

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VALCHLOR™ safely and effectively. See full prescribing information for VALCHLOR.

VALCHLOR (mechlorethamine) gel, for topical use
Initial U.S. Approval: 1949

INDICATIONS AND USAGE

VALCHLOR is an alkylating drug indicated for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy (1).

DOSAGE AND ADMINISTRATION

- For topical dermatological use only (2.1).
- Apply a thin film once daily to affected areas of the skin (2.1, 2.2).

DOSAGE FORMS AND STRENGTHS

- Gel: 0.016% w/w of mechlorethamine (equivalent to 0.02% mechlorethamine HCl) in 60g tubes (3)

CONTRAINDICATIONS

Severe hypersensitivity to mechlorethamine (4)

WARNINGS AND PRECAUTIONS

- Mucosal or eye injury: VALCHLOR exposure to mucous membranes, especially of the eyes, can cause mucosal injury which may be severe. Eye injury may lead to blindness. Immediately irrigate for at least 15 minutes followed by immediate medical consultation (5.1).

- Secondary exposure to VALCHLOR: individuals other than the patient must avoid skin contact with VALCHLOR (2.2, 5.2).
- Dermatitis: Monitor patients for redness, swelling, inflammation, itchiness, blisters, ulceration, and secondary skin infections. Stop treatment or reduce dose frequency (2.1, 5.3).
- Non-melanoma skin cancer: Monitor patients during and after treatment (5.4).
- Embryo-fetal toxicity: Can cause fetal harm. Advise women of potential hazard to a fetus (5.5, 8.1).
- Flammable gel: VALCHLOR is an alcohol-based gel. Avoid fire, flame, and smoking until the gel has dried (2.2, 5.6).

ADVERSE REACTIONS

The most common adverse reactions (≥5%) are dermatitis, pruritus, bacterial skin infection, skin ulceration or blistering, and hyperpigmentation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Ceptaris Therapeutics, Inc. at 1-855-4-VALCHLOR (1-855-482-5245) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing (5.2, 8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VALCHLOR is an alkylating drug indicated for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Dose Modification

For Topical Dermatological Use Only

Apply a thin film of VALCHLOR gel once daily to affected areas of the skin.

Stop treatment with VALCHLOR for any grade of skin ulceration, blistering, or moderately-severe or severe dermatitis (*i.e.*, marked skin redness with edema) [*see Warnings and Precautions (5.3)*]. Upon improvement, treatment with VALCHLOR can be restarted at a reduced frequency of once every 3 days. If reintroduction of treatment is tolerated for at least one week, the frequency of application can be increased to every other day for at least one week and then to once daily application if tolerated.

2.2 Application Instructions

VALCHLOR is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

Patients must wash hands thoroughly with soap and water after handling or applying VALCHLOR.

Caregivers must wear disposable nitrile gloves when applying VALCHLOR to patients and wash hands thoroughly with soap and water after removal of gloves. If there is accidental skin exposure to VALCHLOR, caregivers must immediately wash exposed areas thoroughly with soap and water for at least 15 minutes and remove contaminated clothing [*see Warnings and Precautions (5.2)*].

Patients or caregivers should follow these instructions when applying VALCHLOR:

- Apply immediately or within 30 minutes after removal from the refrigerator. Return VALCHLOR to the refrigerator immediately after each use.
- Apply to completely dry skin at least 4 hours before or 30 minutes after showering or washing. Allow treated areas to dry for 5 to 10 minutes after application before covering with clothing.
- Emollients (moisturizers) may be applied to the treated areas 2 hours before or 2 hours after application.
- Do not use occlusive dressings on areas of the skin where VALCHLOR was applied.
- Avoid fire, flame, and smoking until VALCHLOR has dried [*see Warnings and Precautions (5.6)*].

3 DOSAGE FORMS AND STRENGTHS

The active ingredient in VALCHLOR is mechlorethamine. Each tube of VALCHLOR contains 60g of 0.016% w/w mechlorethamine clear gel (equivalent to 0.02% mechlorethamine HCl).

4 CONTRAINDICATIONS

The use of VALCHLOR is contraindicated in patients with known severe hypersensitivity to mechlorethamine. Hypersensitivity reactions, including anaphylaxis, have occurred with topical formulations of mechlorethamine.

5 WARNINGS AND PRECAUTIONS

5.1 Mucosal or Eye Injury

Exposure of the eyes to mechlorethamine causes pain, burns, inflammation, photophobia, and blurred vision. Blindness and severe irreversible anterior eye injury may occur. Advise patients that if eye exposure occurs, (1) immediately irrigate for at least 15 minutes with copious amounts of water, normal saline, or a balanced salt ophthalmic irrigating solution and (2) obtain immediate medical care (including ophthalmologic consultation).

Exposure of mucous membranes such as the oral mucosa or nasal mucosa causes pain, redness, and ulceration, which may be severe. Should mucosal contact occur, immediately irrigate for at least 15 minutes with copious amounts of water, followed by immediate medical consultation.

5.2 Secondary Exposure to VALCHLOR

Avoid direct skin contact with VALCHLOR in individuals other than the patient. Risks of secondary exposure include dermatitis, mucosal injury, and secondary cancers. Follow recommended application instructions to prevent secondary exposure [see *Dosage and Administration* (2.2)].

5.3 Dermatitis

The most common adverse reaction was dermatitis, which occurred in 56% of the patients [see *Adverse Reactions* (6.1)]. Dermatitis was moderately severe or severe in 23% of patients. Monitor patients for redness, swelling, inflammation, itchiness, blisters, ulceration, and secondary skin infections. The face, genitalia, anus, and intertriginous skin are at increased risk of dermatitis. Follow dose modification instructions for dermatitis [see *Dosage and Administration* (2.1)].

5.4 Non-Melanoma Skin Cancer

Four percent (4%, 11/255) of patients developed a non-melanoma skin cancer during the clinical trial or during one year of post-treatment follow-up: 2% (3/128) of patients receiving VALCHLOR, and 6% (8/127) of patients receiving the mechlorethamine ointment comparator. Some of these non-melanoma skin cancers occurred in patients who had received prior therapies known to cause non-melanoma skin cancer. Monitor patients for non-melanoma skin cancers during and after treatment with VALCHLOR. Non-melanoma skin cancer may occur on any area of the skin, including untreated areas.

5.5 Embryo-fetal Toxicity

Based on its mechanism of action, case reports in humans, and findings in animals, VALCHLOR 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 [see *Use in Specific Populations* (8.1)].

5.6 Flammable Gel

Alcohol-based products, including VALCHLOR, are flammable. Follow recommended application instructions [see *Dosage and Administration* (2.2)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Mucosal or eye injury [see *Warnings and Precautions* (5.1)]
- Secondary exposure to VALCHLOR [see *Warnings and Precautions* (5.2)]

- Dermatitis [see *Warnings and Precautions (5.3)*]
- Non-melanoma skin cancer [see *Warnings and Precautions (5.4)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Trials Experience

In a randomized, observer-blinded, controlled trial, VALCHLOR 0.016% (equivalent to 0.02% mechlorethamine HCl) was compared to an Aquaphor®-based mechlorethamine HCl 0.02% ointment (Comparator) [see *Clinical Studies (14)*]. The maximum duration of treatment was 12 months. Sixty-three percent (63%) of patients in the VALCHLOR arm and 67% in the comparator arm completed 12 months of treatment.

The body system associated with the most frequent adverse reactions was skin and subcutaneous tissue disorders. The most common adverse reactions (occurring in at least 5% of the patients) are shown in Table 1.

Table 1. Most Commonly Reported (≥5%) Cutaneous Adverse Reactions

	VALCHLOR N=128 % of patients		Comparator N=127 % of patients	
	Any Grade	Moderately-Severe or Severe	Any Grade	Moderately-Severe or Severe
Dermatitis	56	23	58	17
Pruritus	20	4	16	2
Bacterial skin infection	11	2	9	2
Skin ulceration or blistering	6	3	5	2
Skin hyperpigmentation	5	0	7	0

In the clinical trial, moderately-severe to severe skin-related adverse events were managed with treatment reduction, suspension, or discontinuation. Discontinuations due to adverse reactions occurred in 22% of patients treated with VALCHLOR and 18% of patients treated with the comparator. Sixty-seven percent (67%) of the discontinuations for adverse reactions occurred within the first 90 days of treatment. Temporary treatment suspension occurred in 34% of patients treated with VALCHLOR and 20% of patients treated with the comparator. Reductions in dosing frequency occurred in 23% of patients treated with VALCHLOR and 12% of patients treated with the comparator.

Reductions in hemoglobin, neutrophil count, or platelet count occurred in 13% of patients treated with VALCHLOR and 17% treated with Comparator.

7 DRUG INTERACTIONS

No drug interaction studies have been performed with VALCHLOR. Systemic exposure has not been observed with topical administration of VALCHLOR; therefore, systemic drug interactions are not likely.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see *Warnings and Precautions (5.5)*]

Risk Summary

Mechlorethamine 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 in animals after a single subcutaneous administration. 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 [see *Warnings and Precautions (5.5)*].

Animal Data

Mechlorethamine caused fetal malformations in the rat and ferret when given as single subcutaneous injections of 1 mg/kg. Other findings in animals included embryoletality and growth retardation when administered as a single subcutaneous injection.

8.3 Nursing Mothers

It is not known if mechlorethamine is excreted in human milk. Due to the potential for topical or systemic exposure to VALCHLOR through exposure to the mother's skin, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

A total of 79 patients age 65 and older (31% of the clinical trial population) were treated with either VALCHLOR or the comparator in the clinical trial. Forty-four percent (44%) of patients age 65 or older treated with VALCHLOR achieved a CAISL response compared to 66% of patients below the age of 65. Seventy percent (70%) of patients age 65 and older experienced cutaneous adverse reactions and 38% discontinued treatment due to adverse reactions, compared to 58% and 14% in patients below the age of 65, respectively. Similar differences in discontinuation rates between age subgroups were observed in the comparator group.

11 DESCRIPTION

VALCHLOR is a topical product that contains mechlorethamine HCl, an alkylating drug. Mechlorethamine HCl is a white to off white solid that is very soluble in water and methanol, partially soluble in acetone, and generally not soluble in organic solvents.

Mechlorethamine HCl is designated chemically as 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine hydrochloride. The molecular weight is 192.52 and the melting point is 108-111°C. The empirical formula is C₅H₁₁Cl₂N•HCl, and the structural formula is: CH₃N(CH₂CH₂Cl)₂•HCl.

Each tube of VALCHLOR contains 60g of a gel containing 0.016% w/w of mechlorethamine (equivalent to 0.02% mechlorethamine HCl) in a base of the following inactive ingredients: diethylene glycol monoethyl ether, propylene glycol, isopropyl alcohol, glycerin, lactic acid, hydroxypropylcellulose, sodium chloride, menthol, edetate disodium, butylated hydroxytoluene.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mechlorethamine, also known as nitrogen mustard, is an alkylating agent which inhibits rapidly proliferating cells.

12.3 Pharmacokinetics

Systemic exposure was undetectable after topical administration of VALCHLOR to patients. Blood samples were analyzed from 16 and 15 patients following treatment with VALCHLOR (mechlorethamine gel 0.016%) and an identical formulation consisting of mechlorethamine 0.032% w/w, respectively. For patients who received mechlorethamine 0.016%, samples were collected to measure mechlorethamine concentrations prior to dosing, on day 1, and at the first month visit. Following the topical administration of mechlorethamine 0.016%, there were no

detectable plasma mechlorethamine concentrations observed in any of the patients. Patients who received mechlorethamine 0.032% had no measurable concentrations of mechlorethamine or half-mustard after 2, 4, or 6 months of treatment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mechlorethamine is a probable carcinogen in humans. There are reports of non-melanoma skin cancer with the use of topical mechlorethamine in patients [see *Warnings and Precautions (5.4)*]. Mechlorethamine was carcinogenic in mice when injected intravenously with four doses of 2.4 mg/kg (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 at a dose of 4 mg/kg for periods of up to 33 weeks resulted in squamous cell tumors in 9 of 33 mice.

Mechlorethamine was genotoxic in multiple genetic toxicology studies, which included mutations in the bacterial reverse mutation assay (Ames test) and chromosome aberrations in mammalian cells. Dominant lethal mutations were produced in ICR/Ha Swiss mice.

The reproductive effects of VALCHLOR have not been studied; however, published literature indicates that fertility may be impaired by systemically administered mechlorethamine. Mechlorethamine impaired fertility in the rat at a daily dose of 500 mg/kg intravenously for two weeks. Treatment with intravenous mechlorethamine has been associated with delayed catamenia, oligomenorrhea, and temporary or permanent amenorrhea.

13.2 Animal Toxicology and/or Pharmacology

Animal studies have shown mechlorethamine to be corrosive to skin and eyes, a powerful vesicant, irritating to the mucous membranes of the respiratory tract, and highly toxic by the oral route.

14 CLINICAL STUDIES

The efficacy of VALCHLOR was assessed in a randomized, multicenter, observer-blind, active-controlled, non-inferiority clinical trial of 260 patients with Stage IA, IB, and IIA mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) who had received at least one prior skin-directed therapy. Qualifying prior therapies included topical corticosteroids, phototherapy, Targretin[®] gel, and topical nitrogen mustard. Patients were not required to be refractory to or intolerant of prior therapies.

Patients were stratified based on Stage (IA vs. IB and IIA) and then randomized to receive VALCHLOR 0.016% (equivalent to 0.02% mechlorethamine HCl) or Aquaphor[®]-based mechlorethamine HCl 0.02% ointment (Comparator) at 13 centers in the United States. Eighteen patients were excluded from the efficacy analysis due to protocol violations involving randomization at a single site.

Study drug was to be applied topically on a daily basis for 12 months. Concomitant use of topical corticosteroids was not permitted during the study. Dosing could be suspended or continued with reduced frequency for dermatitis. The mean daily usage of VALCHLOR gel was 2.8 g (1 to 2 tubes per month). The maximum daily usage was 10.5 g (5 to 6 tubes per month).

Patients were evaluated for a response on a monthly basis for the first 6 months and then every 2 months for the last 6 months using the Composite Assessment of Index Lesion Severity (CAILS) score. The CAILS score is obtained by adding the severity score of each of the following categories for up to 5 index lesions: erythema, scaling, plaque elevation, and surface area. Severity was graded from 0 (none) to 8 (severe) for erythema and scaling; 0 to 3 for plaque elevation; and 0 to 9 for surface area. A response was defined as greater than or equal to 50% reduction in baseline CAILS score which was confirmed at the next visit at least 4 weeks later. A complete response was defined as a confirmed CAILS score of 0. Non-inferiority was considered to have been demonstrated if the lower bound of the 95% confidence interval (CI) around the ratio of response rates (VALCHLOR/Comparator) was greater than or equal to 0.75.

Patients were also evaluated using the Severity Weighted Assessment Tool (SWAT). The SWAT score is derived by measuring each involved area as a percentage of total body surface area (%BSA) and multiplying it by a severity weighting factor (1=patch, 2=plaque, 3=tumor or ulcer). A response was defined as greater than or equal to 50% reduction in baseline SWAT score which was confirmed at the next visit at least 4 weeks later.

The baseline demographics and disease characteristics were balanced between treatment arms. The median age was 57 years in the VALCHLOR arm and 58 years in the comparator arm. The majority of the patients were male (60% in VALCHLOR arm, 59% in Comparator arm) and white (75% in both treatment arms). The median number of prior therapies was 2 in both treatment arms. The most common prior therapy was topical corticosteroids (used in 86% of patients in both treatment arms). The median body surface area (BSA) involvement at baseline was 8.5% (range 1%, 61%) in the VALCHLOR arm and 9% (range 1%, 76%) in the comparator arm.

Sixty percent (60%) of the patients on the VALCHLOR arm and 48% of patients on the comparator arm achieved a response based on the CAILS score. VALCHLOR was non-inferior to the comparator based on a CAILS overall response rate ratio of 1.24 (95% CI 0.98, 1.58). Complete responses constituted a minority of the CAILS or SWAT overall responses (Table 2). The onset of CAILS overall response for both treatment arms showed a wide range from 1 to 11 months.

Table 2. Efficacy in Patients with Mycosis Fungoides-Type CTCL (MF-CTCL)

Response Rates	VALCHLOR N=119	Comparator N=123
CAILS Overall Response (CR+PR), % (N)	60%	48%
Complete Response (CR)	14%	11%
Partial Response (PR)	45%	37%
SWAT Overall Response (CR+PR), %(N)	50%	46%
Complete Response (CR)	7%	3%
Partial Response (PR)	43%	43%

15 REFERENCES

¹ OSHA Hazardous Drugs. OSHA. [Accessed July 3, 2013, from <http://www.osha.gov/SLTC/hazardousdrugs/index.html>]

16 HOW SUPPLIED/STORAGE AND HANDLING

VALCHLOR is supplied in 60g tubes of 0.016% w/w mechlorethamine as a clear gel [NDC 42427-002-60].

Prior to dispensing, store in the freezer at -13°F to 5°F (-25°C to -15°C). Advise patients that refrigerated storage is required once dispensed.

VALCHLOR is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Advise patients of the following and provide a copy of the Medication Guide.

Instructions for Patients and Caregivers for Application of Valchlor:

Apply a thin film of VALCHLOR once daily to affected areas of the skin [see *Dosage and Administration* (2.1)].

Patients must wash hands thoroughly with soap and water after handling or applying VALCHLOR. Caregivers must wear disposable nitrile gloves when applying VALCHLOR to patients and wash hands thoroughly with soap and water after removal of gloves. If there is accidental skin exposure to VALCHLOR, caregivers must immediately wash exposed areas thoroughly with soap and water and remove contaminated clothing [see *Dosage and Administration* (2.2)].

Patients and caregivers should follow these instructions when applying VALCHLOR [see *Dosage and Administration (2.2)*]:

- Apply immediately or within 30 minutes after removal from the refrigerator. Return VALCHLOR to the refrigerator immediately after each use.
- Apply VALCHLOR to completely dry skin at least 4 hours before or 30 minutes after showering or washing. Allow treated areas to dry for 5 to 10 minutes after application before covering with clothing.
- Emollients (moisturizers) may be applied to the treated areas 2 hours before or 2 hours after application of VALCHLOR.
- Occlusive (air or water-tight) dressings should not be used on areas of the skin where VALCHLOR was applied.

Instructions for Patients and Caregivers for Storage of Valchlor

Store VALCHLOR refrigerated at temperatures between 36°F - 46°F (2°C - 8°C). Advise patients that adherence to the recommended storage condition will ensure VALCHLOR will work as expected. Patients should consult a pharmacist prior to using VALCHLOR that has been left at room temperature for longer than one hour per day. Unused product should be discarded after 60 days [see *How Supplied/Storage and Handling (16)*].

With clean hands, replace tube in the original box, then place in the refrigerator. Keep VALCHLOR in its original box out of the reach of children and avoid contact with food when storing in the refrigerator.

Unused VALCHLOR, empty tubes, and used application gloves should be discarded in household trash in a manner that prevents accidental application or ingestion by others, including children and pets.

Mucosal or Eye Injury

Exposure of the eyes to mechlorethamine causes pain, burns, inflammation, photophobia, and blurred vision. Blindness and severe irreversible eye injury may occur. Should eye contact occur, immediately irrigate for at least 15 minutes with copious amounts of water, normal saline, or a balanced salt ophthalmic irrigating solution, followed by immediate ophthalmologic consultation [see *Warnings and Precautions (5.1)*].

Exposure of mucous membranes such as the oral mucosa or nasal mucosa causes pain, redness, and ulceration, which may be severe. Should mucosal contact occur, immediately irrigate for at least 15 minutes with copious amounts of water, followed by immediate medical consultation [see *Warnings and Precautions (5.1)*].

Secondary Exposure to VALCHLOR

Avoid direct skin contact with VALCHLOR in individuals other than the patient. Risks of secondary exposure include dermatitis, mucosal injury, and secondary cancers. Caregivers who help apply VALCHLOR to patients must wear disposable nitrile gloves when handling VALCHLOR. If secondary exposure occurs to eyes, mouth, or nose, immediately irrigate the exposed area for at least 15 minutes with copious amounts of water. Thoroughly wash affected areas of the skin with soap and water [see *Dosage and Administration (2.2)* and *Warnings and Precautions (5.2)*].

Dermatitis

If patients experience skin irritation after applying VALCHLOR, such as redness, swelling, inflammation, itchiness, blisters, ulceration, or secondary skin infections, instruct patients to discuss with their physician options for changes in the treatment plan. The face, genitalia, anus, or intertriginous skin (skin folds or creases) are at increased risk of skin irritation [see *Warnings and Precautions (5.3)*].

Non-Melanoma Skin Cancers

Instruct patients to notify their physician of any new skin lesions and to undergo periodic assessment for signs and symptoms of skin cancer. Non-melanoma skin cancers have been reported in patients receiving the active ingredient in VALCHLOR. Non-melanoma skin cancer may occur at multiple areas, including areas not directly treated with VALCHLOR [see *Warnings and Precautions (5.4)*].

Embryo-fetal Toxicity

Advise women of the potential hazard to a fetus and to avoid pregnancy while using VALCHLOR [see *Warnings and Precautions (5.5)*].

Nursing Mothers

Advise women to discontinue nursing due to the potential for topical or systemic exposure to VALCHLOR [see *Use in Specific Populations* (8.3)].

Manufactured for:
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VALCHLOR is covered by United States Patents 7,872,050; 7,838,564; and 8,450,375.

