LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.532

Cutaneous T-Cell Lymphomas (CTCL): Systemic Therapies

Effective Date:	Jan. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Dec. 10, 2024	8.01.36 Extracorporeal Photopheresis
Replaces:	N/A	

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Introduction

The lymphatic system, which is part of the immune system, is composed of specialized cells. Most of these specialized cells are white blood cells known as lymphocytes. There are two main types of lymphocytes: B-cells and T-cells. Lymphoma is cancer that starts in lymphocytes.

Cutaneous T-cell lymphomas are cancers that start in the T-cell lymphocytes and affect the skin. Mycosis fungoides and Sézary syndrome are two examples of lymphomas of the skin.

T-cell lymphoma can arise in other parts of the body such as lymph nodes, lining of the intestines, or the spleen, liver, or colon.

Treating T-cell lymphomas depends on the specific type of cancer and how slow or fast it's growing. This policy describes when particular chemotherapy drugs may be considered medically necessary for T-cell lymphomas that did not respond to initial treatment.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Oral and Topical Drugs	

• **Generic bexarotene capsules oral**
• **Zolinza (vorinostat) oral**
	Generic bexarotene capsules and Zolinza (vorinostat) may be considered medically necessary for when ALL the following are met:
	• The individual has been diagnosed with ONE of the following:
	  ○ Mycosis fungoides
	  ○ Sezary syndrome
	  ○ Cutaneous T-cell lymphoma
	  ○ Peripheral T-cell lymphoma
	AND
	• For simple skin involvement, has tried ONE of the following:
	  ○ Systemic retinoids (isotretinoin, acitretin, etc.)
	  ○ Interferons (alpha, gamma)
	  ○ Methotrexate
	  ○ Campath (alemtuzumab)
	OR
	• For late-stage disease usually with solid organ involvement, has tried ONE of the following:
	  ○ Gemcitabine
	  ○ Liposomal doxorubicin

Targretin (bexarotene) oral	**Targretin (bexarotene capsules) may be considered medically necessary when ALL the following are met:**
	• The individual has been diagnosed with ONE of the following:
	  ○ Mycosis fungoides
	  ○ Sezary syndrome
	  ○ Cutaneous T-cell lymphoma
	  ○ Peripheral T-cell lymphoma
	AND
	• For simple skin involvement, has tried ONE of the following:
	  ○ Systemic retinoids (isotretinoin, acitretin, etc.)
	  ○ Interferons (alpha, gamma)
	  ○ Methotrexate
	  ○ Campath (alemtuzumab)
	OR

Drug	Medical Necessity
Oral and Topical Drugs	

	• For late-stage disease usually with solid organ involvement, has tried ONE of the following:
	  ○ Gemcitabine
	  ○ Liposomal doxorubicin
	AND
	• Has tried and had an inadequate response or intolerance to generic bexarotene capsules

Generic bexarotene topical gel	**Generic bexarotene topical gel may be considered medically necessary for the topical treatment of cutaneous lesions when ALL the following are met:**
	• The individual has been diagnosed with cutaneous T-cell lymphoma (Stage IA and IB)
	AND
	• Has tried and had an inadequate response or intolerance to THREE of the following:
	  ○ Phototherapy (UVB, NB-UVB, PUVA)
	  ○ Topical imiquimod
	  ○ Topical corticosteroids
	  ○ Topical mechlorethamine
	  ○ Local radiation

Targretin (bexarotene) topical gel	**Targretin (bexarotene) topical gel may be considered medically necessary for the topical treatment of cutaneous lesions when ALL the following are met:**
	• The individual has been diagnosed with cutaneous T-cell lymphoma (Stage IA and IB)
	AND
	• Has tried and had an inadequate response or intolerance to THREE of the following:
	  ○ Phototherapy (UVB, NB-UVB, PUVA)
	  ○ Topical imiquimod
	  ○ Topical corticosteroids
	  ○ Topical mechlorethamine
	  ○ Local radiation
	AND

Drug	Medical Necessity
Oral and Topical Drugs	
	• Has tried and had an inadequate response or intolerance to generic bexarotene topical gel
Valchlor (mechlorethamine) topical gel	**Valchlor (mechlorethamine) may be considered medically necessary for topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in individuals who have tried and failed at least 2 of the following therapies:** • Topical corticosteroids (prednisone, triamcinolone, etc.) • Topical imiquimod • Phototherapy • Local radiation

Drug	Medical Necessity
Intravenous Drugs	

Beleodaq (belinostat) IV	**Beleodaq (belinostat) may be considered medically necessary when ALL the following are met:**
	• The individual has been diagnosed with ONE of the following:
	  ○ Relapsed or refractory angioimmunoblastic T-cell lymphoma
	  ○ Anaplastic large cell lymphoma
	  ○ Enteropathy-associated T-cell lymphoma
	  ○ Other peripheral T-cell lymphoma
	• Has received at least one prior systemic therapy

Istodax (romidepsin) IV, Romidepsin IV	**Istodax (romidepsin) and romidepsin injection may be considered medically necessary for when ALL the following are met:**
	• The individual is aged 18 years or older
	• Has been diagnosed with ONE of the following:
	  ○ Mycosis fungoides
	  ○ Sezary syndrome
	  ○ Cutaneous T-cell lymphoma
	AND
	• For simple skin involvement, has tried ONE of the following:
	  ○ Systemic retinoids (isotretinoin, acitretin, etc.)
	  ○ Interferons (alpha, gamma)
	  ○ Methotrexate

Drug	Medical Necessity
Intravenous Drugs	
	○ Campath (alemtuzumab) **OR** • For late-stage disease usually with solid organ involvement, has tried ONE of the following: ○ Gemcitabine ○ Liposomal doxorubicin
Lymphir (denileukin diftitox-cxdl) IV	**Lymphir (denileukin diftitox-cxdl) may be considered medically necessary for the treatment of relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) when ALL the following are met:** • The individual is aged 18 years or older **AND** • Has received at least one prior systemic therapy
Poteligeo (mogamulizumab-kpkc) IV	**Poteligeo (mogamulizumab-kpkc) may be considered medically necessary for the treatment of relapsed or refractory mycosis fungoides or Sezary syndrome when ALL the following are met:** • The individual is aged 18 years or older **AND** • Has received at least one prior systemic therapy

Drug	Investigational
As listed	**All other uses of the medications listed in this policy are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Oral and topical drugs listed in policy may be approved up to 3 months.**

Length of Approval	
Approval	**Criteria**
	Intravenous drugs listed in policy may be approved up to 6 months.
Re-authorization criteria	**Future re-authorization of oral, topical, and intravenous drugs may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

Code	Description
HCPCS	
C9999	Unclassified drugs or biologicals (Lymphir)
J9032	Injection, belinostat (Beleodaq), 10 mg
J9204	Injection, mogamulizumab-kpkc, (Poteligeo) 1 mg
J9318	Injection, romidepsin, nonlyophilized, (Romidepsin IV) 0.1 mg
J9319	Injection, romidepsin, lyophilized, (Istodax) 0.1 mg
J9999	Not otherwise classified, antineoplastic drugs (Lymphir)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

The drugs included in this policy may be managed under either the pharmacy or medical benefit.

Evidence Review

Description

Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) is a rare type of cancer of unknown etiology. In the United States, the estimated annual incidence of CTCL is 0.4 to 1 case per 100,000 (or 1,000 to 3,000 new cases per year). Since most cases are not fatal and individuals can live with CTCL for 10 or more years, estimated US prevalence is approximately 20,000. Approximately 25% of these cases (5,000) have advanced disease.

CTCL is characterized by abnormal malignant T-cells residing in the skin which cause skin lesions and pruritis. The disease often remains confined to the skin and has an indolent course. However, in more aggressive CTCL, the disease may progress to involve other areas of the body such as lymph nodes, blood, and organs. The most common indolent form is mycosis fungoides. This form usually manifests as flat red or pink scaly patches that first appear in sun-protected areas of the body (e.g., buttocks or trunk). As the disease progresses, the patches evolve into a raised pruritic plaque phase. Plaques can also evolve into nodular skin tumors which may ulcerate.

The most common aggressive form of CTCL is Sézary syndrome. This syndrome accounts for about 5% of all CTCL cases and the prognosis is poor. Median survival is usually less than 3 years. It is characterized by widespread erythroderma and the presence of abnormal CD4+ T-cells (called Sézary cells) in both the skin and peripheral blood. This condition may also be accompanied by scaling pruritic plaques or tumors. In advanced stages, individuals with Sézary syndrome may develop alopecia, leonine facies, hyperkeratosis of the palms and soles, nail dystrophy, and parasthesia.

Therapeutic management of CTCL is based largely on the stage of the disease. In early, mild, and slowly progressive stages of the disease, treatment is mainly targeted at reducing symptoms and lesions with topical therapies (topical corticosteroids, topical retinoids (bexarotene, tazarotene), topical chemotherapy (nitrogen mustard, carmustine), local radiation (for limited skin involvement) or electron beam therapy (for severe skin involvement), phototherapy (UVB, nbUVB or patch/thin plaques; PUVA for thicker plaques), topical imiquimod (for limited localized skin involvement). In individuals with advanced stages of the disease, mycosis fungoides and Sezary syndrome, systemic therapies, such as retinoids (e.g., bexarotene, acitretin), may be employed.

Targretin (bexarotene) is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Retinoids are associated with birth defects in humans. Targretin (bexarotene) also caused birth defects when administered orally to pregnant rats. Therefore, it must not be administered during pregnancy.

Targretin (bexarotene) selectively binds and activates retinoid X-receptor subtypes (RXRα, RXRβ, RXRγ). RXRs can form heterodimers with various receptor partners such as retinoic acid receptors (RARs), vitamin D receptor, thyroid receptor, and peroxisome proliferator activator receptors (PPARs). Once activated, these receptors function as transcription factors that regulate the expression of genes that control cellular differentiation and proliferation. Targretin (bexarotene) inhibits the growth in vitro of some tumor cell lines of hematopoietic and squamous cell origin. It also induces tumor regression in vivo in some animal models. The exact mechanism of action of Targretin (bexarotene) in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown.

Bexarotene (Targretin) is indicated for the treatment of cutaneous manifestations of cutaneous T cell lymphoma in individuals who are refractory to at least one prior systemic therapy.

Zolinza (vorinostat) and Istodax (romidepsin) are a histone deacetylase (HDAC) inhibitors with enzymatic inhibitory activity at nanomolar concentrations for HDAC1, HDAC2, HDAC3 [class I], and HDAC6 [class II]. These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. In some cancer cells, HDACs are overexpressed or are aberrantly recruited for oncogenic transcription causing hypoacetylation of core nucleosomal histones. While the exact mechanism of action of these agents has not been fully characterized, in vitro, they cause accumulation of acetylated histones, induces cell cycle arrest, and/or apoptosis of some transformed cells.

Zolinza (vorinostat) is indicated for treatment of cutaneous manifestations in individuals with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.

Istodax (romidepsin) is indicated for treatment of cutaneous T-cell lymphoma (CTCL) or peripheral T-cell lymphoma in individuals who have received at least one prior systemic therapy.

Rationale

Targretin (bexarotene)

Efficacy

No randomized controlled trial for Targretin (bexarotene) in CTCL was found on literature search. The efficacy of oral bexarotene was demonstrated in 2 pivotal multinational, open-label, phase II-III studies in 94 adults with advanced refractory CTCL and 58 with early-stage refractory or persistent CTCL. At recommended dosing (300 mg/m^2/day), overall response to monotherapy as measured by PGA and CAILDS was about 50%. Two supportive open-label studies show systemic combination therapy to be efficacious as measured by response rates.

The efficacy of topical bexarotene was demonstrated in 1 pivotal multinational, open-label, phase II-III study in 50 adults with treatment refractory early stage CTCL. Like systemic bexarotene, overall response was about 50%. Bexarotene gel is the only topical product treatment of CTCL which has received approval by the US Food and Drug Administration (FDA).

Off-label studies for systemic bexarotene have been reported for prevention of breast cancer, head and neck cancer, psoriasis, non-small cell lung cancer, and acute myeloid leukemia. Off-label studies for topical bexarotene have been reported for alopecia areata, parapsoriasis, severe hand dermatitis, and psoriasis.

No comparative studies between bexarotene and therapeutic alternatives for CTCL have been published and no comparative trials are currently underway.

Safety

Targretin (bexarotene) carries a boxed warning the drug should not be used in pregnant females because of its association with birth defects. Systemic bexarotene induces major lipid abnormalities in most individuals, particularly hypertriglyceridemia. Lipids should be monitored

at baseline, weekly for 2-4 weeks, then at 8-week intervals. Abnormalities are reversible with cessation of therapy and can be managed with dose reduction or concomitant antilipemic agents. Other serious adverse events reported following use of systemic bexarotene are pancreatitis, liver function test abnormalities and hepatotoxicities, hypothyroidism, leukopenia, and cataracts. Regular monitoring of related laboratory measures and ophthalmologic evaluations are recommended.

In oral CTCL trials, adverse events leading to dose reduction or study drug discontinuation in at least two individuals were hyperlipemia, neutropenia/leukopenia, diarrhea, fatigue/lethargy, hypothyroidism, headache, liver function test abnormalities, rash, pancreatitis, nausea, anemia, allergic reaction, muscle spasm, pneumonia, and confusion. In topical CTCL trials, adverse events leading to dose reduction or study drug discontinuation in at least two individuals were rash, contact dermatitis, and pruritus.

In 504 individuals participating in oral CTCL and non-CTCL clinical trials, 3 individuals experienced a severe adverse event that was fatal; one each from acute pancreatitis, a subdural hematoma, and liver failure. In topical CTCL trials, only one individual (2%) experienced a severe adverse event (rash).

The most common adverse events observed in individuals with CTCL (n=86) receiving Zolinza (vorinostat) 400 mg once-daily in uncontrolled clinical were diarrhea, fatigue, nausea, thrombocytopenia, anorexia, and dysgeusia. The most commonly reported serious adverse events, regardless of causality, were pulmonary embolism and anemia. In addition, laboratory abnormalities (e.g., increased serum glucose, increased serum creatinine, proteinuria) were observed in all individuals. Approximately 9% of the 86 individuals discontinued the drug due to adverse events.

Istodax (romidepsin)

Efficacy

Istodax (romidepsin) was evaluated in 2 multicenter, single-arm clinical studies in individuals with CTCL. Overall, 167 individuals with CTCL were treated in the US, Europe, and Australia. Study 1 included 96 individuals with confirmed CTCL after failure of at least 1 prior systemic therapy. Study 2 included 71 individuals with a primary diagnosis of CTCL who received at least 2 prior skin directed therapies or one or more systemic therapies. Individuals were treated with romidepsin at a starting dose of 14 mg/m2 infused over 4 hours on days 1, 8, and 15 every 28 days. In both studies, individuals could be treated until disease progression at the discretion of the investigator and local regulators. Objective disease response was evaluated according to a

composite endpoint that included assessments of skin involvement, lymph node and visceral involvement, and abnormal circulating T-cells ("Sézary cells"). The primary efficacy endpoint for both studies was overall objective disease response rate (ORR) based on the investigator assessments, and defined as the proportion of individuals with confirmed complete response (CR) or partial response (PR). CR was defined as no evidence of disease and PR as ≥50% improvement in disease. Secondary endpoints in both studies included duration of response and time to response. Median time to first response was 2 months (range 1 to 6) in both studies. Median time to CR was 4 months in Study 1 and 6 months in Study 2 (range 2 to 9).

Istodax (romidepsin) was evaluated in a multicenter, single-arm, international clinical study in individuals with PTCL who had failed at least 1 prior systemic therapy (Study 3). Individuals in US, Europe and Australia were treated with romidepsin at a dose of 14 mg/m^2 infused over 4 hours on days 1, 8, and 15 every 28 days. Of the 131 individuals treated, 130 individuals had histological confirmation by independent central review and were evaluable for efficacy (HC Population). Six cycles of treatment were planned; individuals who developed progressive disease (PD), significant toxicity, or who met another criterion for study termination were to discontinue treatment. Responding individuals had the option of continuing treatment beyond 6 cycles at the discretion of the individual and Investigator until study withdrawal criteria were met. Primary assessment of efficacy was based on rate of complete response (CR + CRu) as determined by an Independent Review Committee (IRC) using the International Workshop Response Criteria (IWC). Secondary measures of efficacy included IRC assessment of duration of response and objective disease response (ORR, CR + CRu + PR). The complete response rate was 15% and overall response rate was 25%. Similar complete response rates were observed by the IRC across the 3 major PTCL subtypes (NOS, AITL, and ALK-1 negative ALCL). Median time to objective response was 1.8 months (~2 cycles) for the 33 individuals who achieved CR, CRu or PR and was 3.7 months (~4 cycles) for the 19 individuals with complete response. The responses in 11 of the 19 individuals achieving CR and CRu were known to exceed 9.2 months; the follow-up on the remaining 8 individuals was discontinued prior to 9.2 months.

Safety

The safety of Istodax (romidepsin) was evaluated in 185 individuals with CTCL in 2 single arm clinical studies in which individuals received a starting dose of 14 mg/m^2. The mean duration of treatment in these studies was 5.6 months (range: <1 to 83.4 months). Infections were the most common type of serious adverse event reported in both studies with 8 individuals (8%) in Study 1 and 26 individuals (31%) in Study 2 experiencing a serious infection. Serious adverse reactions reported in > 2% of individuals in Study 1 were sepsis and pyrexia (3%). In Study 2, serious adverse reactions in > 2% of individuals were fatigue (7%), supraventricular arrhythmia, central

line infection, neutropenia (6%), hypotension, hyperuricemia, edema (5%), ventricular arrhythmia, thrombocytopenia, nausea, leukopenia, dehydration, pyrexia, aspartate aminotransferase increased, sepsis, catheter related infection, hypophosphatemia and dyspnea (4%). Most deaths were due to disease progression. In Study 1, there were two deaths due to cardiopulmonary failure and acute renal failure. In Study 2, there were six deaths due to infection (4), myocardial ischemia, and acute respiratory distress syndrome. Discontinuations due to an adverse event occurred in 21% of individuals in Study 1 and 11% in Study 2. Discontinuations occurring in at least 2% of individuals in either study included infection, fatigue, dyspnea, QT prolongation, and hypomagnesemia.

Zolinza (vorinostat)

The efficacy and safety of Zolinza (vorinostat) was established in two nonrandomized, uncontrolled, open-label studies in adult individuals with treatment refractory CTCL. A response rate (defined as at least 50% improvement in cutaneous manifestations) of approximately 30% was observed in individuals receiving the approved dosing regimen of 400 mg once daily. Median time to response was <3 months, median response duration was approximately 3-4 months, and median time to progression was approximately 6-7 months.

Beleodaq (belinostat)

Efficacy

Beleodaq (belinostat) is a histone deacetylase (DHAC) inhibitor indicated for the treatment of individuals with relapsed or refractory peripheral T-cell lymphoma (PTCL). It received accelerated approval based on the results of 1 single-arm, phase 2 study using tumor response rate as the primary outcome measure. An improvement in survival or disease-related symptoms has not been established. The pivotal trial has not been published.

In all evaluable individuals (n=120) treated with belinostat, the overall response rate per independent central review using the International Workshop Group (IWG) criteria was 25.8% (n=31), with rates of 23% for PTCL not otherwise specified (NOS) and 46% for angioimmunoblastic T-cell lymphoma (AITL), the 2 largest subtypes enrolled. Further, the response rate was higher (28%) in individuals with baseline platelet counts at or above 100,000/µL and lower (15%) in those with baseline platelet counts below 100,000/µL. The median duration of response based on the first date of response to disease progression or

death was 8.4 months (95% confidence interval [CI], 4.5 to 29.4). Of the responders, the median time to response was 5.6 weeks (range, 4.3-50.4 weeks).

Safety

Sixty-one individuals (47.3%) in the pivotal study experienced serious adverse reactions (grade 3 or higher) while taking belinostat or within 30 days after their last dose. The most common serious adverse reactions (>2%) were pneumonia, pyrexia, infection, anemia, increased creatinine, thrombocytopenia, and multiorgan failure. One treatment-related death associated with hepatic failure was reported in the study. Twenty-five individuals (19.4%) in the pivotal study discontinued treatment with belinostat due to adverse reactions. Dose adjustments were made in 12%.

Valchlor (mechlorethamine)

Efficacy

Valchlor (mechlorethamine) is an alkylating agent indicated for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in individuals who have received prior skin-directed therapy. The efficacy of Valchlor (mechlorethamine) was assessed in a randomized, multicenter, observer-blind, active-controlled, non-inferiority clinical trial of 260 individuals 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, TargretinR gel, and topical nitrogen mustard. Individuals were not required to be refractory to or intolerant of prior therapies. 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). Individuals 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. Individuals 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. Sixty percent (60%) of the individuals on the Valchlor arm and 48% of individuals on the comparator arm achieved a response based on the CAILS score. Valchlor was noninferior 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.

Safety

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 individuals treated with Valchlor and 18% of individuals 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 individuals treated with Valchlor and 20% of individuals treated with the comparator. Reductions in dosing frequency occurred in 23% of individuals treated with Valchlor and 12% of individuals treated with the comparator. Reductions in hemoglobin, neutrophil count, or platelet count occurred in 13% of individuals treated with Valchlor and 17% treated with Comparator. Systemic exposure was undetectable after topical administration of Valchlor to individuals. Blood samples were analyzed from 16 and 15 individuals following treatment with Valchlor (mechlorethamine gel 0.016%) and an identical formulation consisting of mechlorethamine 0.032% w/w, respectively. For individuals 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 individuals. Individuals who received mechlorethamine 0.032% had no measurable concentrations of mechlorethamine or half-mustard after 2, 4, or 6 months of treatment.

For more details, please see package insert for mechlorethamine.

Lymphir (denileukin diftitox-cxdl)

Efficacy

Lymphir (denileukin diftitox-cxdl) is an IL2-receptor-directed cytotoxin indicated for the treatment of adult patients with relapsed or refractory (R/R) Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy. The approval of Lymphir is based on results from the Phase III pivotal Study 302 of CTCL patients who had previously received at least one systemic treatment. Study patients received a median of 4 (min, max: 1, 18) prior anticancer therapies and the primary efficacy population included 69 patients with stage I-III CTCL who were treated with 9 µg/kg/day. The primary efficacy outcome measure was Objective Response Rate (ORR), as assessed by an Independent Review Committee. The ORR was 36.2%, (95% CI: 25.0-48.7), with 8.7% achieving a Complete Response (CR). The median time to response was rapid at 1.41 months, with the majority of responders (~70%) seeing results after 1–2 cycles of treatment. The duration of response was at least 6 months for 52.0% of the patients and 84.4% (54/64) of skin evaluable subjects had a decrease in skin tumor burden and 12.5% (8/64) saw complete clearing of skin disease. Pruritis was evaluated as an exploratory endpoint with 31.7% of patients demonstrating clinically significant pruritus improvement.

Safety

Across three studies of 119 CTCL patients receiving Lymphir, the most common (≥20%) adverse reactions, including laboratory abnormalities, were increased transaminases, albumin decreased, nausea, edema, hemoglobin decreased, fatigue, musculoskeletal pain, rash, chills, constipation, pyrexia, and capillary leak syndrome (CLS). The Lymphir label includes a Boxed Warning for CLS including life-threatening or fatal reactions. CLS was defined in the clinical trials as the occurrence of at least 2 of the following symptoms at any time during Lymphir therapy: hypotension, edema, and serum albumin <3 g/dL. These symptoms were not required to occur simultaneously to be characterized as CLS. Vigilant monitoring of CLS symptoms during treatment is recommended. Based on severity, dose interruption or discontinuation may be warranted.

2013 Update

A literature search for new publications from 01/01/2012 to 04/30/2013 did not reveal new evidence that would require changes to this policy. The policy was compared with current NCCN guideline recommendations and found to be consistent. An updated systematic review of treatment for mycosis fungoides/Sezary syndrome was published by the Cochrane Skin Group in September 2012.

2014 Update

A literature search for new publications from 01/01/2013 to 10/31/2014 did not reveal new evidence that would require changes to the drugs previously in this policy. Added Beleodaq (belinostat), recently approved by FDA with medically necessary indications consistent with current NCCN guideline recommendations.

2015 Update

Valchlor (mechlorethamine) was added to the policy on 07/27/2015, per the NCCN guideline recommendations.

2016 Update

Safety and efficacy reorganized to be under each relevant drug. No major NCCN guideline changes at this time.

2018 Update

A primary literature search from 04/11/2017 to 03/13/2018 did not reveal new evidence that would require change in this policy. No major NCCN guideline changes at this time.

2019 Update

Reviewed prescribing information for all drugs and conducted a primary literature search from 01/01/2018 to 03/31/2019. No new evidence was identified that would require changes to this policy.

2020 Update

Reviewed prescribing information for all drugs and conducted a primary literature search from 01/01/2019 to 08/31/2020. No new evidence was identified that would require changes to this policy.

2021 Update

Reviewed prescribing information for all drugs and conducted a literature search from July 1, 2020, to June 30, 2021. No new evidence was identified that would require changes to this policy. Added brand romidepsin injection to policy with identical coverage criteria as Istodax (romidepsin). Brand romidepsin injection is supplied as a sterile solution while Istodax is supplied as a sterile lyophilized powder.

2022 Update

Reviewed prescribing information for all drugs and conducted a literature search from July 1, 2021. to June 30, 2022. No new evidence was identified that would require changes to this policy.

2023 Update

Reviewed prescribing information for all drugs. No new evidence was identified that would require changes to this policy.

2024 Update

Reviewed prescribing information for all drugs. Updated Istodax (romidepsin) and romidepsin injection coverage criteria to remove use for the treatment of peripheral T-cell lymphoma as this indication was withdrawn from the prescribing information. Updated coverage criteria for oral Targretin (bexarotene) to require trial and failure with generic bexarotene capsules. Updated coverage criteria for topical Targretin (bexarotene) to require trial and failure with generic topical bexarotene. Added coverage criteria for generic topical bexarotene.

References

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25. Beleodaq (belinostat) prescribing information. Acrotech Biopharma; East Windsor, NJ. Revised May 2023.
26. Targretin (bexarotene) capsules prescribing information. Valeant Pharmaceuticals International; Bridgewater, NJ. Revised April 2020.
27. Valchlor (mechlorethamine) prescribing information. Helsinn Therapeutics; Iselin, NJ. Revised May 2020.
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31. Istodax prescribing information. Celgene Corporation; Summit, NJ. Revised January 2023.
32. Lymphir prescribing information. Citius Pharmaceuticals, Inc.; Cranford, NJ. Revised August 2024.

History

Date	Comments
05/10/11	Add to Prescription Drug Section - New Policy.
04/10/12	Replace policy. Policy updated with romidepsin (Istodax) and a new medically necessary policy statement for the treatment of mycosis fungoides/Sezary syndrome

Date	Comments
	for patients refractory to at least one prior systemic therapy. Description, Policy Guidelines and Rationale also updated.
05/28/13	Replace policy. Policy reviewed with literature search/ reference added. No change in policy statement.
12/08/14	Annual review. Medically necessary policy statement added for belinostat, recently approved by the FDA, per NCCN guideline recommendations; approved by P&T December 2014. Literature review performed.
06/18/15	Update Related Policies. Change title to 8.01.36
08/11/15	Annual Review. Added a new agent Valchlor to the existing policy. Updated Policy Guidelines and Rationale sections accordingly.
01/19/16	Coding update. New HCPCS code J9032, effective 1/1/16, added to policy. Minor edit to correct spelling and punctuation.
02/23/16	Coding update. Add J9315.
01/01/17	Annual Review, changes approved December 13, 2016. Safety and efficacy reorganized. Grammar edits.
05/01/17	Annual Review, changes approved April 11, 2017. Criteria for topical bexarotene gel have been added. Also, statement outlining the length of therapy for initial and subsequent approval has been added to the policy.
10/24/17	Policy moved to new format; no change to policy statements.
07/01/18	Annual Review, approved June 5, 2018. Literature review from 04/11/2017 to 03/13/2018. Revised wording on medical necessity.
02/01/19	Interim Review, approved January 8, 2019. Added Poteligeo (mogamulizumab-kpkc) criteria to policy.
05/01/19	Annual Review, approved April 18, 2019. Added bexarotene capsules to policy. No changes to policy statements. Added HCPCS code J3490.
08/01/19	Interim Review, approved July 9, 2019. Updated criteria for Targretin (bexarotene) topical gel. Removed HCPCS code J3490, added HCPCS code J3590.
10/01/19	Coding update, added HCPCS code J9204 (new code effective 10/1/19). Removed HCPCS code J3590.
11/01/20	Annual Review, approved October 22, 2020. No changes to policy statements.
09/01/21	Annual Review, approved August 3, 2021. Added brand romidepsin injection (solution) to policy with identical coverage criteria as Istodax (romidepsin) injection (lyophilized powder). Added HCPCS code C9065 and J3490.
10/01/21	Coding update, Added HCPCS codes J9318 and J9319. Removed HCPCS code J3490.

Date	Comments
12/01/22	Annual Review, approved November 7, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization. Removed HCPCS codes C9065 and J9315.
07/01/23	Annual Review, approved June 26, 2023. No changes to the policy statements.
04/01/24	Annual Review, approved March 12, 2024. Updated Istodax (romidepsin) and romidepsin injection coverage criteria to remove use for the treatment of peripheral T-cell lymphoma as this indication was withdrawn from the prescribing information. Updated coverage criteria for oral Targretin (bexarotene) to require trial and failure with generic bexarotene capsules. Updated coverage criteria for topical Targretin (bexarotene) to require trial and failure with generic topical bexarotene. Added coverage criteria for generic topical bexarotene.
01/01/25	Interim Review, approved December 10, 2024. Added Lymphir (denileukin diftitox-cxdl) for the treatment of relapsed or refractory Stage I-III CTCL. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Added unlisted HCPCS codes C9399 and J9999.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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Call for free language assistance services and appropriate auxiliary aids and services.
Llame para obtener servicios gratuitos de asistencia lingüística, y ayudas y servicios auxiliares apropiados.
呼吁提供免费的语言援助服务和适当的辅助设备及服务。
呼籲提供免費的語言援助服務和適當的輔助設備及服務。
Gọi cho các dịch vụ hỗ trợ ngôn ngữ miễn phí và các hỗ trợ và dịch vụ phụ trợ thích hợp.
무료 언어 지원 서비스와 적절한 보조 도구 및 서비스를 신청하십시오.
Звоните для получения бесплатных услуг по переводу и других вспомогательных средств и услуг.
Tumawag para sa mga libreng serbisyo ng tulong sa wika at angkop na mga karagdagang tulong at serbisyo.
Звертайтесь за безкоштовною мовною підтримкою та відповідними додатковими послугами.
សូមហៅទូរសព្ទទៅសេវាជំនួយភាសាដោយឥតគិតថ្លៃ ព្រមទាំងសេវាកម្ម និងជំនួយចាំបាច់ដែលសមរម្យផ្សេងៗ។
無料言語支援サービスと適切な補助器具及びサービスをお求めください。
ለነፃ የቋንቋ እርዳታ አገልግሎቶች እና ተገቢ ድጋፍ ሰጪ አጋዥ መሳሪያዎችን እና አገልግሎቶችን ለማግኘት በስልክ ቁጥር
Tajaajiloota deeggarsa afaan bilisaa fi gargaarsaa fi tajaajiloota barbaachisaa ta'an argachuuf bilbilaa.
મુફત ભાષા સહાયિતા સેવાઓ અને ઉચિત સહાયિક ચીજો અને સેવાઓ વાસતે કાલ કરો।
Fordern Sie kostenlose Sprachunterstützungsdienste und geeignete Hilfsmittel und Dienstleistungen an.
ໃຫ້ເພື່ອຮັບການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ ແລະ ການບໍລິການ ແລະ ການຊ່ວຍເຫຼືອພິເສດທີ່ເໝາະສົມແບບບໍ່ເສຍຄ່າ.
Rele pou w jwenn sèvis asistans lengwistik gratis ak èd epi sèvis oksilyè ki apwopriye.
Appelez pour obtenir des services gratuits d'assistance linguistique et des aides et services auxiliaires appropriés.
Zadzwoń, aby uzyskać bezpłatną pomoc językową oraz odpowiednie wsparcie i usługi pomocnicze.
Ligue para serviços gratuitos de assistência linguística e auxiliares e serviços auxiliares adequados.
Chiama per i servizi di assistenza linguistica gratuiti e per gli ausili e i servizi ausiliari appropriati.
اتصل للحصول على خدمات المساعدة اللغوية المجانية والمساعدات والخدمات المناسبة.
برای خدمات کمک زبانی رایگان و کمک‌ها و خدمات امدادی مقتضی، تماس بگیرید.

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