PHARMACY COVERAGE GUIDELINE

ROZLYTREK™ (entrectinib)
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:** Rozlytrek (entrectinib) 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 patient, 18 years of age or older, with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive and have an ECOG performance status of ≤ 2

    b. Adult and pediatric patients 1 month of age and older with solid tumors and **ALL** of the following:
        i. Have a neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion without a known acquired resistance mutation,

ii. Metastatic or where surgical resection is likely to result in severe morbidity
iii. Progressed following treatment or have no satisfactory alternative therapy
iv. ECOG performance status of ≤ 1

c. 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. Assessment of left ventricular ejection fraction in an individual with heart failure symptoms or known risk factors
   b. Electrocardiogram
   c. Liver function tests
   d. Electrolytes
   e. Serum uric acid
   f. Negative pregnancy test in a woman of childbearing potential

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. Agent will not be used in individual with severe renal impairment (CrCl less than 30 mL/min)

6. Agent will not be used in individual with moderate (total bilirubin greater than 1.5 to 3 times ULN with any AST) or severe (total bilirubin greater than 3 times ULN with any AST) hepatic impairment

7. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as:
   a. Coadministration with moderate or strong CYP3A inhibitors (e.g., fluconazole, erythromycin, ketoconazole, itraconazole, posaconazole, others) in pediatric individuals less than 2 years
   b. Coadministration of moderate or strong CYP3A inducers (e.g., armodafinil, bexarotene, bosentan, rifampin, rifabutin, phenobarbital, carbamazepine, others) in all individuals
   c. Coadministration of products with a known potential to prolong QT/QTc interval (e.g., amiodarone, sotalol, quinidine, procainamide, levofloxacin, moxifloxacin, haloperidol, others) in all individuals

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Rozlytrek (entrectinib) 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. ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULT (in the absence of cholestasis or hemolysis) or life-threatening hepatic impairment that recurs or does not resolve within 4 weeks
    b. QTc prolongation, torsades de pointes, polymorphic ventricular tachycardia, or signs and symptoms of serious arrhythmia
    c. Life-threatening congestive heart failure
    d. Worsening left ventricular ejection fraction
    e. Life-threatening central nervous system adverse effects
    f. Toxicity that does not resolve within 4 weeks of dose reduction or recurrence of severe or life-threatening toxicity

6. Individual has not had two dose reductions for adverse reactions

7. Agent will not be used in an individual with severe renal impairment (CrCl less than 30 mL/min)

8. Agent will not be used in individual with moderate (total bilirubin greater than 1.5 to 3 times ULN with any AST) or severe (total bilirubin greater than 3 times ULN with any AST) hepatic impairment

9. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as:
    a. Coadministration with moderate or strong CYP3A inhibitors (e.g., fluconazole, erythromycin, ketoconazole, itraconazole, posaconazole, others) in pediatric individuals less than 2 years
    b. Coadministration of moderate or strong CYP3A inducers (e.g., armodafinil, bexarotene, bosentan, rifampin, rifabutin, phenobarbital, carbamazepine, others) in all individuals
    c. Coadministration of products with a known potential to prolong QT/QTc interval (e.g., amiodarone, sotalol, quinidine, procainamide, levofloxacin, moxifloxacin, haloperidol, others) in all individuals

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**

ROZLYTREK™ (entrectinib)
Generic Equivalent (if available)

Description:

Rozlytrek (entrectinib) is a kinase inhibitor indicated for the treatment of adult patients, 18 years of age or older, with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive; and for adult and pediatric patients 1 month of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy. The NTRK gene fusion positive solid tumor indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Patients should be selected for the treatment of metastatic NSCLC based on the presence of *ROS1* rearrangement(s) in tumor specimens. In addition, patients should be selected for treatment of locally advanced or metastatic solid tumors based on the presence of a *NTRK* gene fusion. However, *a*n FDA-approved test for the for detection of *ROS1* rearrangement(s) in NSCLC and for detection of *NTRK* gene fusion in solid tumors are not available

Entrectinib inhibits tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC. TRKA, TRKB, and TRKC are encoded by neurotrophic receptor tyrosine kinase (NTRK) genes *NTRK1, NTRK2*, and *NTRK3*, respectively. Entrectinib also inhibits proto-oncogenic tyrosine-protein kinase ROS1 and anaplastic lymphoma kinase (ALK). M5 (the major active entrectinib metabolite) demonstrated similar activity (in vitro) against TRK, ROS1, and ALK. Fusion proteins that include TRK, ROS1, or ALK kinase domains act as oncogenic drivers to promote hyperactivation of downstream signaling pathways, resulting in unchecked cell proliferation.

Definitions:

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

Response Evaluation Criteria in Solid Tumors (RECIST):

- Complete response – disappearance of all target lesions
- Partial response – 30% decrease in the sum of the longest diameter of target lesions
- Progressive disease – 20% increase in the sum of the longest diameter of target lesions or the appearance of one or more new lesions
- Stable disease – small changes that so not meet the above criteria of PR and PD

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	

PHARMACY COVERAGE GUIDELINE

ROZLYTREK™ (entrectinib)
Generic Equivalent (if available)

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	

Resources:

Rozlytrek (entrectinib) product information, revised by Genentech, Inc. 01-2024. 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 18, 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.