BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/01/16**
SECTION: DRUGS	**LAST REVIEW DATE: 9/20/18**
	LAST CRITERIA REVISION DATE: 9/20/18
	ARCHIVE DATE:

TARGRETIN® (bexarotene) oral capsule & 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.**

TARGRETIN® (bexarotene) oral capsule & external gel (cont.)

Criteria:

- **Criteria for initial therapy:** Targretin oral capsule & external gel is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual is 18 years of age or older

  2. A confirmed diagnosis of **ONE** of the following:
     - For **oral Targretin capsules**, cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) that is refractory to at least one prior systemic therapy
       - Systemic therapy may include: oral retinoids (acitretin, bexarotene, & isotretinoin), alpha-interferon, Zolinza (vorinostat), Istodax (romidepsin), methotrexate, cyclophosphamide, chlorambucil, Nipent (pentostatin), and other
     - For **Targretin external gel**, CTCL (Stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies
       - Topical therapy may include: topical corticosteroids, topical chemotherapy (such as nitrogen mustard and carmustine), local superficial radiation, phototherapy (such as PUVA and UVB), total skin electron beam radiation and topical imiquimod
     - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1, 2A, or 2B

  3. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - Lipid panel
     - Liver function tests
     - Thyroid function tests
     - Complete blood count with differentia
     - Pregnancy test one week before starting therapy in a woman of child bearing potential

  4. There are **NO** contraindications
     - Contraindications include:
       - Woman of child bearing potential who is pregnant

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Targretin oral capsule & external gel is considered ***medically necessary*** and will be approved with documentation of **ALL** of the following:

  1. The CTCL has not worsened while on therapy
     - Worsening or progression is defined as worsening of index lesion(s) or development of new cutaneous tumor lesions or development of non-cutaneous manifestations of disease

  2. Individual has been adherent with the medication

TARGRETIN® (bexarotene) oral capsule & external gel (cont.)

3. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse drug effect such as:
        - Liver tests that exceed 3x ULN for AST, ALT, or bilirubin
        - Hepatotoxicity
        - Pancreatitis
        - Neutropenia

4. **For a woman**, obtaining monthly pregnancy tests in a woman of child bearing potential or likely to become pregnant

5. **For a woman** of child bearing potential or likely to become pregnant is using two reliable forms of contraception, one of which is non-hormonal

6. **For a male** on Targretin who has a female partner of child bearing potential and is using condoms

7. There are no significant interacting drugs

Renewal duration: 12 months

Description:

Targretin (bexarotene) capsules are indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients who are refractory to at least one prior systemic therapy. Targretin (bexarotene) 1% gel is indicated for the topical treatment of cutaneous lesions in patients with CTCL (Stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies.

Lymphoma is a common blood cancer. There are two main forms of lymphoma: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when lymphocytes grow and multiply uncontrollably, and travel to other parts of the body, such as lymph nodes, spleen, bone marrow, blood, or other organs. Two types of lymphocytes can develop into lymphomas: B-lymphocytes (B-cells) and T-lymphocytes (T-cells). T-cell lymphomas account for approximately 15 percent of all NHLs in the United States.

One of the most common forms of T-cell lymphoma is cutaneous T-cell lymphoma (CTCL), a general term for T-cell lymphomas that involve the skin. CTCL also can involve the blood, the lymph nodes, and other internal organs. Most patients with CTCL experience only skin symptoms, without serious complications; however, approximately 10 percent of those who progress to later stages develop serious complications. Early stage CTCL is typically indolent; some patients with early-stage CTCL might not progress to later stages at all, while others might progress rapidly, with the cancer spreading to lymph nodes and/or internal organs.

Mycosis fungoides (MF) and Sezary syndrome (SS) are two types of CTCL. MF (also known as Alibert-Bazin syndrome or granuloma fungoides) is the most common form of CTCL that generally affects the skin. In MF, malignant T-cells migrate and accumulate in the skin, initially resulting in dry skin and red rash that may or may

not itch, eventually other skin lesions form. The malignant T-cells may also involve lymph nodes and spread to other areas such as liver, spleen, and lungs. SS is a more aggressive form of CTCL with widespread skin involvement, enlarged lymph nodes and malignant lymphocytes (Sezary cells) in the skin, lymph nodes, and blood.

Lymphoma of the skin is classified into various stages depending upon skin (T), node (N), viscera (M), and blood (B) involvement. In Stage IA, less than 10% of the skin is covered with patches, papules, and/or plaques, lymph nodes are not enlarged, there is no visceral involvement, and the blood may or may not contain circulating sezary cells, defined as < 5% of peripheral blood. With Stage IB, 10% or more of the skin is covered with patches, papules, and/or plaques. The lymph nodes are not enlarged, there is no visceral involvement, and the blood may or may not contain circulating sezary cells, defined as < 5% of peripheral blood.

In Stage IIA, any amount of skin may be covered with patches, papules and/or plaques, lymph nodes are enlarged and may or may not have abnormal cells, there is still no visceral involvement, and the blood may or may not contain circulating sezary cells. Stage IIB has the same characteristics except now there are one or more tumorous skin lesions.

With Stage III, there is erythrodermic skin (greater than 80% of body surface with red patches, papules, or plaques), the lymph nodes may or may not be enlarged, when enlarged the nodes may or may not contain abnormal cells, and there is no visceral involvement. With Stage IIIA there are no circulating seazry cells in the blood, with Stage IIIB there are circulating sezary cells.

In Stages IVA and IVB, patches, papules, plaques or tumors involve any amount of the skin surface. The lymph nodes tend to be enlarged and contain atypical cells and there is a significant level of Seazry cells in the blood. Patients with visceral involvement are classified as Stage IVB.

Sezary syndrome is a leukemic form of CTCL in which there is significant blood involvement with sezary cells, lymphadenopathy, and erythrodermic skin.

Stages IA, IB, and IIA are considered early stage MF. Prognosis and survival depends on the stage at diagnosis. In the management of early-stage MF, skin-directed therapies may be categorized in two ways: “skin-limited therapies” for limited or localized disease and “skin-generalized therapies” for generalized skin involvement.

Skin-limited therapies include: topical corticosteroids, topical chemotherapy (such as nitrogen mustard and carmustine), local superficial radiation, topical retinoids (such as bexarotene and tazarotene), phototherapy (such as PUVA and UVB), and topical imiquimod.

Skin-generalized therapies include: topical corticosteroids, topical chemotherapy (such as nitrogen mustard and carmustine), phototherapy (such as PUVA and UVB), and total skin electron beam radiation.

Systemic therapies include: oral retinoids (acitretin, bexarotene, & isotretinoin), alpha-interferon, Zolinza (vorinostat), Istodax (romidepsin), methotrexate, cyclophosphamide, chlorambucil, Nipent (pentostatin), and others.

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).

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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. 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 bexarotene in the treatment of CTCL is unknown.

Resources:

Targretin Capsule. Package Insert. Revised by manufacturer 5/2013. Accessed 08-04-2015, 07-22-2016.

Targretin Gel. Package Insert. Revised by manufacturer 7/2013. Accessed 08-04-2015, 07-22-2016.

Targretin Gel. Package Insert. Revised by manufacturer 10/2015. Accessed 07-27-2017.

Targretin Capsule. Package Insert. Revised by manufacturer 06/2016. Accessed 07-27-2017, 08-16-18

Targretin Gel. Package Insert. Revised by manufacturer 06/2016. Accessed 08-16-2018.

UpToDate: Treatment of early stage (IA to IIA) mycosis fungoides. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-early-stage-ia-to-iia-mycosis-fungoides?source=search_result&search=cutaneous%20t-cell%20lymphoma&selectedTitle=7~108

UpToDate: Treatment of Sezary syndrome. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-sezary-syndrome?source=search_result&search=cutaneous%20t-cell%20lymphoma&selectedTitle=14~108

NCCN Clinical Practice Guidelines in Oncology: T-cell lymphomas. Version 2.2017, Feb 21, 2017. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf

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.

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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.