PHARMACY COVERAGE GUIDELINE

XALKORI® (crizotinib)
Generic Equivalent (if available)

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 prior authorization 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:

➢ **Criteria for initial therapy:** Xalkori (crizotinib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** 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 has a confirmed diagnosis of **ONE** of the following:
    a. Adult (18 years of age or older) with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) rearrangement-positive or c-ros oncogene 1 (ROS-1) positive

    b. Pediatric patient 1 year of age or older (with a body surface area of at least 0.38 m2) and young adult (less than or equal to 21 years of age) with relapsed or refractory, systemic anaplastic large

cell lymphoma (ALCL) that is ALK-positive (the safety and efficacy have not been established in older adults)

c. Adult and pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive

d. 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

3. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Negative pregnancy test in a woman of childbearing potential
   b. Electrocardiogram (ECG) in individuals with a history of or predisposition for QTc prolongation, or who are taking medications that prolong QT
   c. Eastern Cooperative Oncology Group Performance status of 0-2

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as use with:
   a. Strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, others)
   b. Drugs that prolong the QT interval (e.g., Amiodarone, sotalol, quinidine, procainamide, levofloxacin, moxifloxacin, haloperidol, quetiapine, methadone, others)
   c. Drugs that cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Xalkori (crizotinib) and/or generic equivalent (if available) 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 has responded while on therapy with response defined as there is no evidence of disease progression or unacceptable toxicity

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or hemolysis
    b. Interstitial lung disease/pneumonitis
    c. Individual on Xalkori who develops QTc greater than 500 ms or greater than or equal to 60 ms change from baseline with Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia
    d. Life-threatening bradycardia due to Xalkori that is not associated with concomitant medications known to cause bradycardia or hypotension
    e. Severe or life-threatening vision loss
    f. After dose reduction and recovery, a recurrence of neutropenia, thrombocytopenia, or anemia
    g. Unable to tolerate Xalkori after 2 dose reductions

6. The requested dose is at least 250 mg daily

7. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as use with:
    a. Strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, others)
    b. Drugs that prolong the QT interval (e.g., Amiodarone, sotalol, quinidine, procainamide, levofloxacin, moxifloxacin, haloperidol, quetiapine, methadone, others)
    c. Drugs that cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin)

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**

Description:

Xalkori is an oral tyrosine kinase receptor inhibitor indicated for the treatment of individuals with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test and for metastatic NSCLC whose tumors are ROS1 rearrangement positive. Xalkori (crizotinib) is also indicated for the treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive. The safety and efficacy of Xalkori (crizotinib) have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL. Xalkori is also indicated for the treatment of adult and pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive.

PHARMACY COVERAGE GUIDELINE

XALKORI® (crizotinib) Generic Equivalent (if available)

Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of individuals for treatment with Xalkori. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results. The FDA approved the Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular, Inc.) concurrently with the Xalkori approval. This companion diagnostic test is designed to detect rearrangements of the anaplastic lymphoma kinase (ALK) gene in NSCLC.

An FDA-approved test for the detection of the ROS1 rearrangements in NSCLC is not currently available. Identification of individuals with ROS1 rearrangements in NSCLC should use tests performed in the clinical study of the drug. The study included individuals with histologically confirmed advanced NSCLC with ROS1 rearrangement. The ROS1 status of NSCLC tissue samples was determined by laboratory-developed break-apart FISH (96%) or RT-PCR (4%) clinical trial assays. For assessment by FISH, ROS1 positivity required that ≥15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement.

Xalkori is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros) and Recepteur d'Origine Nantais (RON). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE
U.S. department of Health and Human Services, National Institutes of Health, and National Cancer Institute	

Resources:

Xalkori (crizotinib) product information, revised by Pfizer Laboratories Div Pfizer, Inc. 09-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 21, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-small Cell Lung Cancer Version 3.2025 – Updated January 14, 2025. Available at https://www.nccn.org. Accessed April 21, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): T-Cell Lymphomas Version 1.2025 – Updated November 11, 2024. Available at https://www.nccn.org. Accessed April 21, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Soft Tissue Sarcoma Version 5.2024 – Updated March 10, 2025. Available at https://www.nccn.org. Accessed April 21, 2025.

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.