

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Targretin® (bexarotene capsule – Valeant, generics)

TAC APPROVAL DATE: 09/20/2017

OVERVIEW

Bexarotene capsule is 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.¹ Bexarotene capsule has a Boxed Warning about birth defects and bexarotene must not be administered to a pregnant patient.

Bexarotene, a member of the retinoid class of drugs, selectively binds and activates retinoid X receptor subtypes (RXR α , RXR β , RXR γ).¹ Retinoid X receptors, once activated, 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 and it also induces tumor regression (*in vivo*) in some animal models. The exact mechanism of action in the treatment of CTCL is unknown.

DISEASE OVERVIEW

T-cell lymphoma accounts for approximately 15% of all non-Hodgkin lymphoma (NHL) in the US.² CTCL is one of the most common forms of T-cell lymphoma.²⁻³ The World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) published the classification of primary CTCL in 2007.⁴ The CTCLs are grouped according to clinical behavior: indolent: mycosis fungoides, folliculotropic mycosis fungoides, pagetoid reticulosis, granulomatous slack skin, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, subcutaneous panniculitis-like-T-cell lymphoma, and primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional entity); or aggressive: Sézary syndrome, primary cutaneous natural killer/T-cell lymphoma - nasal type, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (provisional entity), cutaneous gamma/delta-positive T-cell lymphoma (provisional entity), and primary cutaneous peripheral T-cell lymphoma-unspecified.

The most common type of CTCL is mycosis fungoides and its variants, which accounts for approximately 50% to 70% of all CTCLs.⁴ Skin symptoms associated with mycosis fungoides include patches, plaques, or tumors and treatment is directed at the skin or the entire body (systemic).²⁻³ Sézary syndrome is an advanced, variant form of mycosis fungoides and is characterized by the presence of lymphoma cells in the blood. Patients with Sézary syndrome will have extensive thin, red, itchy rashes usually covering over 80% of the body and treatment will generally include systemic therapies since the use of skin-directed therapies alone is typically inadequate. Skin-directed therapies are useful for patch and limited plaque disease. Systemic therapies are reserved for more advanced disease and initiation of systemic therapy is usually deferred until patients have not responded well to topical therapies.

Primary cutaneous CD30+T-cell lymphoproliferative disorders represent a spectrum of CTCL that includes primary cutaneous anaplastic large cell lymphoma (ALCL), lymphomatoid papulosis, and “borderline” cases with overlapping clinical and histopathologic features.³ Primary cutaneous ALCL represents about 8% of cutaneous lymphoma cases. Lymphomatoid papulosis has been reported to be associated with other

lymphomas, including mycosis fungoides and primary or systemic ALCL. Treatment is dependent on extent of disease; systemic therapies are recommended for more extensive or advanced disease.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on T-cell lymphomas (version 2.2017) provide treatment recommendations for the different types of CTCLs.³ Initial treatment options for patients with mycosis fungoides or Sézary Syndrome consist of skin-directed therapies with the addition of milder systemic therapies (Category A drugs) for refractory, persistent, or progressive disease with skin-directed therapies. Skin-directed therapy options are grouped into two categories: options for limited/localized skin involvement and options for widespread skin involvement. Topical corticosteroids, topical chemotherapy (Valchlor[®] [mechlorethamine gel]), local radiation, topical retinoids (Targretin[®] gel, Tazorac[®] [tazarotene cream/gel]), phototherapy (ultraviolet B [UVB], narrow band UVB [NB-UVB] for patch/thin plaques, and psoralen and ultraviolet A [PUVA] for thicker plaques) and topical imiquimod cream (Aldara[®], generics; Zyclara[®]) are recommended for limited/localized skin involvement. Options for widespread skin involvement are topical corticosteroids, topical chemotherapy (Valchlor[®]), phototherapy (UVB, NB-UVB, and PUVA), and total skin electron beam therapy (TSEBT). Topical retinoids and topical imiquimod are not recommended for widespread disease due to skin irritation toxicity. Systemic Category A therapies are: retinoids (bexarotene capsules [Targretin[®], generics], tretinoin capsules, isotretinoin capsules [Absorica[®], Amnesteem[®], Claravis[™], Myorisan[™], Zenatane[™], generics], acitretin capsules [Soriatane[®], generics]), interferons (Intron-A[®]/Pegasys[®] [interferon-alpha injection], Actimmune[®] [interferon-gamma injection]), histone deacetylase (HDAC) inhibitors (Zolinza[®] [vorinostat capsules], Istodax[®] [romidepsin injection]), extracorporeal photopheresis, and methotrexate tablets or injection. Systemic Category B and C drugs, consisting of chemotherapeutic drugs (e.g., gemcitabine injection [Gemzar[®], generics], liposomal doxorubicin injection [Doxil[®], generics], Leukeran[®] [chlorambucil tablets], cyclophosphamide tablets or injection, Velcade[®] [bortezomib injection]), are recommended for advanced, refractory, or progressive disease. The NCCN also recommends combination therapies (skin-directed plus systemic therapies or two systemic therapies) in some situations.

The NCCN guidelines also list oral bexarotene as treatment option for patients with primary cutaneous ALCL (multifocal lesions) and lymphomatoid papulosis (extensive lesions or symptomatic disease).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of bexarotene capsules. Because of the specialized skills required for evaluation and diagnosis of patients treated with bexarotene capsules as well as the monitoring required for adverse events, approval requires bexarotene capsules to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of bexarotene capsule is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Cutaneous manifestations of cutaneous T-cell lymphoma (CTCL).

A) Initial therapy. Approve bexarotene capsule for 3 years if the patient meets all of the following criteria (i, ii, and iii):

- i.** Bexarotene capsule is prescribed by, or in consultation with, an oncologist or a dermatologist; AND
- ii.** The patient meets ONE of the following criteria (a or b):
 - a)** The patient has tried ONE oral retinoid (tretinoin capsules, isotretinoin capsules [Amnesteem®, Claravis™, generics], acitretin capsules [Soriatane®, generics]), methotrexate, or phototherapy.
(NOTE: An exception to the requirement for a trial of an oral retinoid, methotrexate, or phototherapy can be made if the patient has already used one of the following: interferons, histone deacetylase [HDAC] inhibitors, or extracorporeal photopheresis. These patients are not required to “step back” and try an oral retinoid, methotrexate, or phototherapy) OR
 - b)** The patient has a type of CTCL (e.g., folliculotropic disease, advanced disease) that, according to the prescribing physician, requires treatment with oral bexarotene capsules; AND
- iii.** If brand Targretin is requested, the patient has tried AND cannot take generic bexarotene capsules due to a formulation difference in the inactive ingredient(s) (e.g., difference in dyes, fillers, preservatives) between the brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or a serious adverse reaction **[documentation required]**.

B) Patient is currently receiving bexarotene capsule (Targretin, generics) or has received bexarotene capsules in the past. Approve bexarotene capsule for 3 years if the patient meets the following criteria (i and ii):

- i.** Bexarotene capsule is prescribed by, or in consultation with, an oncologist or dermatologist; AND
- ii.** If brand Targretin is requested, the patient has tried AND cannot take generic bexarotene capsules due to a formulation difference in the inactive ingredient(s) (e.g., difference in dyes, fillers, preservatives) between the brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or a serious adverse reaction **[documentation required]**.

Bexarotene capsules are available as a branded product (Targretin) and as a generic product. Bexarotene capsules are indicated for the treatment of cutaneous manifestations of CTCL in patients who are refractory to at least one prior systemic therapy.¹

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Bexarotene capsules have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for conditions not included in the Recommended Authorization Criteria.

- 1.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

- 1. Targretin® capsule [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; July 2015.

2. Cutaneous T-cell lymphoma. Available at: <http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300151>. Accessed August 1, 2017.
3. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2017 – February 21, 2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on August 1, 2017.
4. Kinney MC, Jones D. Cutaneous T-cell and natural killer (NK)-cell lymphomas. The World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) classification and the increasing recognition of specialized tumor types.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	---	09/20/2017

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; * For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.