CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202317Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	July 18, 2013
Reviewer(s):	Suzanne Robottom, Pharm.D. Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D. DRISK
Division Director:	Claudia Manzo, Pharm.D. DRISK
Subject:	Review evaluates if a risk evaluation and mitigation strategy (REMS) is needed
Drug Name(s):	mechlorethamine gel
Therapeutic Class:	antineoplastic
Dosage and Route:	topical, once daily to affected areas
Application Type/Number:	NDA 202317
Applicant/sponsor:	Ceptaris Therapeutics, Inc.
OSE RCM #:	2013-73

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the 505b2 NDA for mechlorethamine gel. The applicant submitted voluntarily a proposed REMS consisting of a Medication Guide (b) (4)

1.1 BACKGROUND AND REGULATORY HISTORY

Mycosis fungoides (MF) accounts for approximately half of all cutaneous T-cell lymphomas (CTCL) but is considered a rare disease.[1] The yearly incidence in the United States is estimated between 41 to 64 per 10 million people.[1] Onset of symptoms generally occurs late in middle age with a median of 50 to 60 years.[1] The disease occurs more often in men than women with a ratio of 2:1.[1] The risk of disease progression is related to the clinical staging of the disease. Patients with stage IA disease have a median survival of 20 or more years.[2] The majority of deaths for this group are not caused by, nor are they related to, MF.[2] In contrast, more than 50% of patients with stage III through stage IV disease die of MF, with a median survival of less than 5 years.[2] In early stages of the disease, skin-directed treatment approaches are favored while in later stages, systemic therapy is favored.[1]

Mechlorethamine is proposed as treatment of (b) (4) early stage MF. The clinical review refines the indication for patients with Stage 1A or 1B MF type CTCL who have received at least one prior skin-directed therapy.

The first cycle review of mechlorethamine for MF resulted in a Complete Response issued on May 4, 2012 because of chemistry and manufacturing issues along with an inadequate duration of follow-up for safety events post-treatment. The sponsor resubmitted mechlorethamine for review on February 27, 2013. Both the first cycle and second cycle submissions included a proposed REMS consisting of Medication Guide (b) (4)

1.2 OTHER PRODUCTS IN THE SAME THERAPEUTIC CLASS/THERAPEUTIC ALTERNATIVES

According to the clinical review, the following are FDA-approved treatment options for CTCL or MF:

- Romidepsin (Istodax (intravenous); approved November 2009)
- Vorinostat (Zolinza (oral); approved October 2006)
- Bexarotene (Targretin (topical); approved June 2000)
- Denileukin (Ontak (intravenous); approved February 1999)

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[1] Weberschock T, et al. Interventions for mycosis fungoides. Cochrane Database of Systematic Review 2012(9).

[2] http://www.cancer.gov/cancertopics/pdq/treatment/mycosisfungoides/HealthProfessional; accessed July 3, 2013.

- Vinblastine (intravenous; initially approved 1965)
- Methotrexate (oral and intravenous; initially[3] approved 1959)
- Cyclophosphamide (oral and intravenous; initially approved 1959)
- Methoxsalen (oral, intravenous; initially approved 1954)
- Mechlorethamine (Mustargen (intravenous); initially approved March 1949)

Topical nitrogen mustard (or mechlorethamine) has been evaluated for the management of MF since the 1950s. The NCCN treatment guidelines include topical mechlorethamine as a primary treatment option for mycosis fungoides/Sezary syndrome for limited/localized and generalized skin involvement (stage IA, IB-IIA).[4] The topical formulation is compounded from the FDA-approved intravenous formulation (Mustargen).

The NCCN treatment guidelines also include non-FDA approved treatment options including topical steroids, topical retinoids, local radiation, other topical chemotherapy (carmustine), topical imiquimod, and phototherapy as primary treatment options for stage IA or IB-IIA.

1.2.1 Known Adverse Events

Appendix A provides an overview of the drugs with approved CTCL/MF indications, route of administration, and the Warnings/Precautions listed in labeling for the above reference treatment options.

Many of the drugs have Boxed Warnings and are associated with serious risks. A number of the approved treatment options are approved for more advanced or refractory disease compared to mechlorethamine gel. However, none of the drugs listed have a Medication Guide or an approved REMS but a few do include some other type of patient-friendly information.

2 MATERIALS REVIEWED

- De Claro RA. Clinical Review for mechlorethamine NDA 202317. Signed June 25, 2013.
- Mechlorethamine FDA proposed package insert [draft] dated June 20, 2013.
- De Claro RA. Clinical Review for mechlorethamine NDA 202317. Signed by De Claro RA on March 28, 2012 and Deisseroth AB April 11, 2012.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Please refer to the clinical reviews by Dr. de Claro, MD for the full review of the safety and efficacy.

[3] Initial approval date reflects the first approval date for any indication; not specific to the CTCL or MF indication.

[4] NCCN Clinical Practice Guidelines in Oncology – Non-Hodgkin's Lymphomas. Mycosis Fungoides/Sezary Syndrome. Version 1.2013.

The basis of the application for mechlorethamine was a randomized, active-control, observer-blinded, non-inferiority clinical trial. The trial enrolled 260 patients from 13 sites in the United States. The active control was Aquaphor-based compounded formulation of mechlorethamine. The primary endpoint for non-inferiority was achieved.

Primary Endpoint Response	NDA 202317 N = 119	Active Control N =123
Responder (Complete Response + Partial Response)	71 (60%)	59 (48%)
Non-responder (Stable Disease + Progressive Disease + Unevaluable)	48 (40%)	64 (52%)

The median duration of follow-up for adverse events was 370 days in the NDA 202317 treatment group and 367 days in the active control.

3.2 SAFETY CONCERNS

The following risks are included in the Warnings and Precautions section of the FDA draft labeling (as of June 20, 2013):

- Mucosal or eye injury: exposure of the eyes to mechlorethamine causes pain, burns, inflammation, photophobia, and blurred vision. (b) (4)

  Exposure of mucous membranes causes pain, redness, and ulceration which may be severe.

- Secondary (b) (4) exposure: Avoid direct skin contact with (b) (4) in individuals other than the patient. (b) (4)

- Dermatitis: (b) (4)

- Non-melanoma skin cancer: (b) (4)

- Embryo-fetal toxicity: Based on its mechanism of action, case reports in humans, and findings in animals, (b) (4) can cause fetal harm when administered to a pregnant woman. There are case reports of children born with malformations in pregnant women *systemically administered* mechlorethamine. Mechlorethamine was teratogenic and embryo-lethal after a single subcutaneous

administration to animals. Advise women to avoid becoming pregnant while using VALCHLOR. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

(b) (4)

In summary, the following table provides an overview of the serious adverse experienced in patients treated with NDA 202317 compared to the active control formulation.

	NDA 202317 N = 128	Active Control N=127
Deaths	1* (1%)	0
Serious AE	14 (11%)	11 (9%)
Discontinued treatment due to AE	28 (22%)	236 (18%)
Any Grade 3 to 4 AE	47 (37%)	24 (27%)
Any AE	108 (84%)	115 (91%)

*Death from widely-disseminated metastatic colorectal cancer. The clinical review stated that this cancer is unlikely to be related to topical mechlorethamine given that it is not systemically absorbed and the short lag time (< 2 months).

The April 2012 clinical review states "Dermatitis is a known adverse event with topical mechlorethamine therapy. In this clinical trial, 73% in NDA 202317 arm and 69% in active control arm experienced dermatitis, or a complication from dermatitis. Grade 3-4 dermatitis was reported in 29% of patients in NDA 202317 arm and 19% in control arm. Treatment discontinuations due to AEs (22% in NDA 202317 arm, 18% in active control arm) were due to skin-related AEs. Most cases of dermatitis resolved, however 9% in NDA 202317 arm and 13% in control arm had residual dermatitis at the end of the clinical trial."

3.3 SPONSOR'S PROPOSED REMS

The Sponsor proposed the following goals:

(b) (4)

The proposed REMS included a Medication Guide (b) (4)

(b) (4)

4 DISCUSSION

The risks associated with topical mechlorethamine are what one would expect with topical antineoplastic (i.e., dermatitis, mucosal injury, secondary exposure, and non-melanoma skin malignancies). Moreover, systemic exposure was undetectable after topical administration of mechlorethamine. Patients treated have no measureable concentration of mechlorethamine or half-mustard after 2, 4, or 6 months of treatment. [5] These data allay concern regarding serious systemic toxicities commonly associated with an alkylating agent.

Practitioners currently use a compounded, mechlorethamine formulation for topical treatment of MF. Based on the clinical data, NDA 202317 is non-inferior to the compounded formulation demonstrating a similar efficacy and safety profile. According to the clinical reviewer, topical mechlorethamine has been used for fifty years primarily by dermatologists and cutaneous lymphoma oncologists.[6]

DRISK does not recommend a REMS to address any of the risks associated with topical mechlorethamine at this time. The safety profile for NDA 202317 is consistent with the compounded formulation that is a recognized treatment for MF. Based on the available data, severity of the disease, treatment alternatives and their associated toxicities, familiarity of these adverse drug events and appropriate management within the prescribing population, and the potential benefit of mechlorethamine, these risks can be adequately addressed through labeling, including a Medication Guide to educate patients about proper application. This view is shared by the Division of Hematology Products (DHP).

5 CONCLUSION

In conclusion, DRISK and DHP agree that a REMS is not required for mechlorethamine gel at this time. Please convey to the sponsor (b) (4)

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

[5] Mechlorethamine FDA proposed package insert [draft] dated June 20, 2013.

[6] Email communication. de Claro RA dated Dece4mber 12, 2011.

APPENDIX A: Drugs approved for CTCL/MF				
Drug	**FDA-Approved Indication**	**Route of Administration**	**Patient Labeling?**	**Warnings and Precautions**
Bexarotene (Targretin)	Treatment of cutaneous lesions in patients with CTCL (Stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies.	Topical	Yes Pt Instructions for Use	• Pregnancy – Category X • Vitamin A Supplementation • Photosensitivity • Drug-Drug Interactions • Renal Insufficiency • Hepatic Insufficiency • Protein Binding
	Treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.	Oral		• Birth defect [BW] / Pregnancy Category X • Lipid Abnormalities • Pancreatitis • Liver function test abnormalities • Hepatic Insufficiency • Thyroid Axis Alternations • Leukopenia • Cataracts
Denileukin (Ontak)	Treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor	Intravenous	No	• Serious Infusion Reactions [BW] • Capillary Leak Syndrome [BW] • Loss of Visual Acuity/color vision [BW] • CD25 Tumor Expression and Evaluation • Laboratory Monitoring/Hypoalbuminemia
Romidepsin (Istodax)	Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. These indications are based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.	Intravenous	Yes Patient Medication Information	• Hematologic • Infections • Electrocardiographic Changes • Tumor Lysis Syndrome • Pregnancy
Vorinostat	Treatment of cutaneous manifestations in	Oral	No	• Thromboembolism

(Zolinza)	patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.			• Hematologic • Gastrointestinal • Hepatic • Hyperglycemia • Monitor: Laboratory Tests • Other Histone Deacetylase Inhibitors • Pregnancy
Methoxsalen	Photopheresis (methoxsalen with long wave ultraviolet radiation of white blood cells) is indicated for use with the UVAR* System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) in persons who have not been responsive to other forms of treatment. While this dosage form of methoxsalen has been approved for use in combination with photopheresis, Oxsoralen Ultra Capsules have not been approved for that use.	Oral	Yes – but NA Patient Information on the use of 8-MOP in the treatment of psoriasis and vitiligo	• Use only by physicians who have special competence • May not be interchanged with Oxsoralen-Ultra • Skin burning • Carcinogenicity –squamous cell carcinoma among PUVA pts. • Cataractogenicity • Actinic Degeneration • Basal Cell Carcinomas • Radiation Therapy • Arsenic Therapy • Hepatic Diseases • Cardiac Diseases • Total Dosage • Concomitant Therapy
Cyclophosphamide	Treatment of mycosis fungoides (**advanced** disease)	Oral, Intravenous	No	• Myelosuppression, Immunosuppression, Bone Marrow Failure, and Infections • Urinary Tract and Renal Toxicity • Cardiotoxicity • Pulmonary Toxicity • Secondary Malignancies • Veno-occlusive Liver Disease • Embryo-Fetal Toxicity • Infertility • Impairment of Wound Healing • Hyponatremia
Mechlorethamine	**Palliative treatment** of Hodgkin's	Intravenous	No	• Administered only under supervision of a

	disease (Stages III and IV), lymphosarcoma, chronic myelocytic or chronic lymphocytic leukemia, polycythemia vera**, mycosis fungoides,** and bronchogenic carcinoma.			physician who is experienced. [BW] • This drug is highly toxic [BW] • Pregnancy [BW] • Extravasation [BW] • Careful clinical judgment in selecting patients *See Appendix A for the complete text of the Boxed Warning, Warnings and Precautions*
Methotrexate	Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, **advanced mycosis fungoides (cutaneous T cell lymphoma)**, and lung cancer, particularly squamous cell and small cell types.	Oral, Intravenous	•	• Use only by physicians whose knowledge and experience [BW] • High dose regimens for other neoplastic disease are investigations [BW] • Fetal Death and Congenital anomalies [BW] • Hematologic and Gastrointestinal Toxicity [BW] • Hepatotoxicity [BW] • Methotrexate-induced lung disease • Tumor Lysis Syndrome [BW] • Fatal skin reactions [BW] • Potentially fatal opportunistic infections [BW] • Concomitant use with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis [BW]
Vinblastine	**Palliative treatment** for mycosis fungoides (**advanced** stages)	Intravenous	•	• Intravenous use only (Fatal if given intrathecally)[BW] • Administered by individuals experienced in the administration of vinblastine[BW] • Usage in Pregnancy • Toxicity enhanced by hepatic insufficiency • Leukopenia • Acute shortness of breath and severe bronchospasm

[BW] The risk is a Boxed Warning.

APPENDIX B: Mustargen Package Insert

Boxed Warning

MUSTARGEN* (Mechlorethamine HCl) should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

This drug is HIGHLY TOXIC and both powder and solution must be handled and administered with care. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. 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.

Extravasation of the drug into subcutaneous tissues results in a painful inflammation. The area usually becomes indurated and sloughing may occur. If leakage of drug is obvious, prompt infiltration of the area with sterile isotonic sodium thiosulfate (1/6 molar) and application of an ice compress for 6 to 12 hours may minimize the local reaction. For a 1/6 molar solution of sodium thiosulfate, use 4.14 g of sodium thiosulfate per 100 mL of Sterile Water for Injection or 2.64 g of anhydrous sodium thiosulfate per 100 mL
or dilute 4 mL of Sodium Thiosulfate Injection (10%) with 6 mL of Sterile Water for Injection.

Warnings

Before using MUSTARGEN, an accurate histologic diagnosis of the disease, a knowledge of its natural course, and an adequate clinical history are important. The hematologic status of the patient must first be determined. It is essential to understand the hazards and therapeutic effects to be expected. Careful clinical judgment must be exercised in selecting patients. If the indication for its use is not clear, the drug should not be used.

As nitrogen mustard therapy may contribute to extensive and rapid development of amyloidosis, it should be used only if foci of acute and chronic suppurative inflammation are absent.

Usage in Pregnancy

Mechlorethamine hydrochloride can cause fetal harm when administered to a pregnant woman. MUSTARGEN has been shown to produce fetal malformations in the rat and ferret when given as single subcutaneous injections of 1 mg/kg (2-3 times the maximum recommended human dose). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Precautions

General

This drug is HIGHLY TOXIC and both powder and solution must be handled and administered with care. (See boxed warning and DOSAGE AND ADMINISTRATION, Special Handling.) Since MUSTARGEN is a powerful vesicant, it is intended primarily for intravenous use, and in most cases is given by this route. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment

should be worn when handling MUSTARGEN. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water, for at least 15 minutes while removing contaminated clothing and shoes, followed by 2% sodium thiosulfate solution. Medical attention should be sought immediately. Contaminated clothing should be destroyed. (See DOSAGE AND ADMINISTRATION, Special Handling.)

Because of the toxicity of MUSTARGEN, and the unpleasant side effects following its use, the potential risk and discomfort from the use of this drug in patients with inoperable neoplasms or in the terminal stage of the disease must be balanced against the limited gain obtainable. These gains will vary with the nature and the status of the disease under treatment. The routine use of MUSTARGEN in all cases of widely disseminated neoplasms is to be discouraged.

The use of MUSTARGEN in patients with leukopenia, thrombocytopenia, and anemia, due to invasion of the bone marrow by tumor carries a greater risk. In such patients a good response to treatment with disappearance of the tumor from the bone marrow may be associated with improvement of bone marrow function. However, in the absence of a good response or in patients who have been previously treated with chemotherapeutic agents, hematopoiesis may be further compromised, and leukopenia, thrombocytopenia and anemia may become more severe and lead to the demise of the patient.

Tumors of bone and nervous tissue have responded poorly to therapy. Results are unpredictable in disseminated and malignant tumors of different types.

Precautions must be observed with the use of MUSTARGEN and x-ray therapy or other chemotherapy in alternating courses. Hematopoietic function is characteristically depressed by either form of therapy, and neither MUSTARGEN following x-ray therapy nor x-ray therapy subsequent to the drug should be given until bone marrow function has recovered. In particular, irradiation of such areas as sternum, ribs, and vertebrae shortly after a course of nitrogen mustard may lead to hematologic complications.

MUSTARGEN has been reported to have immunosuppressive activity. Therefore, it should be borne in mind that use of the drug may predispose the patient to bacterial, viral or fungal infection.

Hyperuricemia may develop during therapy with MUSTARGEN. The problem of urate precipitation should be anticipated, particularly in the treatment of the lymphomas, and adequate methods for control of hyperuricemia should be instituted and careful attention directed toward adequate fluid intake before treatment.

Since drug toxicity, especially sensitivity to bone marrow failure, seems to be more common in chronic lymphatic leukemia than in other conditions, the drug should be given in this condition with great caution, if at all.

Extreme caution must be used in exceeding the average recommended dose. (See OVERDOSAGE.)

Laboratory Tests
Many abnormalities of renal, hepatic, and bone marrow function have been reported in patients with neoplastic disease and receiving mechlorethamine. It is advisable to check renal, hepatic, and bone marrow functions frequently.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Therapy with alkylating agents such as MUSTARGEN may be associated with an increased incidence of a second malignant tumor, especially when such therapy is combined with other antineoplastic agents or radiation therapy.

The International Agency for Research on Cancer has judged that mechlorethamine is a probable carcinogen in humans. This is supported by limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals. Young-adult female RF mice were injected intravenously with four doses of 2.4 mg/kg of mechlorethamine (0.1% solution) at 2-week intervals with observations for up to 2 years. An increased incidence of thymic lymphomas and pulmonary adenomas was observed. Painting mechlorethamine on the skin of mice for periods up to 33 weeks resulted in squamous cell tumors in 9 of 33 mice.

Mechlorethamine induced mutations in the Ames test, in E. coli, and Neurospora crassa. Mechlorethamine caused chromosome aberrations in a variety of plant and mammalian cells. Dominant lethal mutations were produced in ICR/Ha Swiss mice.

Mechlorethamine impaired fertility in the rat at a daily dose of 500 mg/kg intravenously for two weeks.

Pregnancy
Pregnancy Category D. See WARNINGS.
Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MUSTARGEN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established by well-controlled studies. Use of MUSTARGEN in pediatric patients has been quite limited. MUSTARGEN has been used in Hodgkin's disease, stages III and IV, in combination with other oncolytic agents (MOPP schedule). The MOPP chemotherapy combination includes mechlorethamine, vincristine, procarbazine, and prednisone or prednisolone.2,3

Geriatric Use
Clinical studies of MUSTARGEN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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/s/

SUZANNE C BERKMAN ROBOTTOM
07/18/2013

CLAUDIA B MANZO
07/18/2013
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	March 12, 2012
Reviewer(s):	Suzanne Robottom, Pharm.D. Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D., DRISK
Drug Name(s):	Mechlorethamine
Dosage and Route:	Gel 0.02%, topical
Application Type/Number:	NDA 202317
Applicant/sponsor:	Yaupon Therapeutics
OSE RCM #:	2011-3131

*** This document contains proprietary and confidential information that should not be released to the public. ***

This document is to defer comment on the proposed risk evaluation and mitigation strategy (REMS) for topical mechlorethamine gel 0.02%.

The Division of Hematology Products (DHP) requested that the Division of Risk Management (DRISK) review the proposed REMS for mechlorethamine gel submitted with NDA 202317 (505(b)(2) application) for the proposed indication of topical treatment of (b) (4) Stage 1A, IB (b) (4) mycosis fungoides type cutaneous T-cell lymphoma (CTCL) who have received at least one prior skin-directed therapy (b) (4)

Due to outstanding chemistry manufacturing and control deficiencies DHP plans to issue a Complete Response (CR) letter.

A final discussion on the appropriate risk management strategy will be undertaken after the sponsor submits a satisfactory response to the Complete Response letter.

Please send DRISK a new consult request at such time. This memo serves to close the existing consult request for mechlormethamine gel under NDA 202317.

Please notify DRISK if you have any questions.

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/s/

SUZANNE C BERKMAN ROBOTTOM
03/12/2012

CYNTHIA L LACIVITA
03/12/2012
Concur