

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202317Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Memorandum

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<b>NDA</b>	202317 (SDN 36)
<b>Submission Date:</b>	27 February 2013
<b>Brand Name:</b>	Valchlor
<b>Generic Name:</b>	Mechlorethamine
<b>Formulation:</b>	Gel (0.16%)
<b>OCP Reviewers:</b>	Rachelle M. Lubin, Pharm.D.
<b>OCP Team Leader:</b>	Julie Bullock, Pharm.D.
<b>OCP Division:</b>	Division of Clinical Pharmacology V
<b>ORM Division:</b>	Division of Drug Hematology Products
<b>Sponsor:</b>	Ceptaris Therapeutics Inc.
<b>Submission Type:</b>	505(b) (2)-Resubmission (Class 2)
<b>Dosing regimen:</b>	Topically, once daily
<b>Indications</b>	Treatment of [REDACTED] (b) (4) [REDACTED] Stage IA or IB mycosis fungoides type cutaneous T-cell lymphoma who have received at least one prior skin directed therapy.

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Mechlorethamine, also known as nitrogen mustard, is an antineoplastic agent that has been previously approved for parenteral administration (marketed under the trade name Mustargen® NDA#6695). Mechlorethamine is used for the palliative treatment of Hodgkin's disease (Stages III and IV) and other cancers.

The sponsor submitted a 505(b)(2) NDA (NDA #202317) for a topical formulation of mechlorethamine on July 27, 2011 for the treatment of early stage mycosis fungoides. At the time of the original submission there were no clinical pharmacology studies conducted to evaluate the human pharmacokinetics and pharmacodynamics of topical mechlorethamine. Following the collection of plasma samples in clinical trial 2005NMMF-201-US, it was noted that there were no detectable drug concentrations of mechlorethamine in any of the samples assayed. For more details, refer to the Clinical Pharmacology review of the original NDA submission in DARRTS (dated March 23, 2012).

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. Refer back to the Clinical Pharmacology review of the original NDA submission (SDN 1 dated 7/27/2011) for details on the clinical trial 2005NMMF-201-US.

### 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.

## Action

No further action.

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Reviewer: **Rachelle M. Lubin, Pharm.D.**  
Division of Clinical Pharmacology 5

Team Leader: **Julie Bullock, Pharm.D.**  
Division of Clinical Pharmacology 5

Cc: DDOP: **CSO - T Newman; MTL - RA DeClaro; MO - V Kwitkowski**  
DCP-5: Reviewer - **R Lubin**, TL - **J Bullock**, DDD - **B Booth**,  
DD - **A Rahman**;

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RACHELLE M LUBIN  
07/08/2013

JULIE M BULLOCK  
07/09/2013

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## Clinical Pharmacology Review

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<b>NDA</b>	202-317
<b>Submission Date:</b>	27 July 2011
<b>Brand Name:</b>	Valchlor
<b>Generic Name:</b>	Mechlorethamine Hydrochloride
<b>Dosage Form &amp; Strength:</b>	Gel 0.02% (w/w)
<b>OCP Reviewers:</b>	Rachelle Marie Lubin, Pharm.D.
<b>OCP Team Leader:</b>	Julie Bullock, Pharm.D.
<b>OCP Division:</b>	Division of Clinical Pharmacology V
<b>ORM Division:</b>	Division of Hematology Products
<b>Sponsor:</b>	Yaupon Therapeutics Inc.
<b>Submission Type:</b>	505(b) (2), Standard
<b>Dosing regimen:</b>	Topically, Once daily
<b>Indications</b>	Treatment of Stage IA, IB <span style="background-color: #cccccc; padding: 0 2px;">(b) (4)</span> mycosis fungoides

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## 1 EXECUTIVE SUMMARY

Mechlorethamine (MCH), also known as nitrogen mustard, is an antineoplastic agent that has been previously approved for parenteral administration (marketed under the trade name Mustargen® NDA#6695) it is used for the palliative treatment of Hodgkin's disease (Stages III and IV) and other cancers. The sponsor has developed a topical formulation of MCH for the treatment of early stage (Stage IA, IB <sup>(b) (4)</sup>) mycosis fungoides (MF). Mechlorethamine has been used without FDA approval for nearly 50 years as a topical treatment to MF at concentrations ranging from 0.01% to 0.04%.

During the IND development of MF the Agency has recommended the collection of plasma samples to measure MCH concentrations to confirm that there is no systemic exposure to the drug. Per the agreement with the FDA, blood samples were collected and analyzed in a subset of patients.

The MCH plasma concentrations were assayed in a cohort of patients in the phase 2/3 pivotal clinical trial 2005NMMF-201-US (n= 260), and both MCH and the half mustard <sup>(b) (4)</sup> plasma concentrations were assayed in a cohort in trial 2007NMMF-202-US (n= 100). In both studies, there were no detectable concentrations of MCH or half mustard in any of the samples assayed, including those taken from patients who received whole body treatment.

### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 202-317. The Clinical Pharmacology information submitted in NDA 202-317 is acceptable from a Clinical Pharmacology perspective to support the approval of Valchlor (MCH HCL) 0.02% Gel.

### 1.2 Post-Marketing Requirements

None

### 1.3 Summary of Clinical Pharmacology Findings

The sponsor submitted a 505(b)(2) NDA for a topical formulation of 0.02% Mechlorethamine HCL gel (MCH, also known as nitrogen mustard (NM)), the same active substance contained in Mustargen® (NDA #6695) which is being used as the reference listed drug (RLD). Mechlorethamine is an alkylating agent that has been used without FDA approval for nearly 50 years as a topical treatment for mycosis fungoides (MF) at concentrations ranging from 0.01% to 0.04%.

There were no clinical pharmacology studies conducted that evaluated human pharmacokinetics and pharmacodynamics of MCH 0.02% gel. During the development of topical MCH, the Agency recommend for collection of plasma samples to measure MCH concentrations to confirm that there is no systemic exposure to the drug. Per FDA's recommendation, the sponsor collected and analyzed blood samples from a total of 38 patients that took part in studies 2005NMMF-201-US and 2007NMMF-202-US.

Study 2005NMMF-201-US was a Phase 2/3 multi-center, randomized, third party (observer) blinded study of previously treated stage I and IIA MF patients to determine if MCH 0.02% propylene glycol (PG; test product) is non-inferior to the formulation of MCH 0.02% compounded in Aquaphor® (AP; reference product). Two hundred and sixty patients were enrolled to begin treatment with either MCH 0.02% PG or MCH 0.02% AP. All affected areas (generally specific lesions for Stage 1A patients and whole body for Stage IB or IIA patients) were treated once daily for up to twelve months, with the frequency of application adjusted for toxicity. Plasma samples were collected from a subset of 23 patients (16-PG; 7-AP) for the analysis of MCH. Samples were collected at predose and at 1, 3, and 6 hours after application on Day 1 and then one time at the Month 1 visit. None of the samples collected contained detectable MCH concentrations.

Subjects that completed Study 2005NMMF-201-US without achieving a complete response were eligible for enrollment into a follow-up study, 2007NMMF-202-US, regardless of whether they had taken MCH HCL 0.02% gel or compounded MCH HCL 0.02%. In this follow-up study, all subjects (n=100) were treated once daily with MCH HCL 0.04% in the same formulation as MCH HCL 0.02% gel that is the subject of this NDA. Blood samples were collected at 0 and 1 hours after 2 or 4 months of treatment from 15 subjects. A single sample per subject was also collected at the next visit (after 4 or 6 months of exposure). For all plasma samples assayed, the concentrations of MCH and half-mustard were below the limit of quantitation, 5 ng/mL. Thus, there were no measurable concentrations of MCH or half-mustard after 2, 4, or 6 months of daily application of MCH HCL 0.04% gel.

## 2 QUESTION BASED REVIEW

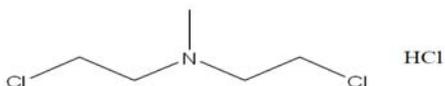
### 2.1 General Attributes

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The Active Pharmaceutical Ingredient in the drug product is MCH HCL. The drug product is a clear to translucent gel dosage form, packaged in a re-sealable multi-use tube, intended for topical administration.

#### Physiochemical Properties:

- Structural Formula



- Molecular Weight: 192.51
- Molecular Formula: C<sub>5</sub>H<sub>11</sub>Cl<sub>2</sub>N·HCL
- Chemical Name: 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
- Solubility: Readily soluble in water and methanol, partially soluble in acetone, generally not soluble in organic solvents

#### 2.1.2 What are the proposed mechanisms of action?

Mechlorethamine is a bifunctional alkylating agent with anti-mitotic effects; however the mechanism of action of topical MCH has not been completely elucidated.

#### 2.1.3 What are the proposed indications and dosing regimen?

Mechlorethamine HCL 0.02% is an antineoplastic agent indicated for the topical treatment of (b) (4) Stage IA, IB (b) (4) mycosis fungoides (MF) type cutaneous T-cell lymphoma (CTCL) who have received at least one prior skin-directed therapy (b) (4). Patients with Stage IA, IB (b) (4) MF should apply a thin film of MCH HCL 0.02% gel once daily to affected areas of the body.

## **2.2 Clinical Pharmacology**

### **2.2.1 What are the bases of the proposed dose and dosage form of Valchlor?**

Mechlorethamine has been used without FDA approval for nearly 50 years as a topical treatment to MF, a form of cutaneous T-cell lymphoma, at concentrations ranging from 0.01% to 0.04%.

### **2.2.2 What are the design features of the clinical pharmacology and clinical studies use to support the dosing claims?**

This application is being submitted under 505(b)(2) for the development of MCH HCL topical formulation, with Mustargen® as the reference listed drug (RLD). The sponsor has conducted two clinical trials with its novel MCH HCL 0.02% gel in patients with early stage (I or IIA) MF type cutaneous T-cell lymphoma (CTCL):

- The first study, 2005NMMF-201-US, was a randomized, observer-blinded, non-inferiority study comparing the safety and efficacy of topical administration of MCH HCL 0.02% gel with a pharmacy-compounded, Aquaphor® based formulation of MCH HCL 0.02%. Patients were instructed to apply the formulation once a day for 12 months. This study has been completed and provides the pivotal safety and efficacy data in support of this NDA.
- The second study, 2007NMMF-202-US, was an open-label follow-on study assessing the safety and efficacy of MCH 0.04% gel formulation which differs from the MCH HCL 0.02% gel only in the concentration of MCH. Enrollment into the trial was available to patients who completed study 2005NMMF-201-US and had not achieved a complete response. MCH HCL 0.04% gel is not the subject of this NDA, nor is this strength proposed in the labeling.

### **2.2.3 What is the relative bioavailability of the proposed to-be-marketed formulation to the reference formulation?**

No detectable concentrations were observed after the administration of MCH HCL 0.02% gel.

### **2.2.4 Does the submission contain sufficient clinical pharmacology information to adequately address clinical systemic safety bridge to RLD?**

Mechlorethamine HCL plasma concentrations were below the limit of quantitation (41.5 ng/mL and 5 ng/mL for 0.02% and 0.04% MCH HCL, respectively). The sponsor did not conduct any specific clinical pharmacology studies with its proprietary formulation of topical MCH HCL 0.02% gel.

### **2.2.5 What is the effect of food on the bioavailability of Valchlor?**

Not applicable.

## **2.2.6 What are the single and multiple dose PK parameters?**

No detectable concentrations of MCH HCL were observed after administration of MCH HCL 0.02% gel.

## **2.3 Intrinsic Factors**

### **2.3.1 What intrinsic factors (gender, age, ethnicity, or disease) affect exposure or response?**

#### **2.3.1.1 Pediatrics**

The application indicates that because of the rarity of MF in children, the sponsor requests a full waiver of pediatric study requirements for the population of patients < 18 years of age.

## **2.4 Extrinsic Factors**

### **2.4.1 Drug Interactions**

Drug interaction potential with MCH HCL was not evaluated in this application. Considering low systemic exposure to MCH HCL following the use of 0.02% gel, no clinically meaningful systemic drug interaction is anticipated.

## **2.5 Analytical Section**

### **2.5.1 What analytical method was used to determine drug concentrations and was the analytical assay adequately validated?**

Study samples were analyzed for MCH concentrations by two analytical methods.

**Analytical Method 1:** The first method, developed by (b) (4), measured MCH (0.02% topical formulation) in plasma and utilized a HPLC method (LOQ of 41.5 ng/mL), which used samples collected from Study 2005NMMF-201-US. Plasma samples were collected from 23 patients (16-PG; 7-AP) for the analysis of MCH. Samples were collected just prior to the application of MCH and at 1, 3, and 6 hours after application on Day 1 and then one time at the Month 1 visit.

The recovery samples were used in the calculation for accuracy. The mean recovery at each concentration ranged from 87.3 – 98.1% (**Table 1**). The deviation of the mean from the true value was 11.3%, 1.9%, and 12.7% at 41.5, 103.7, and 518.4 ng/mL. These results (**Table 1**) were within the criteria of 20% at 41.5 ng/mL and 15% at 103.7 and 518.4 ng/mL. The precision of the method was determined from the 5 replicate analyses of the spiked blood samples used in the accuracy study. The %RSD for each ranged from

0.11% - 0.4%, with an overall %RSD of 5.45%, which passes the requirement of not more than 20% for the lowest level or 15% for all other levels as stated in the qualification protocol. A summary of the method is listed in **Table 1**.

No MCH was detected in any of the blood samples assayed (LOQ 41.5 ng/ml).

**Table 1: Method Qualification Summary**

	Criteria	Result		Pass/Fail
Selectivity	No interfering peaks at the retention time for NM-diDDTC in human plasma samples	No interfering peaks from blank human plasma samples. Baseline resolution with nearest component.		Pass
Linearity	Correlation coefficient ( $r^2$ ) = 0.995 from 40 to 1000 ng/mL and %RSD =15% (=20% at 40 ng/mL) for triplicate injections of each concentration.	$R^2 = 0.9954$ %RSD 0.04 – 1.75		Pass
Accuracy	Calculated mean value within $\pm 15\%$ of actual value ( $\pm 20\%$ at 40 ng/mL)	Level	Recovery	Pass
		41.5ng/mL	88.68	
		103.7ng/mL	98.07	
Precision (Repeatability)	% RSD =15.0% for each level (=20% at 40 ng/mL)	Level	%RSD	Pass
		41.5ng/mL	0.42	
		103.7ng/mL	0.47	
		518.4ng/mL	0.11	
System Suitability	Peak tailing factor from the SST injection =2.0.	1.69		Pass
	column efficiency factor of not less than 2000 (i.e. N = 2000)	4959		Pass

**Analytical Method 2:** The second method, developed by (b) (4), measured MCH (0.04% topical formulation) and half-mustard (b) (4) in plasma and used a fully validated LC/MS/MS method (LLOQ of 5 ng/mL for both MCH and half-mustard), which used samples collected from Study 2007NMMF-202-US. Blood samples were collected at 0 and 1 hours after 2 or 4 months of treatment with MCH 0.04% topical formulation from 15 subjects. A single sample per subject was also collected at the next visit (after 4 or 6 months of exposure).

The intra-run and inter-run accuracy and precision (**Table 2**) were investigated at three different QC concentration levels (15/15 ng/mL, 300/300 ng/mL, and 750/750 ng/mL for MCH/half mustard). The results demonstrated that the intra-run and inter-run precision and accuracy of the method met the acceptance criteria (accuracy within  $100 \pm 15\%$  and %CV no more than 15%).

For all plasma samples assayed, the concentrations of MCH and half-mustard were below the limit of quantitation, 5 ng/mL. Further, there was no evidence of any detectable peaks below the limit of quantitation. During validation, the limits of detection were estimated to be 0.3 ng/mL for MCH and 1.0 ng/mL for half-mustard. There was no evidence of systemic exposure to MCH or half-mustard after 2, 4, or 6 months of daily application of MCH HCL gel 0.04%. A summary of the method is listed in **Table 2**.

**Table 2: Validation Summary Table for the Determination of Nitrogen Mustard and Half Mustard**

(b) (4)



### 3. DETAILED LABELING RECOMMENDATIONS

Sections related to Clinical Pharmacology only are listed below.

~~Strikethrough text~~ means deletion of the sponsor's proposed text. Underscored blue text means recommended addition.

#### 1 INDICATIONS AND USAGE

(b) (4)

#### 7 DRUG INTERACTIONS

(b) (4)

Systemic exposure has not been observed with topical administration of (b) (4); therefore systemic drug interactions are not likely.

#### 12 CLINICAL PHARMACOLOGY

##### 12.1 Mechanism of Action

(b) (4)

##### 12.3 Pharmacokinetics

Systemic exposure was undetectable after topical administration of (b) (4) patients (b) (4). Blood samples were analyzed from 16 and 15 patients following treatment with (b) (4) and an identical formulation consisting of (b) (4).

(b) (4)

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/s/  
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RACHELLE M LUBIN  
03/23/2012

JULIE M BULLOCK  
03/23/2012

# Office of Clinical Pharmacology New Drug Application Filing and Review Form

## General Information

<b>NDA/BLA Number:</b>	202-317/S-000	<b>SDN:</b>	1
<b>Sponsor:</b>	Yaupon Therapeutics Inc.	<b>Date of Submission</b>	27-July-2011
<b>Brand Name:</b>		<b>Generic Name:</b>	mechlorethamine HCl
<b>Drug Class:</b>	bifunctional alkylating agent		
<b>Dosage Form:</b>	topical gel		
<b>Dosing Regimen:</b>	once daily		
<b>Route of Administration:</b>	topical		
<b>Indication:</b>	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)		
<b>OCP Division:</b>	DCP5	<b>OND Division:</b>	DHP
<b>OCP Reviewer:</b>	Julie Bullock, Pharm. D.		
<b>OCP Team Leader:</b>	Brian Booth, Ph.D.		
<b>PM Reviewer:</b>	n/a		
<b>PM Team Leader:</b>	n/a		
<b>GG Reviewer:</b>	n/a		
<b>GG Team Leader:</b>	n/a		
<b>Priority Classification:</b>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	<b>PDUFA Due Date</b>	27-May-2012
<b>OCP Review Due Date:</b>	8-April-2012	<b>OND Division Due Date:</b>	8-April-2012

## Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Critical Comments
Table of Contents present and sufficient to locate reports, tables, data, etc.	<input checked="" type="checkbox"/>		
Tabular Listing of All Human Studies	<input checked="" type="checkbox"/>		
Human PK Summary	<input checked="" type="checkbox"/>		
Labeling	<input checked="" type="checkbox"/>		
Bioanalytical and Analytical Methods	<input checked="" type="checkbox"/>		
<b>I. Clinical Pharmacology</b>			
<b>Mass balance:</b>	<input type="checkbox"/>		
<b>Isozyme characterization:</b>	<input type="checkbox"/>		
<b>Blood/plasma ratio:</b>	<input type="checkbox"/>		
<b>Plasma protein binding:</b>	<input type="checkbox"/>		
<b>Pharmacokinetics (e.g., Phase I) -</b>	<input type="checkbox"/>		
<b>Healthy Volunteers:</b>			
single dose:	<input type="checkbox"/>		
multiple dose:	<input type="checkbox"/>		
<b>Patients:</b>			
single dose:	<input checked="" type="checkbox"/>	1	PK samples were analyzed in a subset of 30 patients in the efficacy trial NMMF-201-US after Day 1 and Week 4
multiple dose:	<input checked="" type="checkbox"/>		
<b>Dose proportionality -</b>			
fasting / non-fasting single dose:	<input type="checkbox"/>		
fasting / non-fasting multiple dose:	<input type="checkbox"/>		
<b>Drug-drug interaction studies -</b>			
In-vivo effects on primary drug:	<input type="checkbox"/>		
In-vivo effects of primary drug:	<input type="checkbox"/>		
Concomitant therapy:	<input type="checkbox"/>		
In-vitro:	<input type="checkbox"/>		

**Subpopulation studies -**

ethnicity:

gender:

pediatrics:

geriatrics:

renal impairment:

hepatic impairment:

**PD -**

Phase 2:

Phase 3:

**PK/PD -**

Phase 1/2, proof of concept:

Phase 3 clinical trial:

**Population Analyses -**

Data rich:

Data sparse:

**QT evaluation:**

**II. Biopharmaceutics**

**Absolute bioavailability:**

**Relative bioavailability -**

solution as reference:

alternate formulation as reference:

**Bioequivalence studies -**

traditional design:

replicate design:

**Food-drug interaction studies:**

**Bio-waiver request based on BCS**

**BCS class**

**Alcohol induced dose-dumping**

**III. Other CPB Studies**

**Genotype/phenotype studies**

**Chronopharmacokinetics**

**Pediatric development plan**

**Literature References**

**Total Number of Studies** 1

**21<sup>st</sup> Century Review Filing Questions**

Question	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>				
1. Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			✓	
2. Has the applicant provided metabolism and drug-drug interaction information?			✓	
3. Has the sponsor submitted bioavailability data satisfying the CFR requirements?	✓			PK samples were analyzed in a subset of 30 patients in the efficacy trail NMMF-201-US
4. Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	✓			
5. Has a rationale for dose selection been submitted?			✓	
6. Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	✓			
7. Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	✓			
8. Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	✓			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>				
<b>Data</b>				
9. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			✓	
10. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			✓	

**Studies and Analyses**

- |  |   |   |
|--|---|---|
| 11. Is the appropriate pharmacokinetic information submitted?  | ✓ |   |
| 12. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?                            |   | ✓ |
| 13. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?   |   | ✓ |
| 14. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? |   | ✓ |
| 15. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?   |   | ✓ |
| 16. Did the applicant submit all the pediatric exclusivity data, as described in the WR?   |   | ✓ |
| 17. Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?   | ✓ |   |

**General**

- |   |   |   |
|---|---|---|
| 18. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | ✓ |   |
| 19. Was the translation (of study reports or other study information) from another language needed and provided in this submission?   |   | ✓ |

**Summary of Application:**

This is a 505(b)(2) application for mechlorethamine HCl topical formulation for the treatment of cutaneous T-cell lymphoma (CTCL). The same active substance (mechlorethamine HCl) was approved in 1949 under the brandname Mustargen® (NDA 6-695). Intravenous Mustargen is approved for the treatment of Hodgkin's disease (Stages III and IV), lymphosarcoma, chronic myelocytic or chronic lymphocytic leukemia, polycythemia vera, mycosis fungoides, and bronchogenic carcinoma. Mustargen, administered intrapleurally, intraperitoneally, or intrapericardially, is indicated for the palliative treatment of metastatic carcinoma resulting in effusion.

**Is the clinical pharmacology section of the application fileable?**

- Yes  
 No (state the reasons and provide comments to be sent to the Applicant).

**Comments to Applicant for the 74-day letter:**

None.

**Signatures:**

Julie M. Bullock, Pharm.D.  
OCP Primary Reviewer

9-Sept-2011  
Date

Brian Booth, Ph.D.  
OCP Team Leader

9-Sept-2011  
Date

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/s/  
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JULIE M BULLOCK  
09/09/2011

BRIAN P BOOTH  
09/09/2011