BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/17/18**
SECTION: DRUGS	**LAST REVIEW DATE: 5/17/18**
	LAST CRITERIA REVISION DATE:
	ARCHIVE DATE:

PANRETIN® (alitretinoin) external gel

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

PANRETIN® (alitretinoin) external gel (cont.)

Criteria:

- **Criteria for initial therapy:** Panretin (alitretinoin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is an Infectious Disease Specialist or HIV/AIDS specialist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of AIDS-related Kaposi sarcoma (KS) cutaneous lesions and **ALL** of the following
     - There are fewer than 10 new KS lesions per month
     - There is **NO** symptomatic lymphedema
     - There is **NO** symptomatic pulmonary KS
     - There is **NO** symptomatic visceral involvement
     - There is **NO** unexplained fever, night sweats, < 10 % involuntary weight loss, or diarrhea persisting > 2 weeks

  4. **ALL** of the following:
     - **IS NOT** a candidate for systemic anti-Kaposi sarcoma therapy
     - **IS NOT** using systemic anti-Kaposi sarcoma therapy
     - **IS NOT** using to prevent new KS lesions developing in other non-affected areas
     - The CD4 cell count is > 200/µL

  5. Individual has failure, contraindication or intolerance to **ALL** the following preferred step therapy agents:
     - Imiquimod 5% cream
     - Intra-lesional vinblastine
     - Local excision
     - Radiation therapy

  6. There are **NO** contraindications.
     - Contraindications include:
       - Known hypersensitivity to retinoids or to any of the ingredients of the product.

  Initial approval duration: Two 60 gm tubes per month for 3 months

- **Criteria for continuation of coverage (renewal request):** Panretin (alitretinoin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by an Infectious Disease Specialist or HIV/AIDS specialist

  2. Individual's condition has responded while on therapy
     - Response is defined as:
       - A reduction of at least 50% in height and area of lesion(s) where the gel was applied
       - No progression of lesion height and area where the gel was applied

PANRETIN® (alitretinoin) external gel (cont.)

3. **ALL** of the following:
   - **IS NOT** a candidate for systemic anti-Kaposi sarcoma therapy
   - **IS NOT** using systemic anti-Kaposi sarcoma therapy
   - **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, < 10 % involuntary weight loss, or diarrhea persisting > 2 weeks

4. Individual has been adherent with the medication

5. There are no significant interacting drugs

Renewal duration: Two 60 gm tubes per month for 6 months

Description:

Panretin gel 0.1% contains alitretinoin, is indicated for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (KS). Panretin 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 gel with systemic anti-KS treatment. Panretin 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 persons.

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.

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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.

The 2018 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for AIDS-related Kaposi sarcoma suggests for patients with asymptomatic and cosmetically acceptable limited cutaneous disease may be observed for development of symptoms while continuing ART optimization. Patients with symptomatic or cosmetically unacceptable limited cutaneous disease should receive ART with or without use of local therapy that is the most minimally invasive and least toxic therapy. Local therapy may include any of the following: local excision, topical therapy (alitretinoin 0.1% gel or imiquimod 5% cream), intra-lesional chemotherapy with vinblastine, or radiation therapy. Patients with advanced symptomatic cutaneous, visceral, nodal, or oral disease should be treated with systemic therapy. Liposomal doxorubicin is preferred or paclitaxel with dexamethasone as an alternative therapy. For progressive disease, pomalidomide is preferred, alternatives include bevacizumab, etoposide, gemcitabine, imatinib, interferon alfa-2b, nab-paclitaxel, thalidomide, or vinorelbine.

Definitions:

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

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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 Karnofsky performance status > 70	S1: History of OI and/or thrush "B" symptoms present 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.

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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:

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.

Panretin. Package Insert. Revised by manufacturer 12/2017. Accessed 2/9/18.

Panretin product information accessed 04-09-18 at DailyMed:
https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=panretin&pagesize=20&page=1

NCCN Clinical Practice Guidelines in Oncology: AIDS-related Kaposi Sarcoma. Version 1.2018, Nov 3, 2017.
https://www.nccn.org/professionals/physician_gls/pdf/kaposi.pdf

UpToDate: Classic Kaposi sarcoma: Clinical features, staging, diagnosis, and treatment. Current through Mar 2018.
https://www-uptodate-com.mwu.idm.oclc.org/contents/classic-kaposi-sarcoma-clinical-features-staging-diagnosis-and-treatment?search=kaposi%20sarcoma&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

UpToDate: AIDS-related Kaposi sarcoma: Clinical manifestations and diagnosis. Current through Mar 2018.
https://www-uptodate-com.mwu.idm.oclc.org/contents/aids-related-kaposi-sarcoma-clinical-manifestations-and-diagnosis?search=kaposi%20sarcoma&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

UpToDate: AIDS-related Kaposi sarcoma: Staging and treatment. Current through Mar 2018.
https://www-uptodate-com.mwu.idm.oclc.org/contents/aids-related-kaposi-sarcoma-staging-and-treatment?search=kaposi%20sarcoma&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.