Clinical Policy Title:	crizotinib
Policy Number:	RxA.310
Drug(s) Applied:	Xalkori®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Crizotinib (Xalkori®) is a kinase inhibitor. Crizotinib is indicated for the treatment of:

- patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test.
- 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.

Limitations of Use: The safety and efficacy of Xalkori® have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
crizotinib (Xalkori®)	NSCLC	250 mg PO BID	500 mg/day
	ALCL	280 mg/m^2 PO BID	BSA of 1.7 m^2 or more: 1,000 mg/day PO BSA of 1.52 to 1.69 m^2: 900 mg/day PO BSA of 1.17 to 1.51 m^2: 800 mg/day PO BSA of 0.81 to 1.16 m^2: 500 mg/day PO BSA of 0.6 to 0.8 m^2: 400 mg/day PO

Dosage Forms

- Capsule: 200 mg, 250 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Non-Small Cell Lung Cancer (must meet all)**:**

1. Diagnosis of recurrent, advanced, or metastatic NSCLC;

2. Prescribed by or in consultation with an oncologist;
3. Age 18 years or older;
4. Disease is ALK, ROS1 or MET positive;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 500 mg (2 capsules) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Anaplastic Large Cell Lymphoma (must meet all)**:**
1. Diagnosis of ALK-positive anaplastic large cell lymphoma (a peripheral T-cell lymphoma);
2. Prescribed by or in consultation with an oncologist;
3. Age ~~1 to ≤21 years~~1 year or older;
4. Dose is within FDA maximum limits (see dosing regimen).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

C. Inflammatory Myofibroblastic Tumor (off-label) (must meet all)**:**
1. Diagnosis of ALK-positive inflammatory myofibroblastic tumor (a soft tissue sarcoma);
2. Prescribed by or in consultation with an oncologist;
3. Age 18 years or older;
4. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

D. Histiocytic Neoplasms (off-label) (must meet all)**:**
1. Diagnosis of Langerhans Cell Histiocytosis, Erdheim-Chester Disease, or Rosai-Dorfman Disease;
2. Prescribed by or in consultation with an oncologist;
3. Age 18 years or older;
4. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication that has been authorized by RxAdvance, or documentation supports that member is currently receiving Xalkori® and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):

a. New dose does not exceed 500 mg (2 capsules) per day;
b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
ALK: anaplastic lymphoma kinase
FDA: Food and Drug Administration
MET: mesenchymal-epithelial transition
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer
ROS1: ROS proto-oncogene 1
ALCL: anaplastic large cell lymphoma

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Indication	Dosing Regimen	Maximum Dose
alectinibi (Alecensa®)	ALK Positive NSCLC	600 mg PO BID	1200 mg/day
ceritinib (Zykadia®)	ALK Positive NSCLC	750 mg PO once daily	750 mg/day
brigatinib (Alunbrig®)	ALK Positive NSCLC	90 mg PO QD for 7 days then 180 mg PO once daily	180 mg/day
entrectinib (Rozlytrek®)	ROS1 Positive NSCLC	600 mg PO once daily	600 mg/day

Therapeutic alternatives are listed as Brand name (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings
- Contraindication(s):
  - None reported
- Boxed Warning(s):
  - None reported

APPENDIX D: General Information
- Anaplastic large cell lymphoma (ALCL) is a type of T-cell lymphoma – a non-Hodgkin lymphoma that develops from white blood cells called T cells. Under a microscope, the cancerous cells in ALCL look large, undeveloped and very abnormal ('anaplastic').
- Dose adjustment/ reductions for Grade 3 or 4 toxicity: Interrupt crizotinib therapy per specific instructions below. Restart crizotinib as appropriate at the following reduced doses:
  - First occurrence: 200 mg PO twice daily

- Second occurrence: 250 mg PO once daily
- Third occurrence: Permanently discontinue crizotinib therapy

References

1. Xalkori® Prescribing Information. New York, NY: Pfizer Inc.; January 2021. Available at https://www.xalkori.com/. Accessed April 02, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed April 02, 2021.
3. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer Version 4.2021. Available at www.nccn.org. Accessed April 02, 2021.
4. National Comprehensive Cancer Network Guidelines. Central Nervous System Cancers Version 4.2020. Available at www.nccn.org. Accessed April 02, 2021.
5. National Comprehensive Cancer Network Guidelines. Soft Tissue Sarcoma Version 1.2021. Available at www.nccn.org. Accessed April 02, 2021.
6. National Comprehensive Cancer Network Guidelines. T-Cell Lymphomas Version 1.2021. Available at www.nccn.org. Accessed April 02, 2021.
7. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Updated January 14, 2020. Accessed April 02, 2021.
8. Crizotinib, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed April 02, 2021.
9. Heigener DF, Reck M. Crizotinib. Recent Results Cancer Res. 2018;211:57-65. Accessed April 02, 2021.
10. Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Ann Oncol. 2018;29(11):2214-2222. Accessed April 02, 2021.
11. Blackhall F, Cappuzzo F. Crizotinib: from discovery to accelerated development to front-line treatment. Ann Oncol. 2016;27 Suppl 3:iii35-iii41. Accessed April 02, 2021.
12. Liu P, Zhao L, Pol J, et al. Crizotinib-induced immunogenic cell death in non-small cell lung cancer. Nat Commun. 2019;10(1):1486. Accessed April 02, 2021.
13. Broniscer A, Jia S, Mandrell B, et al. Phase 1 trial, pharmacokinetics, and pharmacodynamics of dasatinib combined with crizotinib in children with recurrent or progressive high-grade and diffuse intrinsic pontine glioma. Pediatr Blood Cancer. 2018;65(7):e27035. Accessed April 02, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated: Clinical Policy Title was updated to "crizotinib". Drug(s) Applied was updated to "Xalkori®". Line of Business Policy Applies to was updated to "All". 2. Clinical policy was updated: Approval duration was updated for both Initial and Continued Approval Criteria; Continued Approval was	07/14/2020	09/14/2020

rephrased to "Currently receiving medication that has been authorized by RxAdvance"; removed requirement to use for all indications for Continued Approval. 3. Appendix B was updated to add Therapeutic Alternatives. 4. Appendix D was updated: Information regarding dose adjustment for toxicity has been added. 5. References were updated.		
Policy was reviewed: 1. Background was updated: Indication for ALCL was added. 2. Dosing Information was updated: ALCL dosing was added. 3. Initial approval criteria were updated: IB. ALCL (off-label) was updated to ALCL. IB.3 was updated to Age 1 to =21 years. IB.4 was updated to 'Dose is within FDA maximum limit (see dosing regimen)' 4. Initial approval criteria were created for Histiocytic Neoplasms (off label use). 5. Approval duration for HIM was removed. 6. Appendix A: Abbreviation/ Acronym Key was updated. 7. Appendix B: Fixed header verbiage was updated as 'Below are suggested therapeutic alternatives.' 8. Appendix D: General Information was updated. 9. References were updated.	04/02/2021	06/10/2021