Chemists**

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II
for
Division of Hematology Products (DHP)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202317
2. REVIEW #: 2 (Complete Response)
3. REVIEW DATE: 16-JUL-2013
4. REVIEWER: Gaetan Ladouceur, Ph.D. (Drug Substance)
Anne Marie Russell, Ph.D. (Drug Product)
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA submission	27-Jul-2011
Amendment 09	24-Oct-2011
Amendment 12	06-Dec-2011
Amendment 14	23-Dec-2011
Amendment 15	06-Jan-2012
Amendment 17	17-Jan-2012
Amendment 21	06-Mar-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Stamp Date
Complete Response NDA Submission	36	27-Feb-2013
Amendment CMC – eight-week data for in-use temp studies, three primary lots	37	26-Mar-2013
Amendment response to IR, Labeling – Vial, Carton and package insert	41	27-Jun-2013

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name	Ceptaris Therapeutics, Inc.
Address	101 Lindenwood Drive suite 400 Malvern, PA 19355
Representative	Lisa Wittmer, Ph.D., Vice President, Regulatory Affairs
Telephone	610-975-9290

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Valchor™
- b) Non-Proprietary Name:
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5 (new formulation)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

NDA 202-317 was submitted in accordance with 21 CFR Part 314.50 as a 505(b)(2) application for the Reference Listed Drug Mustargen® (NDA # 6695).

10. PHARMACOL. CATEGORY: Antineoplastic for the treatment of mycosis fungoides

11. DOSAGE FORM: gel for topical use

12. STRENGTH/POTENCY: 0.02% mechlorethamine hydrochloride (equivalent to mechlorethamine 0.016% per new salt naming/strength policy)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

CMC Review Data Sheet

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

Chemical Name(s)	2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride 2,2'-dichloro-N-methyldiethylamine hydrochloride bis(2-chloroethyl)methylamine hydrochloride N-methylbis(2-chloroethyl)amine hydrochloride Mechlorethamine hydrochloride (MCH) Nitrogen mustard (NM) Chlormethine hydrochloride
Yaupon/Ceptaris:	Valchlor
Empirical Formula	C ₅ H ₁₁ Cl ₂ N · HCl
Molecular Weight	192.51 g/mol
CAS Registry Number	55-86-7
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: No additional DMFs submitted in the Complete Response.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Meeting minutes	IND 67839	27-Nov-2012
Meeting minutes	IND 67839	15-Jan-2013

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	approval	15-mar-2013	EES
Pharm/Tox	approval	19-Apr-2013	Natalie Simpson
Biopharm	N/A		
EA	N/A		
Microbiology	N/A		

Executive Summary Section

Chemistry Review of Resubmission NDA 202-317

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This is a recommendation to approve this product from a Chemistry, Manufacturing and Controls (CMC) standpoint.

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

None

II. Summary of CMC Assessments

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 non-sterile 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)),

Executive Summary Section

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 off-site.

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.

B. Responses to Complete Response (Summary)

Responses were provided for all 13 CMC deficiencies and 4 CMC comments listed in the Complete Response letter of 04-May-2012. The drug substance deficiencies and comments were all resolved in this resubmission. All but one of the drug product deficiencies (#1/comparability) were also resolved. There remains one outstanding deficiency regarding comparability between clinical and commercial products. See review for evaluation of responses to individual deficiencies.

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

The proposed use is to apply to dry skin once daily (b) (4) During the in-use period, the drug product is to be stored at 2-8°C with daily excursions to room temperature for no more than one hour.

D. Basis for Approvability or Not-Approval Recommendation

The requirements of 21 CFR 314.50(d)(1) have been met by the Applicant .

Executive Summary Section

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

Anne Marie Russell, Ph.D.

*(See appended electronic signature page)***B. Endorsement Block:***(See appended electronic signature page)*

Branch Chief Ali Al Hakim

Acting Division Director Sarah Pope Miksinski

C. CC Block: entered electronically in DARRTS

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/s/

ANNE M RUSSELL
08/01/2013

ALI H AL HAKIM
08/01/2013

I concur with the conclusion of the reviewer regarding the approval recommendation for this NDA from CMC perspective

NDA 202-317
Addendum to CMC Review #1

Valchlor
(mechlorethamine hydrochloride gel 0.02%)

Yaupon Therapeutics, Inc.*

***corporate name changed to Ceptaris Therapeutics during the review cycle.**

CMC Review Team:

Gaetan Ladoucer, Ph.D. (Drug Substance)

Anne Marie Russell, Ph.D. (Drug Product)

Office of New Drug Quality Assessment

Division I Branch II

for

The Division of Oncology Products 2 (DOP2)

Addendum:

The following information was missing from CMC Review#1 (highlighted):

9. LEGAL BASIS FOR SUBMISSION:

NDA 202-317 was submitted in accordance with 21 CFR Part 314.50 as a 505(b)(2) application for the Reference Listed Drug Mustargen[®] (NDA#6695).

APPEARS THIS
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/s/

ANNE M RUSSELL
04/22/2012

SARAH P MIKSINSKI
04/24/2012

NDA 202-317

Valchlor
(mechlorethamine hydrochloride gel 0.02%)

Yaupon Therapeutics, Inc.*

**corporate name changed to Ceptaris Therapeutics during the review cycle.*

CMC Review Team:

Gaetan Ladouceur, Ph.D. (Drug Substance)

Anne Marie Russell, Ph.D. (Drug Product)

Office of New Drug Quality Assessment

Division I Branch II

for

The Division of Oncology Products 2 (DOP2)

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Chemistry Review Data Sheet

1. NDA 202-317
2. REVIEW #1
3. REVIEW DATE: 22-APR-2012
4. REVIEW TEAM: Gaetan Ladouceur, Ph.D (Drug Substance)
Anne Marie Russell, Ph.D. (Drug Product)
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission	Contents	Receipt date
Original NDA		27-JUL-2011
Amendment	Response to IR#1 (74 Day letter): <ul style="list-style-type: none"> •cmc information on the drug substance and the drug product •information on the use of the drug product in the clinical study • (b)(4) Report VR -1 08 (Validation of Method for Determination of Related Substances by Gas Chromatography) 	24-OCT-2011
Amendment	Response to IR#1: Resubmission of M3 pdf files in readable text format	06-DEC-2011
Amendment	Response to CMC IR#2 (DP impurities)	23-DEC-2011
Amendment	Notification of change sponsor corporate name (old name: Yaupon changed to Ceptaris Therapeutics)	06-JAN-2012
Amendment	Additional info to respond to IR#2 <ul style="list-style-type: none"> •characterization of the clinical trial material used in Study 2005NMMF-201-US • bridging between the two manufacturing sites ((b)(4) and UIP) 	17-JAN-2012
Amendment	<ul style="list-style-type: none"> • updated DUNS for the drug product manufacturer • updated letters of authorization for referenced DMFs • corrected container/closure information for the drug product 	06-MAR-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Yaupon, Inc*.
Address:	101 Lindenwood Drive Suite 400 Malvern, PA 19355
Representative:	Lisa Wittmer, Ph.D., Vice President, Regulatory Affairs
Telephone:	610-975-9290

*corporate name changed to Ceptaris Therapeutics during the review cycle.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Valchlor
- b) Non-Proprietary Name (USAN): no USAN name submitted (see deficiencies) -commonly known as mechlorethamine hydrochloride.
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem Type: 5 (new formulation)
 - Submission Priority: standard (10 mos)

9. LEGAL BASIS FOR SUBMISSION:

NDA 202-317 was submitted in accordance with 21 CFR Part 314.50.

10. PHARMACOL. CATEGORY: Antineoplastic for the treatment of mycosis fungoides

11. DOSAGE FORM: gel

12. STRENGTH/POTENCY: 0.02%

13. ROUTE OF ADMINISTRATION: topical

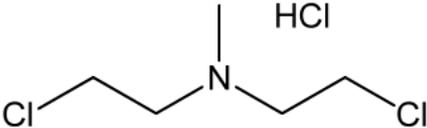
14. Rx/OTC DISPENSED: Rx OTC

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:

Chemical Name(s)	2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride 2,2'-dichloro-N-methyldiethylamine hydrochloride bis(2-chloroethyl)methylamine hydrochloride N-methylbis(2-chloroethyl)amine hydrochloride Mechlorethamine hydrochloride (MCH) Nitrogen mustard (NM) Chlormethine hydrochloride
Yaupon/Ceptaris:	Valchlor
Empirical Formula	$C_5H_{11}Cl_2N \cdot HCl$
Molecular Weight	192.51 g/mol
CAS Registry Number	55-86-7
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	5	N/A	22-APR-2012	as reviewed by Dr. Ladouceur in this review.
	III		4	N/A	22-APR-2012	as reviewed by Dr. Russell in this review.	
	IV		4	N/A	22-APR-2012	as reviewed by Dr. Russell in this review.	
	III		4	N/A	22-APR-2012	as reviewed by Dr. Russell in this review.	

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: IND 67,839

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	16-NOV-2011	Office of Compliance/reviewer not specified
Pharm/Tox	pending	N/A	Yash Chopra
Biopharm	N/A	N/A	N/A
Labeling Nomenclature Committee (LNC)	N/A	N/A	N/A
Methods Validation	Acceptable	N/A	Methods are standard; no methods require post-approval validation.
DMEPA	Consult-Review - labeling	N/A	N/A due to planned action
EA	Categorical Exclusion Claim under 21 CFR 25.31(a).	22-APR-2012	Anne Marie Russell, Ph.D.
Microbiology	Recommend for approval	26-MAR-2012	Stephen Langille, Ph.D.

The Chemistry Review for NDA 202-317

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This is a recommendation to not approve this product from a Chemistry, Manufacturing and Controls standpoint. The clinical supplies for the single pivotal trial were not tested for impurities on release or stability, and were therefore insufficiently characterized. As a result, there are several outstanding deficiencies regarding comparability between clinical and commercial products, product specifications and expiry. Therefore the submitted information does not support a commercially viable product.

These, and additional deficiencies and comments, are listed below and at the end of this review and should be referenced in future review cycles.

The following language should be inserted in the Complete Response Action letter:

CMC Deficiencies:

1. Due to insufficient characterization, comparability between the clinical and commercial products has not been demonstrated.
2. At time of release, the proposed commercial drug product lots (UIP lots 094I1209B, 013I0210B and 017I0210B) were not sufficiently characterized.
3. Impurity levels in the commercial product cannot be qualified by clinical experience as proposed due to insufficient characterization of clinical and commercial lots on release and stability. Consequently, the proposed acceptance criteria for impurities in the proposed drug product specifications are not acceptable.
4. A product expiry cannot be established due to insufficient release data for the commercial lots of drug product and the lack of established acceptance criteria for the stability specifications.
5. Specify the supplier(s) of the starting material (b) (4) in section S.2.3.
6. Correct the discrepancy in Table (3.2.S.4) 2 of page 7, section 3.2.S.4. (b) (4)
7. Validation of the analytical method for assay/impurities submitted was for Method (b) (4) which is not the method identified in the drug product specifications. Provide validation for the assay/impurities method (b) (4) identified as the NDA method in the drug product specifications

8. The validation report submitted for the analytical method for BHT (b) (4) indicates that a placebo formulation (lot 04201009 trial 1) was used in place of product. Identify the test sample used in the submitted validation report. Provide validation of the method with product or demonstrate that the submitted validation conducted with placebo provides comparable results as product.
9. Batch Analysis: Revise Table (3.2.P.5.4)2 titled “Batch Analyses of Drug Product – NDA Stability Lots – Manufactured at UIP; (b) (4) Batch Size; 60g Tubes” to report only data collected at release (b) (4) and by the proposed specification methods submitted in Table 3 “Drug Product Specification – Release”.

Alternately, revise the table to include in the body of the table, for each data point:

- date the test was conducted
- age of lot at test date, measured from date of lot manufacture
- storage conditions of the lot from manufacture to test date
- analysis method used, including method identification to correlate to submitted NDA methods listed in the specifications.

Provide analytical procedures for analytical methods not already submitted and discuss correlation of results to those obtained by the NDA method. Explain the suitability of any data collected beyond release and using non-NDA methods for establishing the quality of the commercial product

10. Specifications: Impurity levels in the commercial product cannot be evaluated for qualification because a maximum daily dose has not been established. Establish a maximum daily dose.
11. Specifications: (b) (4) acceptance criteria in the commercial product cannot be evaluated for release specification due to the absence of clinical and commercial lot release data. Further, the proposed level (b) (4) in the stability specification is not supported by commercial lot manufacturing experience. Revise the proposed acceptance criteria (b) (4) in the drug product to reflect lot history.
12. Stability specifications: The proposed specifications submitted for stability of the drug product do not include the test method. Revise the specifications to include attribute, method and acceptance criteria.
13. Expiry: (b) (4) establish an in-use expiry period, based on study results, to begin at first dispense.

CMC Comments:

The following additional issues were identified during this review cycle and are provided for your reference. While not comprehensive, consider these comments in your development of a complete and updated Module 3:

1. Provide a USAN name for the drug substance in section S.1.1.
2. Provide a CAS number for the starting material (b) (4) in section S.2.3.
3. In section 3.2.S.4, the proposed acceptance criterion for the individual related substances of drug substance specification is above the ICH qualification threshold. Tighten this acceptance criterion according to the ICH Q3A guidelines.
4. In section 3.2.S.4, the proposed acceptance criterion for the total related substances of the drug substance specification appears to be too wide based on your submitted batch history. Tighten this acceptance criterion to more accurately reflect your drug substance manufacturing capability.

:

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

None

II. Summary of Chemistry Assessments**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 as a non-sterile gel with a 0.02% concentration of mechlorethamine hydrochloride 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 off-site.

The clinical product used in the single pivotal trial was the same formulation as the commercial product, but packaged in (b) (4) tubes. (b) (4) clinical product was manufactured (b) (4). The remainder clinical product was manufactured by the commercial process by University of Iowa Pharmaceuticals (UIP) (b) (4). 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 and commercial 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. As a result, specifications and expiry cannot be established for the commercial product and there is no basis for labeling.

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

The proposed use is to apply to dry skin once dail (b) (4)

The drug product is to be stored at 2-8°C. There is no approved expiry.

C. Basis for Approvability or Not-Approval Recommendation

The requirements of 21 CFR 314.50(d)(1) have not been adequately met by the Applicant. A Complete Response action is recommended.

III. Administrative

- A. Reviewer's Signature** {see electronic signature page}
- B. Endorsement Block** {see electronic signature page}

53 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

ANNE M RUSSELL
04/20/2012

SARAH P MIKSINSKI
04/20/2012

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number:	Supplement Number and Type:	Established/Proper Name:
202317	Original NDA	Mechlorethamine hydrochloride (MCH)
Applicant:	Letter Date:	Stamp Date:
Yaupon Therapeutics, Inc.	27-Jul-2011	27-Jul-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
E. drug product (dp)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N.A.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		See below

CMC issues to be communicated in the 74-day letter.

1. Submit the following drug substance information:

- a. A summary on the actual and potential impurities in the drug substance (b)(4)
 (b)(4)
 (b)(4) Include a justification for setting the acceptance criteria for individual and total impurities and how the proposed limits are qualified. Submit the results of impurity identification and degradation products greater than the identification threshold in any batch manufactured by the proposed commercial process.
- b. Submit the results of drug substance stress testing. As described in ICH Q1A(R2), data should include the effects of temperature, pH, humidity, oxidation and photostability of the drug substance.
- c. If the DMF holder has performed the studies requested in 1a and 1b, you may submit a letter of authorization from the drug substance manufacturer allowing the agency to reference the confidential information in their DMF.

2. As described in ICH Q6A, the drug product specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria. Submit a revised drug product specification to include a reference to the analytical method.

3. Provide a comparison of the relative amounts of the two different products ((b)(4) tube and UIP 60 g tube) used in the pivotal clinical trial. Include the following information for each lot listed in Table (3.2.P.5.4)1 - Batch Analysis of Drug Product Clinical Lots:
 - a) Number of units released (e.g. (b)(4) tubes, 60g tubes).
 - b) Number of units dispensed in the pivotal clinical study.
 - c) Number of units consumed in the pivotal clinical study.

4. Most of the PDF documents do not contain recognizable text which can be copied. This issue results in unnecessary delays and can affect the overall efficiency of the review.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

When submitting PDF documents it's important to comply with Portable Document Format Specifications (PDF - 57KB)²² (6/4/2008). Also, please review section J on page 8 in the Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications (PDF - 132KB)¹³ (June 2008).

Please re-submit the documents in module 3 and the QOS in module 2 which were previously submitted to NDA 202317 that didn't contain recognizable text that can be copied and ensure the new PDF documents contain text that can be copied. The submission should be an amendment to NDA 202317 and you should include a statement in the cover letter attesting that the content didn't change from what was previously submitted and only the format changed.

{See appended electronic signature page}

Janice Brown
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 22-Aug-2011

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch 2
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 22-Aug-2011

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

/s/

JANICE T BROWN
09/08/2011

SARAH P MIKSINSKI
09/08/2011