Rozlytrek

**Description**

Rozlytrek (entrectinib)

**Background**

Rozlytrek (entrectinib) is an inhibitor of the tropomyosin receptor kinases (TRK) TRKA, TRKB, and TRKC, proto-oncogene tyrosine-protein kinase 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 indication: Rozlytrek is a kinase inhibitor indicated for the treatment of:

1. Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive.
2. Adult and pediatric patients 12 years of age and older with solid tumors that (1):
   a. Have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion 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 12 years 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 in patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive, or for solid tumors with NTRK gene fusion, and if the conditions indicated below are met.

Rozlytrek is 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)
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a. 18 years of age or older
b. ROS1-positive

2. NTRK Gene Fusion-Positive Solid Tumors with **ALL** of the following:
   a. 12 years of age or older
   b. Neurotrophic tyrosine receptor kinase (NTRK) gene fusion 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. Prescriber agrees to advise females of reproductive potential to use effective contraception during treatment and for at least 5 weeks after the last dose
5. Prescriber agrees to advise males with female partners of reproductive potential 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. 12 years 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. Prescriber agrees to advise females of reproductive potential to use effective contraception during treatment and for at least 5 weeks after the last dose.

6. Prescriber agrees to advise males with female partners of reproductive potential 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 270 capsules per 90 days

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 kinase ROS1, and anaplastic lymphoma kinase (ALK) with IC\textsubscript{50} values of 0.1 to 2 nM. TRKA, B, and C are encoded by the genes \textit{NTRK1}, \textit{NTRK2}, and \textit{NTRK3}, respectively. Rozlytrek also inhibits JAK2 and TNK2 with IC\textsubscript{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 12 years 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**

**Policy History**

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**Keywords**

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 6, 2019 and is effective on January 1, 2020.