BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 3/13/12**
SECTION: DRUGS	**LAST REVIEW DATE: 5/16/19**
	LAST CRITERIA REVISION DATE: 5/16/19
	ARCHIVE DATE:

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.

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.**

XALKORI® (crizotinib) oral capsule (cont.)

Criteria:

- **Criteria for initial therapy:** Xalkori (crizotinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is an Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - Single-agent treatment for recurrent limited or extensive brain metastases in patients with Anaplastic lymphoma kinase (ALK)-positive **or** ROS1-positive non-small cell lung cancer (NSCLC) and stable systemic disease or reasonable systemic treatment options
     - Single-agent therapy for ALK-positive recurrent, advanced or metastatic adenocarcinoma (with mixed subtypes), large cell, squamous cell NSCLC as first-line therapy or continuation of therapy if used first line, except in cases of symptomatic brain lesions or symptomatic systemic disease with multiple lesions
     - Single-agent therapy for recurrent, advanced or metastatic adenocarcinoma (with mixed subtypes) or large cell NSCLC in patients with ROS1-positive tumors as first-line therapy
     - For high level MET amplification or MET exon 14 skipping mutation in adenocarcinoma (with mixed subtypes), large cell, squamous cell lung cancer
     - Single-agent therapy for the treatment of soft tissue sarcoma inflammatory myofibroblastic tumor (IMT) with ALK translocation
     - Second-line and subsequent therapy for relapsed/refractory ALK-positive peripheral T-cell anaplastic large cell lymphoma (ALCL) as a single agent
     - 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:
     - Negative pregnancy test in a woman of child bearing potential
     - Electrocardiogram (ECG) in individuals with a history of or predisposition for QTc prolongation, or who are taking medications that prolong QT
     - Comprehensive metabolic panel
     - Complete blood count with differential

  Initial approval duration: 60 capsules per month for 6 months

XALKORI® (crizotinib) oral capsule (cont.)

- **Criteria for continuation of continuation of coverage (renewal request):** Xalkori (crizotinib) 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 cancer has not progressed or has not worsened while on therapy
  3. Individual has been adherent with the medication
  4. Individual has not developed any significant level 4 adverse drug effects that may exclude use
     - Significant adverse effect such as:
       - Hepatotoxicity
       - Interstitial lung disease/pneumonitis
       - 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
       - Life-threatening bradycardia due to Xalkori that is not associated with concomitant medications known to cause bradycardia or hypotension
       - Severe vision loss
  5. There are no significant interacting drugs

  Renewal duration: 60 capsules per month for 12 months

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 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® (crizotinib) oral capsule (cont.)

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 Comprehensive Cancer Network (NCCN): NSCLC v3.2019 Jan 18, 2019:

Targeted Therapy for advanced or metastatic NSCLC – category 2A (alphabetically by generic name)	
Sensitizing *EGFR* Mutation Positive	*ROS1* Rearrangement Positive
First line therapy:	First line therapy:
Gilotrif (afatinib)	Zykadia (ceritinib)
Tarceva (erlotinib)	Xalkori (crizotinib)
Vizimpro (dacomitinib)	
Iressa (gefitinib)	*BRAF* V600E Mutation Positive
Tagrisso (osimertinib)	First line therapy:
Subsequent therapy:	Tafinlar (dabrafenib)/Mekinist (trametinib)
Tagrisso (osimertinib)	Subsequent therapy:
	Tafinlar (dabrafenib)/Mekinist (trametinib)
ALK Rearrangement Positive	
First line therapy:	*NTRK* Gene Fusion Positive
Alecensa (alectinib)	First line/Subsequent therapy:
Akunbrig (brigatinib)	Vitrakvi (larotrectinib)
Zykadia (ceritinib)	
Xalkori (crizotinib)	PD-L1 Expression $\geq$ 50%
Subsequent therapy:	Keytruda (pembrolizumab)
Alecensa (alectinib)	(Carboplatin or cisplatin) / pemetrexed / Keytruda (pembrolizumab) [non-squamous]
Alunbrig (brigatinib)	Carboplatin / paclitaxel / Avastin (bevacizumab) / Tecentriq (atezolizumab) [non-squamous]
Zykadia (ceritinib)	(Carboplatin or cisplatin) / paclitaxel or albumin bound paclitaxel / Keytruda (pembrolizumab) [squamous]
Lorbrena (lorlatinib)	

XALKORI® (crizotinib) oral capsule (cont.)

Emerging Biomarkers to identify novel therapies for metastatic NSCLC	
Genetic Alteration (i.e., Driver Event)	Available Target Agents with activity against Driver Event
High-level *MET* amplification **or** *MET* exon 14 skipping mutation	Xalkori (crizotinib)
RET rearrangements	Cabozantinib Caprelsa (vandetanib)
ERBB2 (HER2) mutations	Kadcyla (ado-trastuzumab)
Tumor mutation burden (TMB)*	Opdivo (nivolumab) + Yervoy (ipilimumab) Opdivo (nivolumab)
*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.	

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.

Resources:

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 3/2016, reviewed on 04/13/2017.

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

XALKORI® (crizotinib) oral capsule (cont.)

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

Xalkori package insert, revised by manufacturer on 2/2018, reviewed on 04/19/2018.

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.

NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. Version 3.2018, Feb 21, 2018. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Xalkori (crizotinib) product information accessed 03-27-19 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2a51b0de-47d6-455e-a94c-d2c737b04ff7

NCCN Compendium: Xalkori (crizotinib) accessed 03-27-19

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information			
Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:
Prescribing Provider Information			
Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	
Dispensing Pharmacy Information			
Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:	
Requested Medication Information			
Medication Name:	Strength:	Dosage Form:	
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:	

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.