

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/or 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.
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Medical Necessity Requirements for ROZLYTREK (entrectinib)

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by an oncologist or in consultation with an oncologist

Indication

- Metastatic non-small cell lung cancer (NSCLC) with tumors that are *ROS1*-positive
- Solid tumors with ALL the following:
 - Neurotrophic tyrosine receptor kinase (NTRK) gene fusion without known acquired resistance mutation

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- Metastatic or surgical resection likely to result in severe morbidity
- Progressed following treatment or no satisfactory alternative therapy
- Other oncologic direct treatment uses listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement

- **NSCLC:** 18 year or older
- **Solid tumors:** 1 month or older

Baseline Clinical Evaluation

- **NSCLC:** Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- **Solid tumors:** ECOG performance status 0-1
- Left ventricular ejection fraction assessment (if heart failure symptoms or risk factors)
- Electrocardiogram
- Liver function tests
- Electrolytes
- Serum uric acid
- Negative pregnancy test (if woman of childbearing potential)

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the United States Food and Drug Administration (FDA)

Safety

- No use in severe renal impairment (creatinine clearance less than 30 mL/min)
- No use in moderate (total bilirubin greater than 1.5 to 3 times upper limit of normal with any AST) or severe (total bilirubin greater than 3 times upper limit of normal with any AST) hepatic impairment
- No concomitant use of:
 - Moderate or strong CYP3A inhibitors (e.g., fluconazole, erythromycin, ketoconazole, itraconazole, posaconazole, etc.) in pediatric individuals less than 2 years
 - Moderate or strong CYP3A inducers (e.g., armodafinil, bexarotene, bosentan, rifampin, rifabutin, phenobarbital, carbamazepine, etc.)
 - Products with known potential to prolong QT/QTc interval (e.g., amiodarone, sotalol, quinidine, procainamide, levofloxacin, moxifloxacin, haloperidol, etc.)

Documentation Requirements

- A completed request form must be submitted, including:
 - Chart notes
 - Lab results (left ventricular ejection fraction, electrocardiogram, liver function tests, electrolytes, serum uric acid, pregnancy test)
 - Supporting clinical documentation

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Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications

- Continues to be seen by a physician specializing in or is in consultation with an oncologist

Clinical Response

- No evidence of disease progression or unacceptable toxicity

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No significant adverse drug effects such as:
 - ALT or AST greater than 3 times upper limit of normal with concurrent total bilirubin greater than 1.5 times upper limit of normal (in absence of cholestasis or hemolysis)
 - Life-threatening hepatic impairment that recurs or does not resolve within 4 weeks
 - QTc prolongation, torsades de pointes, polymorphic ventricular tachycardia, or serious arrhythmia
 - Life-threatening congestive heart failure
 - Worsening left ventricular ejection fraction
 - Life-threatening central nervous system adverse effects
 - Toxicity that does not resolve within 4 weeks of dose reduction or recurrence of severe or life-threatening toxicity
- No more than two dose reductions for adverse reactions
- No use in severe renal impairment (creatinine clearance less than 30 mL/min)
- No concomitant use of:
 - Moderate or strong CYP3A inhibitors (e.g., fluconazole, erythromycin, ketoconazole, itraconazole, posaconazole, etc.) in pediatric individuals less than 2 years
 - Moderate or strong CYP3A inducers (e.g., armodafinil, bexarotene, bosentan, rifampin, rifabutin, phenobarbital, carbamazepine, etc.)
 - Products with known potential to prolong QT/QTc interval (e.g., amiodarone, sotalol, quinidine, procainamide, levofloxacin, moxifloxacin, haloperidol, etc.)

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Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use from above criteria

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year
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Criteria for Off-Label Use Requests:

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
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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, an FDA-approved test for the 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.

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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 do 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

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

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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.

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