Introduction

The anaplastic lymphoma kinase (ALK) gene provides instructions for making a specific kind of protein called ALK receptor tyrosine kinase. This protein helps cells communicate. When this gene is damaged, cell growth can get stuck in the “on” position and cells grow uncontrollably. Changes to the ALK gene can lead to non-small-cell lung cancer. Tyrosine kinase inhibitors block specific enzymes, essentially working to turn the cell growth to the “off” position. ALK tyrosine kinase inhibitors specifically targets cancers caused by changes to the ALK gene. This policy describes when this specific form of chemotherapy may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Note: Initial approval period for agents listed below will be 3 months. Continued approval beyond the first 3 months will require documentation showing objective response to therapy
## Drug Medical Necessity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xalkori® (crizotinib)</td>
<td>Xalkori® (crizotinib) may be considered medically necessary for the treatment of advanced or metastatic non-small cell lung cancer that is anaplastic lymphoma kinase (ALK)-positive or ROS proto-oncogene 1 receptor tyrosine kinase (ROS1)-positive, and treatment of inflammatory myofibroblastic tumor (iMT) with the ALK translocation.</td>
</tr>
<tr>
<td>Zykadia® (ceritinib), Alecensa® (alectinib), Alunbrig® (brigatinib)</td>
<td>Zykadia® (ceritinib) and Alecensa® (alectinib) and Alunbrig® (brigatinib) may be considered medically necessary for the treatment of advanced or metastatic non-small cell lung cancer that is anaplastic lymphoma kinase (ALK)-positive.</td>
</tr>
</tbody>
</table>
| Lorbrena® (lorlatinib)       | Lorbrena® (lorlatinib) may be considered medically necessary for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer whose disease has progressed on:  

- Xalkori® (crizotinib) and at least one other ALK inhibitor for metastatic disease  

OR  

- Alecensa® (alectinib) as the first ALK inhibitor therapy for metastatic disease  

OR  

- Zykadia® (ceritinib) as the first ALK inhibitor therapy for metastatic disease |

## Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Approval: All oral oncology drugs, unless otherwise specified</td>
<td>Initial approval for three months, according to the medical necessity criteria specified for each drug.</td>
</tr>
<tr>
<td>Reauthorization</td>
<td>Continued therapy will be approved for periods of one year as long as the drug-specific conditions are met, and the patient has shown and continues to show clinical benefit.</td>
</tr>
</tbody>
</table>
| Documentation             | Initial: Chart notes demonstrating that the patient meets the stated criteria for medical necessity.  

Reauthorization: Chart notes demonstrating that the patient continues to show clinical benefit. |
<table>
<thead>
<tr>
<th>Indication</th>
<th>Investigational</th>
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<tbody>
<tr>
<td>All other uses</td>
<td>All other uses of Xalkori® (crizotinib), Zykadia® (ceritinib), Alecensa® (alectinib), Alunbrig® (brigatinib), and Lorbrena® (lorlatinib) are considered investigational.</td>
</tr>
</tbody>
</table>

**Coding**

N/A

**Related Information**

**Benefit Application**

This policy is managed through the Pharmacy benefit.

**Evidence Review**

**Description**

*The ALK Oncogene*

Activation of ALK occurs through a chromosomal rearrangement that places one of several different 5’ fusion partners and their associated promoter upstream of the 3’ kinase domain of ALK. The most common 5’ fusion partner in NSCLC is EML4, but other, rarer 5’ fusion partners that cause oncogenic transformations have been described. The formation of ALK fusion proteins results in activation and dysregulation of gene expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. EML4-ALK translocations are usually mutually exclusive of EGFR and KRAS mutations.
**Xalkori® (crizotinib)**

Xalkori® (crizotinib) is a small-molecule tyrosine kinase receptor inhibitor, which inhibits ALK, Hepatocyte Growth Factor Receptor (HGFR, c-MET), and Recepteur d’Origine Nantais (RON). ALK gene abnormalities due to mutations or translocations may result in expression of oncogenic fusion proteins (ie, EML4-ALK fusion protein) which alter signaling and expression and result in increased cellular proliferation and survival in tumors which express these fusion proteins. Crizotinib selectively inhibits ALK tyrosine kinase, which reduces proliferation of cells expressing the genetic alteration.

**Zykadia® (ceritinib)**

Zykadia® (ceritinib) is a small-molecule tyrosine kinase receptor inhibitor similar to crizotinib. Ceritinib was approved for treatment of ALK+ NSCLC on the basis of one single-arm, open-label, dose-finding Phase I study. This study started with 59 patients in the dose-escalation phase and recruited an additional 71 patients in the expansion phase, for a total of 130 patients. All patients had ALK-mutated tumors, with the majority (94%) with NSCLC; 68% of patients had previous progression of cancer while receiving crizotinib. The primary outcome was the finding the maximum tolerated dose and secondary outcome was tumor response as measured according to RECIST v1.0 by investigators and a BIRC. The drop-out rate was not reported. There was a partial response in less than half of the patients (41.1% as evaluated by BIRC) and a complete response in only 2.5% of patients. The average progression free survival was 7 months. Previously approved second line agents (docetaxel, pemetrexed, erlotinib) did not have response rates greater than 10% and had progression free survival time of at most 12.3 weeks.

Common adverse events experienced with ceritinib include nausea, elevated liver function tests, diarrhea, and vomiting. Uncommon but serious events reported include interstitial lung disease, hyperglycemia, dyspnea, and prolonged QT interval. Fatal reactions occurred in 5% of patients in clinical trials due to pneumonia, respiratory failure, pneumonitis, pneumothorax, gastric hemorrhage, pulmonary tuberculosis, cardiac tamponade, and sepsis.

**Alunbrig® (brigatinib)**

Alunbrig®(brigatinib) received accelerated FDA approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Brigatinib has in vitro
activity against multiple kinases including ALK, ROS1, IGF-1R, and FLT-3, as well as EGFR deletion and point mutations. Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling proteins STAT3, AKT, ERK1/2, and S6 in in vitro and in vivo assays. Brigatinib also inhibited the in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins. It inhibited the in vitro viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to ALK inhibitors EGFR-Del (E746-A750), ROS1-L2026M, FLT3-F691L, and FLT3-D835Y. Brigatinib exhibited in vivo anti-tumor activity against 4 mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumors in patients who have progressed on crizotinib. Brigatinib is indicated for treating metastatic ALK+ NSCLC in patients that progressed on or were intolerant to crizotinib. It will be available through a limited network of specialty pharmacies.

Brigatinib offers an additional treatment option for NSCLC patients that have progressed on prior targeted therapies as described above. Staff recommends PA to labeled indication, with further research to determine required genetic testing.

**Alecensa® (alectinib)**

Alecensa® (alectinib) is a tyrosine kinase inhibitor indicated for the treatment of patients with ALK-positive, metastatic NSCLC who have progressed on, or are intolerant to crizotinib. In nonclinical studies, alectinib inhibited ALK phosphorlylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT, and decreased tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations. The major active metabolite of alectinib, M4, showed similar in vitro potency and activity. Alectinib and M4 demonstrated in vitro and in vivo activity against multiple mutant forms of the ALK enzyme, including some mutations identified in NSCLC tumors in patients who have progressed on crizotinib.

**ALK+ Non-Small Cell Lung Cancer**

Lung cancer consists of two major types: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). Approximately 85% to 90% of lung cancers are NSCLC. NSCLC is further categorized into three major histological subtypes: adenocarcinoma, squamous cell (epidermoid) carcinoma, and large cell (undifferentiated) carcinoma. Adenocarcinoma is the most common subtype of NSCLC in the United States (about 40% of lung cancers). Several biomarkers have emerged as prognostic and predictive makers for NSCLC. These biomarkers
include epidermal growth factor receptor (EGFR), the 5’ endonuclease of the nucleotide excision repair complex (ERCC1), the k-ras oncogene, the regulatory subunit of ribonucleotide reductase (RRM1), and EML4-ALK fusion oncogene. Activation of ALK has been described as a primary oncogenic driver in about 2-7% of NSCLC patients, or about 10,000 patients in the United States. ALK-positive NSCLC is associated with distinct clinical features, including younger age of onset, absent or minimal smoking history, and adenocarcinoma histology.

In the United States, lung cancer is the second most common cancer and is the primary cause of cancer-related death in both men and women. It is estimated that 226,160 new cases of lung cancer (116,470 in men and 109,690 in women) are expected to be diagnosed in the United States in 2012. An estimated 160,340 deaths from lung cancer, accounting for about 28% of all cancer deaths, are expected to occur in the United States in 2012. More than 70% of patients are diagnosed with stage III to IV disease. Survival outcomes in people with lung cancer vary depending on the stage of the cancer at diagnosis. Only about 15.6% of all lung cancer patients are alive 5 years or more after diagnosis. The financial burden of lung cancer treatment in the United States is estimated to be $10.3 billion per year.

**Xalkori® (crizotinib)**

Xalkori® (crizotinib) efficacy was demonstrated in two multicenter, single-arm studies that enrolled 255 patients with locally advanced or metastatic ALK-positive NSCLC: a phase II study (Study A [PROFILE 1005]) and a part two expansion cohort of a phase I dose-escalation study (Study B [Study 1001]). Patients enrolled into these studies had received prior systemic therapy, with the exception of 15 patients in Study B who had no prior systemic treatment for locally advanced or metastatic disease. The primary efficacy endpoint in both studies was investigator-determined Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST). Patients received 250 mg of crizotinib orally twice daily until disease progression or until intolerable side effects were reported. In Study A, there was 1 complete and 67 partial responses for an ORR of 50% (95% CI: 42%, 59%). In Study B, there were 2 complete and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%). The median response duration was 41.9 weeks and 48.1 weeks in Studies A and B, respectively. Resistance to therapy was not addressed because of the short duration of follow-up; but this is under study. Two ongoing phase III clinical trials are comparing the efficacy of crizotinib versus traditional chemotherapy in ALK-positive NSCLC patients; however, comparative effectiveness has not been demonstrated.

Adverse effects were less than would be expected with conventional cytotoxic chemotherapy, but serious adverse events and treatment-related deaths related to crizotinib have been observed. Adverse events led to dosage reductions in 44% and 29% of patients in Studies A and
B, respectively. Most adverse events were mild to moderate (Grade 1 or Grade 2). The most common (≥ 25%) adverse events were vision disorder, nausea, vomiting, diarrhea, edema, and constipation. Grade 3 or Grade 4 adverse events observed in ≥ 2% of patients included dyspnea, increased ALT levels, and neutropenia. Severe or fatal pneumonitis was reported in a small number of patients on crizotinib therapy.

2013 Update

Added treatment of inflammatory myofibroblastic tumor with ALK translocation (NCCN category 2A).

2014 Update

Policy updated with new ALK tyrosine kinase inhibitor, ceritinib.

2015 Update

Added treatment of ROS1-positive non-small-cell lung cancer with crizotinib (NCCN category 2A).

2016 Update

Policy updated with new ALK tyrosine kinase inhibitor, alectinib.

2017 Update

Policy updated with literature review for the previous year. A statement outlining the length of therapy for initial and subsequent approval has been added to the policy.
2018 Update

Policy updated with no changes. Third-generation inhibitor loratinib is currently in phase III clinical trials, expecting FDA approval in August 2018. Added reauthorization criteria and documentation statement.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/12/12</td>
<td>New policy, add to Prescription Drug section.</td>
</tr>
<tr>
<td>07/08/13</td>
<td>Minor Update – Clarification was added to the policy that it is managed through the member’s pharmacy benefit; this is now listed in the header and within the coding section.</td>
</tr>
<tr>
<td>10/14/13</td>
<td>Replace policy. Medically necessary indications for crizotinib expanded to include treatment of inflammatory myofibroblastic tumor (iMT) with the ALK translocation.</td>
</tr>
<tr>
<td>11/10/14</td>
<td>Annual Review. Policy updated with literature review; medically necessary policy statement added for the new ALK tyrosine kinase inhibitor, ceritinib. References 12-15 added.</td>
</tr>
<tr>
<td>09/08/15</td>
<td>Annual Review. Policy updated with literature review; reference 16 added. Medically necessary policy statement for Xalkori® (crizotinib) updated to include the indication of ROS proto-oncogene 1 receptor tyrosine kinase (ROS1)-positive.</td>
</tr>
<tr>
<td>04/01/16</td>
<td>Interim update, changes approved March 8, 2016. Medically necessary policy statement added for the new ALK tyrosine kinase inhibitor, alectinib.</td>
</tr>
<tr>
<td>05/01/17</td>
<td>Annual Review, changes approved April 11, 2017. A statement outlining the length of therapy for initial and subsequent approval has been added to the policy.</td>
</tr>
<tr>
<td>07/01/17</td>
<td>Interim update. approved June 13, 2017. Policy moved into the new format. Added coverage criteria for Alunbrig® (brigatinib).</td>
</tr>
<tr>
<td>10/01/17</td>
<td>Interim review approved September 21, 2017. Alecensa, Zykdia, Alunbrig changed to first-line.</td>
</tr>
<tr>
<td>07/01/18</td>
<td>Annual Review, approved June 22, 2018. Added reauthorization criteria and documentation statement.</td>
</tr>
<tr>
<td>03/01/19</td>
<td>Interim Review, approved February 12, 2019. Added coverage criteria for Lorbrena® (lorlatinib).</td>
</tr>
</tbody>
</table>
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytay a Pakdaar ket naglaon iti Napatge nga Impormasion. Daytay a pakdaar malabin nga adda ket naglaon iti napatge nga impormasion maipanggep a iti aplikasyon yyo coverage babaen iti Premera Blue Cross. Daytay ket malabin dagiti importante a pelsa iti daytay a pakdaar. Malabin nga adda rumbeng nga aramideng nga adda sakkay dagiti partikular a naituding nga adda tapno mapagtaliadegy a ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytay nga impormasion ken tulong ti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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Premera Blue Cross. This statement will contain key dates that are important to maintain your health insurance or cost assistance. Please call 800-722-1471 (TTY: 800-842-5357) to receive your personal information.

Kosa (Burmese): အိန္ဒိယဘာသာ;
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