MECHLORETHAMINE GEL

Generic	Brand	HICL	GCN	Exception/Other
MECHLORETHAMINE HCL	VALCHLOR		35387	

This drug requires a written request for prior authorization.

GUIDELINES FOR USE

1. Does the patient have a diagnosis of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (CTCLs)?

   If yes, continue to #2.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

2. Has the patient tried prior skin-directed therapy (such as corticosteroids, carmustine, topical retinoids (Targretin, Tazorac), imiquimod, or local radiation therapy)?

   If yes, **approve for 12 months by GPID.**
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

DENIAL TEXT: Approval requires a diagnosis of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (CTCLs) and prior skin-directed therapy (such as corticosteroids, carmustine, topical retinoids (Targretin, Tazorac), imiquimod, or local radiation therapy).

RATIONALE

To promote appropriate utilization of Valchlor based on FDA approved indication and NCCN guidelines.

Valchlor is 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). 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.

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RATIONALE (CONTINUED)
Warnings and precautions include: mucosal or eye injury; secondary exposure to Valchlor; dermatitis; non-melanoma skin cancer; embryo-fetal toxicity; and flammable gel. The most common adverse reactions (≥5%) are dermatitis, pruritus, bacterial skin infection, skin ulceration or blistering, and hyperpigmentation. Valchlor is contraindicated in patients with severe hypersensitivity to mechlorethamine.

Valchlor is pregnancy category D. 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.

Valchlor is a gel formulation of mechlorethamine (nitrogen mustard), an alkylating agent which inhibits rapidly proliferating cells. Mechlorethamine was previously approved as an intravenous formulation for the treatment of mycosis fungoides. Prior to the approval of Valchlor, there were no FDA-approved topical mechlorethamine products; only pharmacy-compounded petroleum ointment or aqueous-based topical preparations were available.

Developed primarily in the skin, CTCLs may progress to involve lymph nodes, blood and visceral organs. They account for about 5 percent of all non-Hodgkin lymphomas (NHL). There will be an estimated 69,740 new cases of NHL and 19,020 deaths from NHL in 2013. The overall 5-year relative survival rate for patients with NHL is 68 percent.

The National Comprehensive Cancer Network (NCCN) recommends skin-directed therapies for the initial treatment of patients with patch/plaque mycosis fungoides-type CTCL with the addition of milder systemic therapy. Localized skin-directed therapies include topical therapy with corticosteroids, mechlorethamine (previously compounded formulations and now Valchlor), carmustine, topical retinoids (Targretin, Tazorac), imiquimod, or local radiation therapy. Generalized skin directed therapies such as phototherapy (UVB or PUVA) and total skin electronic beam therapy are indicated for patients with widespread skin involvement. Systemic therapies with extracorporeal photopheresis, interferons, systemic retinoids, or histone deacetylase inhibitors are preferred over traditional chemotherapy for patients who do not respond to initial skin-directed therapies. They include oral Targretin and intravenous formulations Istodax and Ontak.

The efficacy of Valchlor was assessed in a randomized, active-controlled, non-inferiority clinical trial of 260 patients with Stage IA, IB, and IIA mycosis fungoides-type cutaneous T-cell lymphoma (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.

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RATIONALE (CONTINUED)
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). 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. The onset of CAILS overall response for both treatment arms showed a wide range from 1 to 11 months.

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RATIONALE (CONTINUED)

Efficacy in Patients with Mycosis Fungoides-Type CTCL (From Valchlor Prescribing Information)

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%

FDA APPROVED INDICATIONS

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

REFERENCES

- Ceptaris Therapeutics, Inc. Valchlor [Prescribing Information]. August 2013. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo [Accessed October 21, 2013]
- NCCN Clinical Practice Guidelines in Oncology. Non-Hodgkin's Lymphomas. Version 2.2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf [Accessed October 21, 2013]
- American Cancer Society. Lymphoma of the Skin Detail Guide. Available at: http://www.cancer.org/cancer/lymphomaoftheskin/detailedguide/lymphoma-of-the-skin-detailed-guide-toc [Accessed October 21, 2013]

Library	Commercial	NSA
Yes	Yes	No

Part D Effective: N/A
Commercial Effective: 01/01/14
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Client Approval: 11/13
P&T Approval: 11/13