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Section:	Prescription Drugs	**Effective Date:**	January 1, 2024
Subsection:	Antineoplastic Agents	**Original Policy Date:**	August 30, 2019
Subject:	Rozlytrek	**Page:**	1 of 5

Last Review Date: December 8, 2023

Rozlytrek

Description

Rozlytrek (entrectinib)

Background

Rozlytrek (entrectinib) is an inhibitor of the tropomyosin receptor kinases (TRK) TRKA, TRKB, and TRKC, proto-oncogene tyrosine-protein kinsase ROS1, and anaplastic lymphoma kinase (ALK) with IC_{50} values of 0.1 to 2 nM. TRKA, B, and C are encoded by the genes *NTRK1*, *NTRK2*, and *NTRK3,* respectively. Rozlytrek also inhibits JAK2 and TNK2 with IC_{50} values > 5nM. Fusion proteins that include TRK, ROS1, or ALK kinase domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation (1).

Regulatory Status

FDA-approved indications: Rozlytrek is a kinase inhibitor indicated for the treatment of: (1)

1. Adult patients with *ROS1*-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.
2. Adult and pediatric patients older than 1 month of age with solid tumors that:
   a. Have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion as detected by an FDA-approved test without a known acquired resistance mutation,
   b. Are metastatic or where surgical resection is likely to result in severe morbidity, and
   c. Have progressed following treatment or have no satisfactory alternative therapy.

Hepatotoxicity may occur in patients on Rozlytrek therapy. Liver tests should be monitored including ALT and AST every 2 weeks during the first month of treatment, then monthly thereafter and as clinically indicated (1).

Monitoring should occur in patients who have or who are at risk for QTc interval prolongation, including assessing QT interval and electrolytes at baseline and periodically during treatment. For those patients with symptoms of known risk factors for congestive heart failure, assessment of left ventricular ejection fraction should be completed prior to initiation of Rozlytrek (1).

Females of reproductive potential should be advised to avoid becoming pregnant while being treated, as Rozlytrek may cause fetal harm. Females of reproductive potential should be advised to use effective contraception during treatment with Rozlytrek and for 5 weeks after the final dose. Males with a female partner of reproductive potential should be advised to use effective contraception during treatment with Rozlytrek and for 3 months after the final dose (1).

Patients on Rozlytrek should avoid coadministration with moderate and strong CYP3A4 inhibitors, inducers, or with sensitive CYP3A4 substrates (1).

The safety and effectiveness of Rozlytrek in pediatric patients less than 1 month of age with solid tumors who have an NTRK gene fusion have not been established. The safety and effectiveness of Rozlytrek in pediatric patients less than 18 years of age with ROS1-positive NSCLC have not been established (1).

Related policies
Vitrakvi

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Rozlytrek may be considered **medically necessary** if the conditions indicated below are met.

Rozlytrek may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Metastatic Non-Small Cell Lung Cancer (NSCLC)
    a. 18 years of age or older
    b. *ROS1*-positive as detected by an FDA-approved test

2. NTRK Gene Fusion-Positive Solid Tumors with **ALL** of the following:
    a. 1 month of age or older
    b. Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion as detected by an FDA-approved test without a known acquired resistance mutation
    c. Metastatic **OR** surgical resection is likely to result in severe morbidity
    d. Patient has progressed following treatment **OR** patient has no satisfactory alternative therapy

AND ALL of the following for **ALL** diagnoses:

1. Prescriber agrees to monitor AST and ALT
2. Prescriber agrees to monitor for QTc prolongation
3. Prescriber agrees to monitor for signs and symptoms of congestive heart failure (CHF)
4. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment and for at least 5 weeks after the last dose
5. Males with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment and for at least 3 months after the last dose

Prior – Approval *Renewal* Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Metastatic Non-Small Cell Lung Cancer (NSCLC)
    a. 18 years of age or older

2. NTRK Gene Fusion-Positive Solid Tumors with **ALL** of the following:
    a. 1 month of age or older

AND ALL of the following for **ALL** diagnoses:

1. **NO** disease progression or unacceptable toxicity

2. Prescriber agrees to monitor AST and ALT
3. Prescriber agrees to monitor for QTc prolongation
4. Prescriber agrees to monitor for signs and symptoms of CHF
5. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment and for at least 5 weeks after the last dose
6. Males with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment and for at least 3 months after the last dose

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 600 mg per day

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Rozlytrek (entrectinib) is an inhibitor of the tropomyosin receptor kinases (TRK) TRKA, TRKB, and TRKC, proto-oncogene tyrosine-protein kinsase ROS1, and anaplastic lymphoma kinase (ALK) with IC_{50} values of 0.1 to 2 nM. TRKA, B, and C are encoded by the genes *NTRK1*, *NTRK2*, and *NTRK3,* respectively. Rozlytrek also inhibits JAK2 and TNK2 with IC_{50} values > 5nM. Fusion proteins that include TRK, ROS1, or ALK kinase domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. The safety and effectiveness of Rozlytrek in pediatric patients less than 1 month of age with solid tumors who have an NTRK gene fusion have not been established. The safety and effectiveness of Rozlytrek in pediatric patients less than 18 years of age with ROS1-positive NSCLC have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Rozlytrek while maintaining optimal therapeutic outcomes.

References

1. Rozlytrek [package insert]. South San Francisco, CA: Genentech USA, Inc.; October 2023.
2. NCCN Drugs & Biologics Compendium® Entrectinib 2023. National Comprehensive Cancer Network, Inc. Accessed on November 7, 2023.

Policy History

Date	Action
August 2019	New Addition
December 2019	Annual review
June 2020	Annual review
September 2021	Annual review and reference update
September 2022	Annual editorial review and reference update. Revised contraception requirements for consistency and added “as detected by an FDA-approved test” for ROS1 and NTRK testing
September 2023	Annual review and reference update
November 2023	Per PI update, lowered age requirement for solid tumors from 12 years of age or older to 1 month of age or older. Changed quantity limit from 270 per 90 days to 600 mg per day
December 2023	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 8, 2023 and is effective on January 1, 2024.