PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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ROZLYTREK™ (entrectinib)

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.**

ROZLYTREK™ (entrectinib)

Criteria:

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

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. 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 12 years 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. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring 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 child bearing potential

  4. Will not be used in individual with severe renal impairment (CrCl < 30 mL/min)

  5. Will not be used in individual with moderate (total bilirubin > 1.5-3x ULN) or severe (total bilirubin > 3x ULN) hepatic impairment

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Rozlytrek (entrectinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

ROZLYTREK™ (entrectinib)

2. Individual's condition responded while on therapy
    a. Response is defined as:
        i. No evidence of disease progression
        ii. Documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication

4. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Hepatic impairment
        ii. QTc prolongation
        iii. Torsades de pointes, polymorphic ventricular tachycardia, or signs and symptoms of serious arrhythmia
        iv. Heart failure
        v. Intolerable central nervous system adverse effects such as mood disorders, dizziness, sleep disturbances, memory impairment, amnesia, hallucinations, and delirium
        vi. Toxicity that does not resolve within 4 weeks of dose reduction or recurrence of severe or life-threatening toxicity
        vii. Skeletal fractures

5. Has not had two dose reductions for adverse reactions

6. Will not be used in individual with severe renal impairment (CrCl < 30 mL/min)

7. Will not be used in individual with moderate (total bilirubin > 1.5-3x ULN) or severe (total bilirubin > 3x ULN) hepatic impairment

8. There are no significant interacting drugs

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**

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

ROZLYTREK™ (entrectinib)

patients 12 years 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:

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	

Resources:

Rozlytrek (entrectinib) product information, revised by Genentech, Inc. 11-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2022.

ROZLYTREK™ (entrectinib)

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.