BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

Bexarotene external gel
Bexarotene oral capsule
TARGRETIN® (bexarotene) oral capsule
TARGRETIN® (bexarotene) external gel

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 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 precertification 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.

Criteria:

Bexarotene oral capsule
TARGRETIN (bexarotene) oral capsule

- **Criteria for initial therapy:** Targretin (bexarotene) or generic bexarotene oral capsule is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. Individual is 18 years of age or older

3. A confirmed diagnosis of **ONE** of the following:
    a. Cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) that is refractory to at least one prior systemic therapy
        i. Systemic therapy may include: oral retinoid (acitretin or isotretinoin), alpha-interferon, Zolinza (vorinostat), Istodax (romidepsin), methotrexate, cyclophosphamide, chlorambucil, Nipent (pentostatin), and other

    b. 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 and 2A

4. Request for **brand Targretin (bexarotene) oral capsule**: Individual has failure, contraindication per FDA label or intolerance to **generic bexarotene oral capsule**

5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    a. Fasting lipid profile
    b. Thyroid function tests
    c. Negative pregnancy test one week before starting therapy in a woman of childbearing potential

6. There are **NO** FDA-label contraindications, such as:
    a. Woman of childbearing potential who is pregnant

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Targretin (bexarotene) or generic bexarotene oral capsule is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met (**samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual's condition responded while on therapy with response defined as:
    a. No evidence of disease progression
        i. 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
    b. Documented evidence of efficacy, disease stability and/or improvement
        i. Evidence of efficacy or improvement ids defined as at least a 50% improvement or complete disappearance of the index lesion(s)

3. Individual has been adherent with the medication

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

5. There are no significant interacting drugs

6. For woman of childbearing potential there are monthly negative pregnancy tests

Renewal duration: 12 months

- 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:

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

2. **Off-Label Use of Cancer Medications**

Bexarotene gel
TARGRETIN (bexarotene) gel

- **Criteria for initial therapy:** Targretin (bexarotene) external gel or generic bexarotene external gel is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Dermatologist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of **ONE** of the following:
    a. Cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) Stage IA and IB who have refractory or persistent disease after other therapies or who have not tolerated other therapies
        i. 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

    b. 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 and 2A

4. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    a. Negative pregnancy test one week before starting therapy in a woman of childbearing potential

5. Request for **brand Targretin external gel**: Individual has documented failure, contraindication per FDA label or intolerance to **generic bexarotene external gel**

6. There are **NO** FDA- label contraindications, such as:
    a. Woman of childbearing potential who is pregnant

7. There are no significant interacting drugs

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Targretin (bexarotene) external gel or generic bexarotene external gel is considered ***medically necessary*** and will be approved with documentation of **ALL** of the following (**samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Dermatologist

2. Individual's condition responded while on therapy with response defined as:
    a. No evidence of disease progression
        i. 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
    b. Documented evidence of efficacy, disease stability and/or improvement
        i. Evidence of efficacy or improvement is defined as at least a 50% improvement or complete disappearance of the index lesion(s)

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse drug effect such as:
        a. Severe skin rash, itching or skin pain

5. There are no significant interacting drugs

6. For woman of childbearing potential there are monthly negative pregnancy tests

Renewal duration: 12 months

PHARMACY COVERAGE GUIDELINE

Bexarotene external gel
Bexarotene oral capsule
TARGRETIN® (bexarotene) oral capsule
TARGRETIN® (bexarotene) external gel

- 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:

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

  2. **Off-Label Use of Cancer Medications**

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 Sezary 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 Sezary 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 depend 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).

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.

PHARMACY COVERAGE GUIDELINE

Bexarotene external gel
Bexarotene oral capsule
TARGRETIN® (bexarotene) oral capsule
TARGRETIN® (bexarotene) external gel

Resources:

Bexarotene capsule product information, revised by Upsher-Smith Laboratories, Inc. 06-2017. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 25, 2021.

Bexarotene liquid filled capsule product information, revised by Mylan Pharmaceuticals, Inc. 06-2018. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 25, 2021.

Targretin (bexarotene) liquid filled capsule product information, revised by Bausch Health US, Inc. 04-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 25, 2021.

Targretin (bexarotene) gel product information, revised by Bausch Health US, Inc. 02-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 25, 2021.

Hoppe RT, Kim YH. Clinical manifestations, pathologic features, and diagnosis of mycosis fungoides. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed August 25, 2021.

Hoppe RT, Kim YH, Horwitz S. Treatment of early stage (IA to IIA) mycosis fungoides. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed August 25, 2021.

Hoppe RT, Kim YH, Horwitz S. Treatment of advanced stage (IIB to IV) mycosis fungoides. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed August 25, 2021.

Rook AH, Olen EA. Clinical manifestations, pathologic features, and diagnosis of Sezary syndrome. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed August 25, 2021.

Hoppe RT, Kim YH. Staging and prognosis of mycosis fungoides and Sezary syndrome. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed August 25, 2021.

Kim EJ, Rook AH. Treatment of Sezary syndrome. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed August 25, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Primary Cutaneous Lymphomas Version 2.2021 – Updated March 04, 2021. Available at https://www.nccn.org. Accessed August 25, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): T-Cell Lymphomas Version 1.2021 – Updated October 05, 2020. Available at https://www.nccn.org. Accessed August 25, 2021.

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.