BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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XALKORI® (crizotinib) 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.

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.

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

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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:

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE):

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 activities of daily living (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 adverse event.

Activities of daily living (ADL):

Instrumental ADL: preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Self-care ADL: bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Drug related events:

Ineffective / failure

Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance

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Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer's labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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.

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Criteria:

See "Resources" section for FDA-approved dosage.

- Precertification for Xalkori requires completion of the specific request form in its entirety. 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 will be returned.

- **Initial therapy:** FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Xalkori is considered ***medically necessary*** when **ALL** of the following criteria are met:

1. Individual is 18 years of age or older

2. Individual has medical record documentation of a confirmed diagnosis of metastatic non-small cell lung cancer (NSCLC) with **ONE** of the following:
   - Anaplastic lymphoma kinase (ALK)-positive tumors
   - ROS1- positive tumors

3. **ALL** of the following baseline tests have been completed before initiation of treatment:
   - Electrocardiogram (ECG) in individuals with a history of or predisposition for QTc prolongation, or who are taking medications that prolong QT
   - Comprehensive metabolic panel
   - **ONE** of the following:
     - FDA-approved test confirming the presence of Anaplastic lymphoma kinase (ALK)-positive tumors, such as the Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular, Inc.) or other FDA-approved test
     - Laboratory-developed break-apart FISH clinical trial assay confirming the presence of ROS1-positive tumors. For assessment by FISH, ROS1 positivity require that ≥15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement

4. Absence of **ALL** of the following exclusions:
   - Individual with congenital long QT syndrome
   - Individual on dialysis
   - Individual with ALT or AST > 2.5 times the upper limit of normal (ULN), or > 5 times ULN, if due to liver metastases
   - Individual with total bilirubin > 1.5 times ULN
   - Simultaneous use with drugs known to cause bradycardia such as beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin unless heart rate is ≥ 60 bpm or asymptomatic
   - Simultaneous use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice
   - Simultaneous use with strong CYP3A inducers, such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort
   - Woman of child bearing potential who is pregnant or not currently using effective contraception
   - Woman who is breast feeding an infant or child

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- Male on Xalkori with a female partner of reproductive potential who is not using condoms

➢ **Continuation of coverage (renewal request):** Xalkori is considered ***medically necessary*** with documentation of **ALL** of the following:

1. The individual has benefited from therapy but remains at high risk

2. The condition has not progressed or worsened while on therapy

3. Individual has not developed any contraindications or other exclusions to its continued use
   - Absence of ALL of the following exclusions:
     - Individual on Xalkori who develops QTc > 500 ms or ≥ 60 ms change from baseline with Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia
     - Individual on Xalkori who develops life-threatening bradycardia due to Xalkori that is not associated with concomitant medications known to cause bradycardia or hypotension
     - Individual on Xalkori who develops any grade drug-related interstitial lung disease/pneumonitis
     - Individual on Xalkori who develops an ALT or AST elevation > 3 times ULN with concurrent total bilirubin elevation > 1.5 times ULN (in the absence of cholestasis or hemolysis)

OR

➢ A **non-FDA approved use for the treatment of cancer** of Xalkori is considered ***medically necessary*** when **ONE** of the following criteria are met:

1. **A non-FDA approved use for the treatment of cancer** is recognized as safe and effective for the requested type of cancer, that is listed and supported by in **ONE** of the nationally recognized compendia or guidelines:
   - American Hospital Formulary Service
   - National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium
   - Thomson Micromedex compendium DrugDex
   - Elsevier Gold Standard's Clinical Pharmacology compendium
   - American Society of Clinical Oncologist (ASCO) treatment guidelines
   - Other authoritative reference as identified by the Secretary of the United States Department of Human Health Services

2. **A non-FDA approved use for the treatment of cancer** that is established from clinical trial(s) that have been published in peer reviewed professional medical journal(s) that has been submitted by the prescriber if **ALL** of the following apply:
   - At least two articles from major peer reviewed professional medical journals have recognized, based on scientific or medical criteria, the drug's safety and effectiveness for treatment of the indication for which the drug has been prescribed
   - No article from a major peer reviewed professional medical journal has concluded, based on scientific or medical criteria, that the drug is unsafe or ineffective or that the drug's safety and effectiveness cannot be determined for the treatment of the indication for which the drug has been prescribed

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- The literature meets the uniform requirements for manuscripts submitted to biomedical journals established by the international committee of medical journal editors or is published in a journal specified by the United States department of health and human services as acceptable peer reviewed medical literature pursuant to section 186(t)(2)(B) of the social security act (42 United States Code section 1395x(t)(2)(B))

- Xalkori® for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

Resources:

Xalkori package insert, revised by manufacturer on 3/2016, reviewed on 04/13/2017.

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.

Xalkori package insert, revised by manufacturer on 11/2013, reference ID 3007054) reviewed on 04/24/2014

Xalkori package insert (dated as Revised 08/2011, reference ID 3007054) reviewed on 09/27/2011

2009 Sept 15: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02.

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FDA Product Approved Information for Xalkori:

FDA Approved Indication	FDA Approved Dosage
Xalkori is 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. Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of individuals for treatment with Xalkori. The FDA approved the Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular, Inc.). 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. 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. ROS1 rearrangement positive was determined by laboratory-developed break-apart FISH or RT-PCR clinical trial assays. For assessment by FISH, ROS1 positivity required that ≥15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement. The safety and efficacy of Xalkori in pediatric patients has not been established.	The recommended dose and schedule of Xalkori is 250 mg taken orally twice daily until disease progression or no longer tolerated by the patient Dose modification Tables 1 and 2: Reduce dose as below, if one or more dose reductions are necessary due to adverse reactions of Grade 3 or 4 severity, as defined by NCI Common Terminology Criteria for Adverse Events version 4.0: • First dose reduction: 200 mg taken orally twice daily • Second dose reduction: 250 mg orally taken once daily • Permanently discontinue if unable to tolerate 250 mg taken once daily Dose reduction guidelines for hematologic and non-hematologic toxicities are provided in Tables 1 and 2.

Table 1: Xalkori Dose Modification - Hematologic Toxicities [a]	
CTCAE [b] Grade	Xalkori dosing
Grade 3	Withhold until recovery to Grade 2 or less, then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade 2 or less, then resume at next lower dose
[a] Except lymphopenia (unless associated with clinical event, e.g., opportunistic infections). [b] NCI Common Terminology Criteria for Adverse Events.	

Monitor complete blood counts including differential white blood cell counts monthly and as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs.

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Table 2: Xalkori Dose Modification – Non-Hematologic Toxicities	
Criteria	Xalkori dosing
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 1.5 times ULN	Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume at reduced dose
ALT or AST elevation greater than 3 times ULN with concurrent total bilirubin elevation greater than 1.5 times ULN (in absence of cholestasis or hemolysis)	Permanently discontinue
Any Grade drug-related interstitial lung disease/pneumonitis	Permanently discontinue
QTc greater than 500 ms on or at least 2 separate ECGs	Withhold until recovery to baseline or to a QTc less than 481 ms, then resume at reduced dose
QTc greater than 500 ms or greater than or equal to 60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue
Bradycardia [a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above
Bradycardia [a,b] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring
[a] Heart rate less than 60 beats per minutes (bpm). [b] Permanently discontinue for recurrence.	