BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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TRETINOIN (all-trans retinoic acid [ATRAC]) oral capsule

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.**

TRETINOIN (all-trans retinoic acid [ATRAC]) oral capsule

Criteria:

- **Criteria for initial therapy:** Tretinoin (all-trans retinoic acid [ATRAC]) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in cancer care or is in consultation with an Oncologist, hematologist, or other cancer specialist, depending upon indication or use

2. Individual is 1 year of age or older

3. A confirmed diagnosis of **ONE** of the following:
   - Acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARα gene

   - 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 or 2A

4. Use is for induction of remission

5. Individual has failure, contraindication or intolerance to:
   - Anthracycline chemotherapy

6. Tretinoin for induction therapy is used in combination with arsenic trioxide, gemtuzumab, idarubicin, daunorubicin, or cytarabine depending on white blood cell count and cardiac status

7. After completion of induction therapy with tretinoin, all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL

8. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   - Negative pregnancy test in a woman of child bearing potential
   - Liver function tests
   - Complete blood count

9. There are **NO** contraindications.
   - Contraindications include:
     - Hypersensitivity to tretinoin, any of its components, or other retinoids

10. There is evidence for pregnancy testing and contraception counseling monthly throughout the period of treatment in a woman of child bearing potential

11. Woman patient of child bearing potential is using 2 forms of effective contraception during and for 1 months after therapy

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12. Woman patient who is breast feeding an infant or child should stop breast feeding during therapy

Initial approval duration: 3 months

- **Criteria for continuation of coverage (renewal request):** Tretinoin (all-trans retinoic acid [ATRAC]) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by an Oncologist

2. Individual's condition responded while on therapy
   - Response is defined as:
     - No evidence of disease progression
     - No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use

3. Individual has been adherent with the medication

4. 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 effect such as:
     - Retinoic acid-APL syndrome
     - Rapidly evolving leukocytosis
     - Pseudotumor cerebri
     - Thrombosis (venous and arterial)
     - Respiratory compromise – pleural effusion, pulmonary edema, respiratory insufficiency
     - Hepatotoxicity

5. There is evidence for pregnancy testing and contraception counseling monthly throughout the period of treatment in a woman of child bearing potential

6. Woman patient of child bearing potential is using 2 forms of effective contraception during and for 1 month after therapy

7. Woman patient who is breast feeding an infant or child should stop breast feeding during therapy

8. There are no significant interacting drugs

Renewal duration: 6 months

TRETINOIN (all-trans retinoic acid [ATRAC]) oral capsule

Description:

Tretinoin (all-trans retinoic acid [ATRAC]) capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARα gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline based chemotherapy is contraindicated. Tretinoin is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with tretinoin.

In general therapy with tretinoin should be discontinued 30 days after achievement of complete remission or after 90 days of treatment, whichever occurs first. Initiation of therapy with tretinoin may be based on the morphological diagnosis of acute promyelocytic leukemia. Confirmation of the diagnosis of APL should be sought by detection of the t(15;17) genetic marker by cytogenetic studies. If these are negative, PML/RARα fusion should be sought using molecular diagnostic techniques. The response rate of other AML subtypes to tretinoin has not been demonstrated; therefore, patients who lack the genetic marker should be considered for alternative treatment.

Tretinoin appears to bind to one or more nuclear receptors and it decreases proliferation and induces differentiation of APL cells; initially it produces maturation of primitive promyelocytes and repopulates the marrow and peripheral blood with normal hematopoietic cells to achieve complete remission. Chemically, tretinoin, USP is all-*trans* retinoic acid and is related to retinol (Vitamin A).

FDA Indication:
Tretinoin capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RAR-alpha gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. Tretinoin is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with tretinoin.

NCCN recommendations:
Acute Myeloid Leukemia - Acute Promyelocytic Leukemia
IMMEDIATE THERAPY:

- Start upon first suspicion of acute promyelocytic leukemia (APL) in patients with clinical and pathologic features of APL. - Category 2A
- Early initiation of tretinoin (ATRA) may prevent the lethal complication of bleeding.

INDUCTION THERAPY:
Low-risk disease (white blood cell count ≤ 10,000/mcL) – All are Category 1

- in combination with arsenic trioxide given daily (preferred regimen)
- in combination with arsenic trioxide given on days 1-5 of week 1 and twice weekly in weeks 2-8 (other recommended regimen)
- in combination with idarubicin (other recommended regimen)

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High-risk disease (white blood cell count > 10,000/mcL) in patients ***with no cardiac issues***
- In combination with arsenic trioxide given on days 1-5 of week 1 and twice weekly in weeks 2-8 and gemtuzumab ozogamicin (preferred regimen) - Category 1
- In combination with arsenic trioxide given daily and gemtuzumab ozogamicin (preferred regimen) - Category 2A
- In combination with idarubicin and arsenic trioxide (preferred regimen) - Category 2A
- In combination with daunorubicin and cytarabine (other recommended regimen) - Category 2A
- In combination with idarubicin (other recommended regimen) - Category 2A

High-risk disease (white blood cell count > 10,000/mcL) in patients ***with cardiac issues*** (low ejection fraction [EF] or prolonged QTc)
- In combination with arsenic trioxide given on days 1-5 of week 1 and twice weekly in weeks 2-8 and gemtuzumab ozogamicin (preferred regimen) - Category 1
- In combination with arsenic trioxide given daily and gemtuzumab ozogamicin - Category 2A
- In combination with gemtuzumab ozogamicin (for patients not able to tolerate arsenic trioxide for reasons which may include prolonged QTc) - Category 2A

CONSOLIDATION THERAPY:
Low-risk disease (white blood cell count ≤ 10,000/mcL) – All are Category 1
- Given daily for 2 weeks every 4 weeks for a total of 7 cycles, in combination with arsenic trioxide (preferred regimen)
- In combination with idarubicin and mitoxantrone (other recommended regimen)
- Given daily for 2 weeks every 4 weeks in consolidation courses 1-4, in combination with arsenic trioxide (other recommended regimen)

High-risk disease (white blood cell count > 10,000/mcL) in patients ***with no cardiac issues***
- Given daily for 2 weeks every 4 weeks in consolidation courses 1-4, in combination with arsenic trioxide (preferred regimen) - Category 1
- Given daily for 28 days for 1 cycle, then daily for 7 days every 2 weeks for 3 cycles, in combination with arsenic trioxide (preferred regimen) - Category 2A
- Given daily for 2 weeks every 4 weeks for a total of 7 cycles, in combination with arsenic trioxide (preferred regimen) - Category 2A
- In combination with gemtuzumab ozogamicin if arsenic trioxide was discontinued due to toxicity - Category 2A
- In combination with arsenic trioxide and daunorubicin (other recommended regimens) - Category 2A
- In combination with idarubicin, cytarabine, and mitoxantrone (other recommended regimen) - Category 2A

High-risk disease (white blood cell count > 10,000/mcL) in patients ***with cardiac issues*** (low ejection fraction [EF] or prolonged QTc)
- Given daily for 2 weeks every 4 weeks in consolidation courses 1-4, in combination with arsenic trioxide - Category 1
- Given daily for 2 weeks every 4 weeks for a total of 7 cycles, in combination with arsenic trioxide - Category 2A

- In combination with gemtuzumab ozogamicin if arsenic trioxide was discontinued due to toxicity - Category 2A
- In combination with gemtuzumab ozogamicin (for patients not able to tolerate arsenic trioxide for reasons which may include prolonged QTc) - Category 2A

FIRST RELAPSE THERAPY (morphologic or molecular): All are Category 2A

- In combination with idarubicin and arsenic trioxide, or in combination with daunorubicin and cytarabine, or in combination with idarubicin, as part of an anthracycline-based regimen in patients with early relapse (<6 months) after ATRA and arsenic trioxide (no anthracycline)
- In combination with arsenic trioxide, with or without gemtuzumab ozogamicin, in patients with no prior exposure to arsenic trioxide or early relapse (<6 months) after ATRA + anthracycline-containing regimen
- In combination with arsenic trioxide, with or without anthracycline or gemtuzumab ozogamicin, in patients with late relapse (≥6 months) after arsenic trioxide-containing regimen

T-Cell Lymphomas - Mycosis Fungoides (MF)/Sézary Syndrome (SS)

Systemic therapy as ***primary*** treatment for

- Stage IB-IIA MF with histologic evidence of folliculotropic or large-cell transformed MF, with or without local radiation therapy for limited tumor lesions - Category 2A
- Stage IB-IIA MF with histologic evidence of folliculotropic or large-cell transformed MF, with or without skin-directed therapy for generalized tumor lesions - Category 2A
- Stage IIB MF with limited tumor lesions, with or without local radiation therapy - Category 2A
- Stage IIB MF with generalized tumor lesions, with or without skin-directed therapy - Category 2A
- Stage III MF with blood B1 involvement, with or without skin-directed therapy - Category 2A
- Stage IV SS - Category 2A
- Stage IA MF with blood B1 involvement, with or without skin-directed therapy - Category 2B
- Stage IB-IIA MF with blood B1 involvement, with or without skin-directed therapy - Category 2B

Systemic therapy as treatment for

- Stage IA MF refractory to multiple previous therapies or progression to > stage IA on skin-directed therapies, with histologic evidence of folliculotropic or large-cell transformed MF, with or without local radiation for limited tumor lesions - Category 2A
- Stage IA MF refractory to multiple previous therapies or progression to > stage IA on skin-directed therapies, with histologic evidence of folliculotropic or large-cell transformed MF, with or without skin-directed therapy for generalized tumor lesions - Category 2A
- Stage IB-IIA MF refractory to multiple previous therapies or progression to > stage IB-IIA - Category 2A
- Stage IIB MF with limited tumor lesions that is relapsed with T3 limited extent disease or has persistent T3 limited extent disease, with or without local radiation therapy - Category 2A
- Stage IIB MF with limited tumor lesions refractory to multiple previous therapies or progression, with or without skin-directed therapies - Category 2A
- Stage IIB MF with generalized tumor lesions that is relapsed with T3 disease or has persistent T3 disease, with or without skin-directed therapy - Category 2A
- Stage III MF with blood B1 involvement that is relapsed or persistent, with or without skin-directed therapy - Category 2A

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- Stage IV SS that is relapsed or persistent - Category 2A
- Stage IA MF with blood B1 involvement refractory to multiple previous therapies or progression to > stage IA on skin-directed therapies, with or without skin-directed therapy - Category 2B

Skin-directed/systemic combination therapy (phototherapy + retinoid) or systemic/systemic combination therapy (retinoid + interferon, photopheresis + retinoid, or photopheresis + retinoid + interferon) as ***primary*** treatment for

- Stage IB-IIA MF with histologic evidence of folliculotropic or large-cell transformed MF, with or without skin-directed therapy for generalized tumor lesions - Category 2A
- Stage IIB MF with generalized tumor lesions, with or without skin-directed therapy - Category 2A
- stage IV SS - Category 2A

Skin-directed/systemic combination therapy (phototherapy + retinoid) or systemic/systemic combination therapy (retinoid + interferon, photopheresis + retinoid, or photopheresis + retinoid + interferon) as treatment for

- Stage IB-IIA MF that is refractory to multiple previous therapies or progression to > stage IB-IIA, with or without skin-directed therapy - Category 2A
- Stage IIB MF with limited tumor lesions refractory to multiple previous therapies or progression, with or without skin-directed therapies - Category 2A
- Stage IIB MF with generalized tumor lesions that is relapsed with T3 disease or has persistent T3 disease, with or without skin-directed therapies - Category 2A
- Stage III MF that is relapsed or persistent - Category 2A
- Stage IV SS that is relapsed or persistent - Category 2A

Resources:

Tretinoin product information accessed 07-21-18 at DailyMed

Tretinoin (all-trans retinoic acid [ATRAC]) product information accessed 07-17-19 at DailyMed

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.

NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. Version 1.2018, Feb 7, 2018.

NCCN Clinical Practice Guidelines in Oncology: T-Cell Lymphomas. Version 4.2018, May 14, 2018.

UpToDate: Molecular biology of acute promyelocytic leikemia. Current through Jun 2018.

UpToDate: Initial treatment of acute promyelocytic leukemia in adults. Current through Jun 2018.

UpToDate: Treatment of relapsed or refractory acute promyelocytic leukemia in adults. Current through Jun 2018.