BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

PANRETIN® (alitretinoin) Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for: PANRETIN (alitretinoin)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in the diagnosis or in consultation with an Infectious Disease Specialist

Indication
- AIDS-related Kaposi sarcoma (KS) cutaneous lesions and ALL of the following:
  - Fewer than 10 new KS lesions per month

- No symptomatic lymphedema
- No symptomatic pulmonary Kaposi sarcoma
- No symptomatic visceral involvement
- No unexplained fever, night sweats, greater than 10 percent involuntary weight loss, or diarrhea persisting longer than 2 weeks

Age Requirement
- 18 years or older

Baseline Clinical Evaluation
- **ALL** of following:
  - Not a candidate for systemic anti-Kaposi sarcoma therapy
  - Not using systemic anti-Kaposi sarcoma therapy
  - Not using Panretin to prevent new KS lesions developing in other non-affected areas
  - CD4 cell count is greater than 200/µL
  - On potent combination antiretroviral therapy

Alternative Therapies
- Failure, contraindication, intolerance to **ALL** the following:
  - Imiquimod 5% cream
  - Intra-lesional vinblastine
  - Local excision
  - Cryotherapy

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the United States Food and Drug Administration (FDA) (see Definitions section)

Documentation Requirements
- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (CD4 cell count)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- Two 60 gm tubes per month for 3 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

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PANRETIN® (alitretinoin)
Generic Equivalent (if available)

Prescriber Qualification
- Continues to be seen by a physician specializing in or is in consultation with an Infectious Disease Specialist

Clinical Response
- Reduction of at least 50 percent in height and area of lesions where gel was applied
- No progression of lesion height and area where gel was applied
- **ALL** of the following:
  - Individual IS NOT a candidate for systemic anti-Kaposi sarcoma therapy
  - Individual IS NOT using systemic anti-Kaposi sarcoma therapy
  - Individual IS NOT using to prevent new KS lesions developing in other non-affected areas
  - There is NO symptomatic lymphedema
  - There is NO symptomatic pulmonary KS
  - There is NO symptomatic visceral involvement
  - There is NO unexplained fever, night sweats, greater than 10 % involuntary weight loss, or diarrhea persisting > 2 week

Adherence
- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- No significant adverse drug effects such as intense erythema, edema, vesiculation, exfoliative dermatitis
- No significant interacting drugs

Documentation Requirements
- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use (CD4 cell count)

Continuation Therapy Criteria Approval Duration
- Two 60 gm tubes per month for 6 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

PHARMACY COVERAGE GUIDELINE

PANRETIN® (alitretinoin) Generic Equivalent (if available)

1. Off-Label Use of Non-Cancer Medications
2. Off-Label Use of Cancer Medications

Description:

Panretin (alitretinoin) gel, is indicated for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (KS). Panretin (alitretinoin) gel is not indicated when systemic anti-KS therapy is required (e.g., more than 10 new KS lesions in the prior month, symptomatic lymphedema, symptomatic pulmonary KS, or symptomatic visceral involvement). There is no experience to date using Panretin (alitretinoin) gel with systemic anti-KS treatment. Panretin (alitretinoin) gel is not indicated to prevent the development of new KS lesions where it has not been applied.

Alitretinoin (a 9-*cis*-retinoic acid that is related to vitamin A) is a naturally occurring endogenous retinoid that binds to and activates all known intracellular retinoid receptor subtypes (RARα, RARβ, RARγ, RXRα, RXRβ and RXRγ). Once activated these receptors function as transcription factors that regulate the expression of genes that control cellular differentiation and proliferation in both normal and neoplastic cells.

KS is a low-grade vascular tumor that requires infection with human herpes virus 8 (HHV-8, also known as KS-associated herpes virus (KSHV), for development. KS is classified into four types based upon the clinical circumstances in which it develops: classic (sporadic); endemic (especially in Africa); iatrogenic (related to drug induced immune suppression); and epidemic (AIDS-related).

AIDS-related KS is characterized by angiogenesis, inflammation, and cellular proliferation. It has a variable clinical course, ranging from minimal disease presenting as an incidental finding to a rapidly progressing neoplasm that can result in significant morbidity and mortality, depending upon the sites of involvement. KS is the most common tumor arising in HIV-infected people.

KS typically presents as a cutaneous disease with lesions usually occurring on the distal extremities (particularly the lower legs and feet), oral mucosa, face (especially the nose) and genitalia. Other visceral organs can be affected including the gastrointestinal tract, and lungs. Visceral involvement is usually a late manifestation of disease and is unusual as an isolated site for the initial presentation. Although the diagnosis can be made based on the characteristic appearance of the cutaneous lesions, a confirmatory biopsy should be done whenever possible. A biopsy is particularly important in cases with atypical features.

Widespread use of potent combination antiretroviral therapy (ART) has led to a marked decline in the incidence of KS. AIDS-related KS is now seen predominantly among homosexual men rather than in other HIV-infected groups (IV drug users, women, transfusion recipients). The CD4 cell count and HIV viral load are important for staging and prognosis and may be useful in making treatment decisions.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Epidemiologic and clinical types of Kaposi sarcoma:

Type	Predominant risk groups	Cutaneous presentation	Visceral involvement	Clinical course
Classic (sporadic)	3:1 M:F ratio Age > 60 Mediterranean or Central/Eastern European Origin; Middle East	Distal lower extremities	Uncommon	Usually indolent; rarely aggressive & disseminated
Endemic (African)	Male adults Children of both sexes Equatorial Africa	Various (may be similar to classic or more locally aggressive); lower extremity lymphedema in adults; cutaneous disease often absent in children	Internal organs involved in a subset of adult patients Common (lymph nodes and viscera) in children	Indolent to locally invasive in adults Occasional rapid progression with visceral disease in adults Aggressive in children
Iatrogenic (immune suppression related)	Exogenous immunosuppression, esp. solid organ transplant Older patients (> 50) Use of cyclosporine A	Distal lower extremities; may be disseminated	Relatively common	May regress with modification of immunosuppression May be aggressive
Epidemic (AIDS-associated)	Men who have sex with men (developed countries) Heterosexual men & women (Africa)	Localized or disseminated	Common with poor HIV control	Aggressive or indolent May regress with effective HIV treatment

Staging classification for AIDS-related KS:

	Good risk (all of the following)	Poor risk (any of the following)
Tumor (T)	T0: Confined to skin and/or lymph nodes and/or minimal oral disease (non-nodular KS confined to palate)	T1:Tumor-associated edema or ulceration Extensive oral KS Gastrointestinal KS KS in other non-nodal viscera
Immune system (I)	I0: CD4 cell count > 200/µL*	I1: CD4 cell count < 200/µL
Systemic illness (S)	S0: No history of OI or thrush No "B" symptoms	S1: History of OI and/or thrush "B" symptoms present

	Karnofsky performance status > 70	Karnofsky performance status < 70 Other HIV-related illness (eg, neurologic disease, lymphoma)

* A CD4 lymphocyte cut-off of 150 µL may be more discriminatory.
OI: opportunistic infection
"B" symptoms: unexplained fever, night sweats, > 10 % involuntary weight loss, or diarrhea persisting > 2 weeks

Krown, SE, Metroka, C, Wernz, JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol 1989; 7(9):1201-1207.
Krown, SE, Testa, MA, Huang, J. AIDS-related Kaposi's sarcoma: prospective validation of the AIDS Clinical Trials Group staging classification. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol 1997; 15:3085.

Quantity of ointment based on fingertip units:

Area of the Body	FTU required for one application	Weight of ointment required for one application (g)	Weight of ointment required for an adult male to treat BID x 1 week (g)
Face and neck	2.5	1.25	(1.25 x 14) → 17.5 g
Trunk (front or back)	7	3.5	(3.5 x 14) → 49 g
One arm	3	1.5	(1.5 x 14) → 21 g
One hand (one side)	0.5	0.25	(0.25 x 14) → 3.5 g
One leg	6	3	(3 x 14) → 42 g
One foot	2	1	(1 x 14) → 14 g

Resources:

Panretin (alitretinoin) gel product information, revised by Advanz Pharma (US) Corp. 11-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 21, 2025.

Groopman JE. AIDS-related Kaposi sarcoma: Clinical manifestations and diagnosis. In: UpToDate, Aboulafia DM, Baldini EH, Yushak M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2025. Topic last updated August 07, 2024. Accessed April 18, 2025.

Groopman JE. AIDS-related Kaposi sarcoma: Staging and treatment. In: UpToDate, Aboulafia DM, Yushak M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2025.Topic last updated October 02, 2024. Accessed April 18, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Kaposi Sarcoma Version 2.2025 – Updated January 14, 2025. Available at https://www.nccn.org. Accessed April 18, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.