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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ROZLYTREK® safely and effectively. See full prescribing information for ROZLYTREK.

ROZLYTREK® (entrectinib) capsules, for oral use

ROZLYTREK® (entrectinib) oral pellets
Initial U.S. Approval: 2019

RECENT MAJOR CHANGES

Indications and Usage (1.2)	10/2023
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.6, 2.7, 2.8, 2.9)	10/2023
Warnings and Precautions (5.3)	10/2023

INDICATIONS AND USAGE

ROZLYTREK is a kinase inhibitor indicated for the treatment of:

- Adult patients with *ROS1*-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test. (1.1)
- Adult and pediatric patients older than 1 month of age with solid tumors that:
  - have a neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion, as detected by an FDA-approved test 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.

  This 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. (1.2)

DOSAGE AND ADMINISTRATION

- Select patients for treatment based on the presence of *ROS1* rearrangement(s) or *NTRK* gene fusion. (2.1)
- Evaluate left ventricular ejection fraction prior to initiation in patients with symptoms or known risk factors for CHF. Evaluate serum uric acid levels and QT interval and electrolytes prior to ROZLYTREK administration. (2.2)
- Select appropriate dosage form: oral capsules, capsules prepared as an oral suspension or oral pellets. (2.3)
- Use capsules prepared as suspension for enteral tube administration. Do not use pellets for enteral tube administration. (2.3)
- Administer ROZLYTREK capsules, capsules prepared as a suspension, or pellets once daily, with or without food. (2.4)
- Adult Dosage for *ROS1*-Positive Non-Small Cell Lung Cancer: 600 mg orally once daily. (2.5)
- Adult and Pediatric Dosage for *NTRK* Gene Fusion-Positive Solid Tumors:
  - Adults: 600 mg orally once daily. (2.6)
  - Pediatric Patients: Recommended dosage is based on age and body surface area (BSA) as shown below. (2.6)

Age	Recommended Daily Dosage
>6 months	≤0.50 m^2: 300 mg/m^2 0.51 to 0.80 m^2: 200 mg 0.81 to 1.10 m^2: 300 mg 1.11 to 1.50 m^2: 400 mg BSA ≥1.51 m^2: 600 mg once daily
>1 month to ≤6 months	250 mg/m^2 once daily

- Modify dosage of ROZLYTREK if coadministration with moderate or strong CYP3A inhibitors cannot be avoided. (2.8)
- See preparation and administration instructions. (2.9)

DOSAGE FORMS AND STRENGTHS

- Capsules: 100 mg and 200 mg (3)
- Pellets: 50 mg per packet (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Congestive Heart Failure (CHF): Assess left ventricular ejection fraction (LVEF) prior to initiation of ROZLYTREK in patients with symptoms or known risk factors for CHF. Monitor patients for clinical signs and symptoms of CHF. For patients with myocarditis, with or without a decreased ejection fraction, MRI or cardiac biopsy may be required to make the diagnosis. For new onset or worsening CHF, withhold ROZLYTREK, reassess LVEF and institute appropriate medical management. Reduce dose or permanently discontinue ROZLYTREK based on severity of CHF or worsening LVEF. (2.7, 5.1)
- Central Nervous System (CNS) Effects: CNS adverse reactions including cognitive impairment, mood disorders, dizziness, and sleep disturbances can occur with ROZLYTREK. Withhold and then resume at same or reduced dose upon improvement or permanently discontinue ROZLYTREK based on severity. (2.7, 5.2)
- Skeletal Fractures: ROZLYTREK increases the risk of fractures. Promptly evaluate patients with signs or symptoms of fractures. (5.3)
- Hepatotoxicity: Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue ROZLYTREK based on severity. If withheld, resume ROZLYTREK at same or reduced dose based on severity. (2.7, 5.4)
- Hyperuricemia: Assess serum uric acid levels prior to initiation and periodically during treatment with ROZLYTREK. Monitor patients for signs and symptoms of hyperuricemia. Initiate treatment with urate-lowering medications as clinically indicated and withhold ROZLYTREK for signs and symptoms of hyperuricemia. Resume at same or reduced dose upon improvement based on severity. (2.7, 5.5)
- QT Interval Prolongation: Monitor patients who have or who are at risk for QTc interval prolongation. Assess QT interval and electrolytes at baseline and periodically during treatment. Withhold and then resume at same or reduced dose, or permanently discontinue ROZLYTREK based on severity. (2.7, 5.6)
- Vision Disorders: Withhold for new visual changes or changes that interfere with activities of daily living until improvement or stabilization. Conduct an ophthalmological evaluation as appropriate. Resume at same or reduced dose upon improvement or stabilization. (2.7, 5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Moderate and Strong CYP3A Inhibitors:
  - For adult and pediatric patients 2 years and older, reduce the dose of ROZLYTREK if coadministration of moderate or strong CYP3A inhibitors cannot be avoided. (2.8, 7.1)
  - For pediatric patients less than 2 years, avoid coadministration with ROZLYTREK. (7.1)
- Moderate and Strong CYP3A Inducers: Avoid coadministration with ROZLYTREK. (7.1)
- Drugs That Prolong QTc Interval: Avoid concomitant use with ROZLYTREK. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2023

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1.2 *NTRK* Gene Fusion-Positive Solid Tumors
2 DOSAGE AND ADMINISTRATION
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 *ROS1*-Positive Non-Small Cell Lung Cancer

ROZLYTREK is indicated for the treatment of adult patients with *ROS1*-positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test.

1.2 *NTRK* Gene Fusion-Positive Solid Tumors

ROZLYTREK is indicated for the treatment of adult and pediatric patients older than 1 month of age with solid tumors that:

- have a neurotrophic tyrosine receptor kinase *(NTRK)* gene fusion, as detected by an FDA-approved test 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.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

- Select patients for the treatment of metastatic NSCLC with ROZLYTREK based on the presence of *ROS1* rearrangement(s) in tumor or plasma specimens *[see Clinical Studies (14.1)]*. Testing using plasma specimens is only appropriate for patients for whom tumor tissue is not available for testing.

  Information on FDA-approved tests for the detection of *ROS1* rearrangement(s) in NSCLC is available at http://www.fda.gov/CompanionDiagnostics.

- Select patients for treatment of locally advanced or metastatic solid tumors with ROZLYTREK based on the presence of a *NTRK* gene fusion in tumor or plasma specimens *[see Clinical Studies (14.2)]*. Testing using plasma specimens is only appropriate for patients for whom tumor tissue is not available for testing.

  Information on FDA-approved tests for the detection of *NTRK* gene fusion(s) in solid tumors is available at http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Evaluation and Testing Before Initiating ROZLYTREK

Before initiating ROZLYTREK, evaluate:

- left ventricular ejection fraction (LVEF) in patients with symptoms or known risk factors for CHF *[see Warnings and Precautions (5.1)]*
- serum uric acid levels *[see Warnings and Precautions (5.5)]*
- QT interval and electrolytes *[see Warnings and Precautions (5.6)]*

2.3 ROZLYTREK Dosage Form Overview

The physician should prescribe the most appropriate dosage form of ROZLYTREK according to the dose required and patient needs.

ROZLYTREK is available in two dosage forms, and can be administered either as capsules swallowed whole, capsules made into an oral suspension (or for enteral tube administration) and as oral pellets swallowed with soft food.

ROZLYTREK Capsules 100 mg and 200 mg

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- Whole capsules: For patients who can swallow whole capsules and whose doses are multiples of 100 mg.
- Capsules prepared as an oral suspension:
  - For patients who have difficulty or are unable to swallow capsules or who require enteral administration (e.g., gastric or nasogastric tube). *[see Dosage and Administration (2.7)]*.
  - For dose increments of 10 mg, only use capsules prepared as a suspension.

ROZLYTREK Oral Pellets 50 mg per packet

- Pellets sprinkled on one or more spoonfuls of soft food:
  - For patients who have difficulty or are unable to swallow capsules but can swallow soft food and whose doses are multiples of 50 mg. *[see Dosage and Administration (2.7)]*.
  - Do not use pellets for preparation of suspension.
  - Do not attempt to use partial quantities of pellets from 50 mg pellet packets to prepare a dose.
  - Do not use the pellet formulation for enteral tube administration as the pellets may clog the tube.

2.4 ROZLYTREK Administration Overview

- Administer ROZLYTREK capsules, capsules prepared as a suspension, or pellets once daily, with or without food.
- If a dose of ROZYTREK is missed, make up that dose unless the next dose is due within 12 hours.
- If vomiting occurs immediately after taking a dose of ROZLYTREK, repeat that dose.

2.5 ROZLYTREK Recommended Dosage for *ROS1*-Positive Non-Small Cell Lung Cancer

The recommended dosage of ROZLYTREK is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity.

2.6 ROZLYTREK Recommended Dosage for *NTRK* Gene Fusion-Positive Solid Tumors

The recommended dosages of ROZLYTREK for the treatment of adult and pediatric patients with NTRK Gene Fusion-Positive Solid Tumors are provided in Table 1.

Administer the recommended dosage of ROZLYTREK capsules and oral pellets with or without food until disease progression or unacceptable toxicity.

Sprinkle ROZLYTREK oral pellets on one or more spoonfuls of soft food as a vehicle.

Table 1. Recommended dosage for Adults and Pediatric patients for the Treatment of *NTRK* Gene Fusion-Positive Solid Tumors

Patient Population	Recommended Dosage of ROZLYTREK	Duration of Treatment
Adults Pediatric patients with BSA ≥ 1.51 m^2:	600 mg orally once daily	Until disease progression or unacceptable toxicity.
Pediatric patients > 6 months:	see Table 2	
Pediatric patients > 1 month to ≤ 6 months:	250 mg/m^2 orally once daily*	

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* To enable dosing increments of 10 mg, capsules prepared as an oral suspension must be used *[see Dosage and Administration (2.9)]*.

The recommended dosages of ROZLYTREK for the treatment of pediatric patients older than 6 months with NTRK Gene Fusion-Positive Solid Tumors is provided in Table 2.

Table 2. Recommended dosage for Pediatric Patients Older than 6 Months for the Treatment of NTRK Gene Fusion-Positive Solid Tumors

Body Surface Area (BSA)*	Recommended Dosage Orally Once Daily
≤0.50 m^2	300 mg/m^2 **
0.51 to 0.80 m^2	200 mg
0.81 to 1.10 m^2	300 mg
1.11 to 1.50 m^2	400 mg
≥ 1.51 m^2	600 mg

*BSA categories and recommended dosage above are based on closely matching exposures to a target dose of 300 mg/m^2
**To enable dosing increments of 10 mg, capsules prepared as an oral suspension must be used *[see Dosage and Administration (2.9)]*.

2.7 ROZLYTREK Dosage Modifications for Adverse Reactions

The recommended dosage reductions of ROZLYTREK for the management of adverse reactions for adults and pediatric patients are provided in Table 3.

Table 3. Recommended Dose Reductions for ROZLYTREK for the Management of Adverse Reactions

Starting Dose once daily	First dose reduction	Second dose reduction	
250 mg/m^2 or 300 mg/m^2	Reduce the once daily dose to two thirds of the starting dose*	Reduce the once daily dose to one third of the starting dose*	Permanently discontinue ROZLYTREK in patients who are unable to tolerate ROZLYTREK after two dose reductions.
200 mg	150 mg once daily	100 mg once daily	
300 mg	200 mg once daily	100 mg once daily	
400 mg	300 mg once daily	200 mg once daily	
600 mg	400 mg once daily	200 mg once daily	

*To enable dosing increments of 10 mg, capsules prepared as an oral suspension must be used *[see Dosage and Administration (2.9)]*.

Table 4 provides the ROZLYTREK recommended dosage modifications for the management of adverse reactions.

Table 4. ROZLYTREK Dosage Modifications for the Management of Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Congestive Heart Failure *[see Warnings and Precautions (5.1)]*	Grade 2 or 3	• Withhold ROZLYTREK until recovered to less than or equal to Grade 1. • Resume at reduced dose.
	Grade 4	• Permanently discontinue ROZLYTREK.

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Adverse Reaction	Severity*	Dosage Modification
Central Nervous System Effects *[see Warnings and Precautions (5.2)]*	Intolerable Grade 2	• Withhold ROZLYTREK until recovery to less than or equal to Grade 1 or to baseline. • Resume at same dose or reduced dose, as clinically appropriate.
	Grade 3	• Withhold ROZLYTREK until recovery to less than or equal to Grade 1 or to baseline. • Resume at reduced dose.
	Grade 4	• Permanently discontinue ROZLYTREK.
Hepatotoxicity *[see Warnings and Precautions (5.4)]*	Grade 3	• Withhold ROZLYTREK until recovery to less than or equal to Grade 1 or to baseline. • Resume at same dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks.
	Grade 4	• Withhold ROZLYTREK until recovery to less than or equal to Grade 1 or to baseline. • Resume at reduced dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or hemolysis).	• Permanently discontinue ROZLYTREK.
Hyperuricemia *[see Warnings and Precautions (5.5)]*	Symptomatic or Grade 4	• Initiate urate-lowering medication. • Withhold ROZLYTREK until improvement of signs or symptoms. • Resume ROZLYTREK at same or reduced dose.
QT Interval Prolongation *[see Warnings and Precautions (5.6)]*	QTc greater than 500 ms	• Withhold ROZLYTREK until QTc interval recovers to baseline. • Resume at same dose if factors that cause QT prolongation are identified and corrected. • Resume at reduced dose if other factors that cause QT prolongation are not identified.
	Torsade de pointes; polymorphic ventricular	• Permanently discontinue ROZLYTREK.

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Adverse Reaction	Severity*	Dosage Modification
	tachycardia; signs/symptoms of serious arrhythmia	
Vision Disorders *[see Warnings and Precautions (5.7)]*	Grade 2 or above	• Withhold ROZLYTREK until improvement or stabilization. • Resume at same dose or reduced dose, as clinically appropriate.
Anemia or Neutropenia *[see Adverse Reactions (6.1)]*	Grade 3 or 4	• Withhold ROZLYTREK until recovery to less than or equal to Grade 2. • Resume at the same dose or reduced dose, as clinically appropriate.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	• Withhold ROZLYTREK until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline. • Resume at the same or reduced dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.

*Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

2.8 ROZLYTREK Dosage Modifications for Drug Interactions

Moderate and Strong CYP3A Inhibitors

Adults and Pediatric Patients 2 Years and Older

Avoid coadministration of ROZLYTREK with moderate or strong CYP3A inhibitors. If coadministration cannot be avoided, reduce the ROZLYTREK dose as shown in Table 5 and limit coadministration to 14 days or less.

Table 5. Recommended Dose Modifications of ROZYLTREK for Concomitant Use with Moderate or Strong CYP3A Inhibitors for Adults and Pediatric Patients 2 Years and Older

Starting dose*	Moderate CYP3A inhibitor	Strong CYP3A inhibitor
200 mg	50 mg once daily	50 mg on alternate days
300 mg	100 mg once daily	50 mg once daily
400 mg	200 mg once daily	50 mg once daily
600 mg	200 mg once daily	100 mg once daily
* For pediatric patients with a starting dose less than 200 mg, avoid coadministration with moderate or strong CYP3A inhibitors		

After discontinuation of a strong or moderate CYP3A inhibitor for 3 to 5 elimination half-lives, resume the ROZLYTREK dose that was taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

2.9 ROZLYTREK Preparation and Administration Instructions

ROZLYTREK Capsules

Swallow capsules whole. Do not crush or chew the capsules.

ROZLYTREK Capsules Prepared as a Suspension for Oral or Enteral Tube Administration

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It is recommended that a healthcare provider discuss with the patient or caregiver, the volume of water or milk to be added and oral suspension to withdraw, prior to administration of the first dose (see Table 6).

Table 6 provides the ROZLYTREK dose and volume of room temperature drinking water or milk required to prepare an oral suspension. Instruct patients or caregivers to carefully open capsules(s) and pour the contents into room temperature drinking water or milk to prepare an oral suspension. Let sit for 15 minutes.

Table 6. Preparation of ROZLYTREK Capsules as an Oral Suspension

Dose of ROZLYTREK to be administered	Dose needed for suspension (using 100 mg or 200 mg capsules, as appropriate)	Volume of water or milk to be added	Volume of oral suspension to withdraw and administer
20 mg	100 mg	5 mL	1 mL
30 mg	100 mg	5 mL	1.5 mL
40 mg	100 mg	5 mL	2 mL
50 mg	100 mg	5 mL	2.5 mL
60 mg	100 mg	5 mL	3 mL
70 mg	100 mg	5 mL	3.5 mL
80 mg	100 mg	5 mL	4 mL
90 mg	100 mg	5 mL	4.5 mL
100 mg	100 mg	5 mL	5 mL
110 mg	200 mg	10 mL	5.5 mL
120 mg	200 mg	10 mL	6 mL
130 mg	200 mg	10 mL	6.5 mL
140 mg	200 mg	10 mL	7 mL
150 mg	200 mg	10 mL	7.5 mL
200 mg	200 mg	10 mL	10 mL
300 mg	300 mg	15 mL	15 mL
400 mg	400 mg	20 mL	20 mL
600 mg	600 mg	30 mL	30 mL

Administer ROZLYTREK oral suspension immediately after preparation.

Discard any unused suspension if not used within 2 hours.

Instruct patients to drink water after taking the oral suspension to ensure ROZLYTREK has been completely swallowed.

Enteral Tube Administration

If enteral administration (e.g., gastric or nasogastric tube) is required, administer the oral suspension via the tube. Use an enteral tube that is 8 FR or higher to administer dosing volumes of 3 mL or higher. Instruct patients to divide dosing volumes of 3 mL or higher into at least two aliquots and flush the tube after each administration. Flush the tube with a volume of water or milk that is equal to the aliquot administered. For a dose volume of 30 mL, divide into at least three (10 mL) aliquots. The tube should be flushed with water or milk after delivering each aliquot of ROZLYTREK.

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Refer to the Instructions for Use for detailed instructions on preparation and administration of ROZLYTREK capsules as an oral suspension via an enteral tube.

ROZLYTREK Oral Pellets

Sprinkle pellets on one or more spoonfuls of a soft food (e.g., applesauce, yogurt, or pudding) and take within 20 minutes of preparation. Do not crush or chew to avoid a bitter taste.

The patient should drink water after taking the pellets to ensure the drug has been completely swallowed.

Do not attempt to use partial quantities of pellets from 50 mg pellet packets to prepare a dose.

Do not use the pellet formulation for enteral tube administration as the pellets may clog the tube.

Refer to the Instructions for Use for detailed instructions on preparation and administration of ROZLYTREK oral pellets.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 100 mg: Size 2 yellow opaque body and cap, with “ENT 100” printed in blue ink on body.
- 200 mg: Size 0 orange opaque body and cap, with “ENT 200” printed in blue ink on body.

Pellets:

- 50 mg: Supplied as brownish orange or grayish orange pellets in packets.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Congestive Heart Failure

Among the 355 patients who received ROZLYTREK across clinical trials, congestive heart failure (CHF) occurred in 3.4% of patients, including Grade 3 (2.3%) *[see Adverse Reactions (6.1)]*. In clinical trials, baseline cardiac function and routine cardiac monitoring other than electrocardiograms (ECGs) were not conducted and eligibility criteria excluded patients with symptomatic CHF, myocardial infarction, unstable angina, and coronary artery bypass graft within 3 months of study entry. Among the 12 patients with CHF, the median time to onset was 2 months (range: 11 days to 12 months). ROZLYTREK was interrupted in 6 of these patients (50%) and discontinued in 2 of these patients (17%). CHF resolved in 6 patients (50%) following interruption or discontinuation of ROZLYTREK and institution of appropriate medical management. In addition, myocarditis in the absence of CHF was documented in 0.3% of patients.

Assess left ventricular ejection fraction (LVEF) prior to initiation of ROZLYTREK in patients with symptoms or known risk factors for CHF. Monitor patients for clinical signs and symptoms of CHF, including shortness of breath and edema. For patients with myocarditis, with or without a decreased ejection fraction, MRI or cardiac biopsy may be required to make the diagnosis. For patients with new onset or worsening CHF, withhold ROZLYTREK, institute appropriate medical management, and reassess LVEF. Based on the severity of CHF or worsening LVEF, resume ROZLYTREK at a reduced dose upon recovery to baseline or permanently discontinue *[see Dosage and Administration (2.7)]*.

5.2 Central Nervous System Effects

A broad spectrum of central nervous system (CNS) adverse reactions occurred in patients receiving ROZLYTREK, including cognitive impairment, mood disorders, dizziness, and sleep disturbances.

Among the 355 patients who received ROZLYTREK across clinical trials, 96 (27%) experienced cognitive impairment; symptoms occurred within 3 months of starting ROZLYTREK in 74 (77%). Cognitive impairment included cognitive disorders (8%), confusional state (7%), disturbance in attention (4.8%), memory impairment

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(3.7%), amnesia (2.5%), aphasia (2.3%), mental status changes (2%), hallucinations (1.1%), and delirium (0.8%). Grade 3 cognitive adverse reactions occurred in 4.5% of patients. Among the 96 patients with cognitive impairment, 13% required a dose reduction, 18% required dose interruption and 1% discontinued ROZLYTREK due to cognitive adverse reactions.

Among the 355 patients who received ROZLYTREK across clinical trials, 36 (10%) experienced mood disorders. The median time to onset of mood disorders was 1 month (range: 1 day to 9 months). Mood disorders occurring in ≥ 1% of patients included anxiety (4.8%), depression (2.8%) and agitation (2%). Grade 3 mood disorders occurred in 0.6% of patients. One completed suicide was reported 11 days after treatment had ended. Among the 36 patients who experienced mood disorders, 6% required a dose reduction, 6% required dose interruption and no patients discontinued ROZLYTREK due to mood disorders.

Dizziness occurred in 136 (38%) of the 355 patients. Among the 136 patients who experienced dizziness, Grade 3 dizziness occurred in 2.2% of patients. Ten percent of patients required a dose reduction, 7% required dose interruption and 0.7% discontinued ROZLYTREK due to dizziness.

Among the 355 patients who received ROZLYTREK across clinical trials, 51 (14%) experienced sleep disturbances. Sleep disturbances included insomnia (7%), somnolence (7%), hypersomnia (1.1%), and sleep disorder (0.3%). Grade 3 sleep disturbances occurred in 0.6% of patients. Among the 51 patients who experienced sleep disturbances, 6% required a dose reduction and no patients discontinued ROZLYTREK due to sleep disturbances.

The incidence of CNS adverse reactions was similar in patients with and without CNS metastases; however, the incidence of dizziness (38% vs 31%), headache (21% vs 13%), paresthesia (20% vs 6%), balance disorder (13% vs 4%), and confusional state (11% vs 2%) appeared to be increased in patients with CNS metastases who had received prior CNS irradiation (n = 90) compared to those who did not (n = 48).

Advise patients and caregivers of these risks with ROZLYTREK. Advise patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue ROZLYTREK based on severity *[see Dosage and Administration (2.7)]*.

5.3 Skeletal Fractures

ROZLYTREK increases the risk of fractures. In an expanded safety population that included 338 adult patients and 76 pediatric patients who received ROZLYTREK across clinical trials, 5% of adult patients and 25% of pediatric patients experienced fractures *[see Use in Specific Population (8.4)]*. In adult and pediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area; in pediatric patients some fractures occurred with no trauma. In general, there was inadequate assessment for tumor involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumor involvement were reported in some adult patients. In both adult and pediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). In two pediatric patients, bilateral femoral neck fractures occurred. A total of 41 fracture events were reported in 19 pediatric patients, with 13 patients who experienced more than one occurrence of fracture. Among the 19 pediatric patients who experienced fractures, 17 patients were less than 12 years of age. Among the 41 fracture events, 27 fracture events resolved, 4 fracture events resolved with sequelae and 3 events were resolving. The median time to fracture was 3.8 months (range 0.3 to 18.5 months) in adults and 4.3 months (range: 2 months to 28.7 months) in pediatric patients. ROZLYTREK was interrupted in 41% of adults and 16% of pediatric patients who experienced fractures. Five pediatric patients discontinued treatment due to fractures.

Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. There are no data on the effects of ROZLYTREK on healing of known fractures and risk of future fractures.

5.4 Hepatotoxicity

Among the 355 patients who received ROZLYTREK, increased AST of any grade occurred in 42% of patients and increased ALT of any grade occurred in 36%. Grade 3 – 4 increased AST or ALT occurred in 2.5% and

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2.8% of patients, respectively; the incidence may be underestimated as 4.5% of patients had no post-treatment liver function tests *[see Adverse Reactions (6.1)]*. The median time to onset of increased AST was 2 weeks (range: 1 day to 29.5 months). The median time to onset of increased ALT was 2 weeks (range: 1 day to 9.2 months). Increased AST or ALT leading to dose interruptions or reductions occurred in 0.8% and 0.8% of patients, respectively. ROZLYTREK was discontinued due to increased AST or ALT in 0.8% patients.

Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue ROZLYTREK based on the severity. If withheld, resume ROZLYTREK at the same or reduced dose *[see Dosage and Administration (2.7)]*.

5.5 Hyperuricemia

Among 355 patients who received ROZLYTREK across clinical trials, 32 patients (9%) experienced hyperuricemia reported as adverse reactions with symptoms, as well as elevated uric acid levels. Grade 4 hyperuricemia occurred in 1.7% of patients, including one patient who died due to tumor lysis syndrome. Among the 32 patients with hyperuricemic adverse reactions, 34% required urate-lowering medication to reduce uric acid levels, 6% required dose reduction and 6% required dose interruption. Hyperuricemia resolved in 73% of patients following initiation of urate-lowering medication without interruption or dose reduction of ROZLYTREK. No patients discontinued ROZLYTREK due to hyperuricemia.

Assess serum uric acid levels prior to initiation of ROZLYTREK and periodically during treatment. Monitor patients for signs and symptoms of hyperuricemia. Initiate treatment with urate-lowering medications as clinically indicated and withhold ROZLYTREK for signs and symptoms of hyperuricemia. Resume ROZLYTREK at same or reduced dose upon improvement of signs or symptoms based on severity *[see Dosage and Administration (2.7)]*.

5.6 QT Interval Prolongation

Among the 355 patients who received ROZLYTREK across the clinical trials, 3.1% of patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of > 60 ms after starting ROZLYTREK and 0.6% had a QTcF interval > 500 ms *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*.

Monitor patients who already have or who are at significant risk of developing QTc interval prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Assess QT interval and electrolytes prior to initiation of ROZLYTREK and periodically during treatment, adjusting frequency based upon risk factors such as congestive heart failure, electrolyte abnormalities, or concomitant medications known to prolong the QTc interval. Based on the severity of QTc interval prolongation, withhold ROZLYTREK and then resume at same or reduced dose, or permanently discontinue *[see Dosage and Administration (2.7)]*.

5.7 Vision Disorders

Among the 355 patients who received ROZLYTREK across clinical trials, vision changes occurred in 21% of patients, including Grade 1 (17%), Grade 2 (2.8%) and Grade 3 (0.8%) *[see Adverse Reactions (6.1)]*. Vision disorders occurring in ≥ 1% included blurred vision (9%), photophobia (5%), diplopia (3.1%), visual impairment (2%), photopsia (1.1%), cataract (1.1%), and vitreous floaters (1.1%).

For patients with new visual changes or changes that interfere with activities of daily living, withhold ROZLYTREK until improvement or stabilization and conduct an ophthalmological evaluation as clinically appropriate. Upon improvement or stabilization, resume ROZLYTREK at same or reduced dose *[see Dosage and Administration (2.7)]*.

5.8 Embryo-Fetal Toxicity

Based on literature reports in humans with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, ROZLYTREK can cause fetal harm when administered to a

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pregnant woman. Administration of entrectinib to pregnant rats resulted in malformations at exposures approximately 2.7 times the human exposure at the 600 mg dose based on area under the curve (AUC).

Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with ROZLYTREK and for 5 weeks following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ROZLYTREK and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Congestive Heart Failure *[see Warnings and Precautions (5.1)]*
- Central Nervous System Effects *[see Warnings and Precautions (5.2)]*
- Skeletal Fractures *[see Warnings and Precautions (5.3)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*
- Hyperuricemia *[see Warnings and Precautions (5.5)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.6)]*
- Vision Disorders *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Data in WARNINGS AND PRECAUTIONS and below reflect exposure to ROZLYTREK in 355 patients, including 172 (48%) patients exposed for 6 months or longer and 84 (24%) patients exposed for 1 year or longer. ROZLYTREK was studied in one dose-finding trial in adults [ALKA (n = 57)], one dose-finding and activity-estimating trial in adults [STARTRK-1 (n = 76)], one dose-finding and activity-estimating trial in pediatric and adult patients [STARTRK-NG (n = 16)], and one single arm, activity-estimating trial in adults [STARTRK-2 (n = 206)].

The population characteristics were: median age 55 years (range: 4 to 86 years); 5% (n = 17) were less than 18 years of age; 55% were female; and 66% were White, 23% were Asian, and 5% were Black; 3% were Hispanic/Latino. The most common tumors (≥ 5%) were lung (56%), sarcoma (8%), and colon (5%). *ROS1* gene fusions were present in 42% and *NTRK* gene fusions were present in 20%. Most adults (75%) received ROZLYTREK 600 mg orally once daily. The doses ranged from 100 mg/m^2 to 1600 mg/m^2 once daily in adults and 250 mg/m^2 to 750 mg/m^2 once daily in pediatric patients.

Serious adverse reactions occurred in 39% of patients. The most frequent serious adverse reactions (≥ 2%) were pneumonia (3.9%), dyspnea (3.7%), pleural effusion (3.4%), sepsis (2.5%), pulmonary embolism (2.3%), respiratory failure (2%), and pyrexia (2%). Grade 3 or 4 adverse reactions occurred in 60% of patients; the most common (≥ 2%) were lung infection (5%), increased weight (7%), dyspnea (6%), fatigue/asthenia (5%), cognitive disorders (4.5%), syncope (2.5%), pulmonary embolism (3.4%), hypoxia (3.4%), pleural effusion (3.1%), hypotension (2.8%), diarrhea (2%), and urinary tract infection (2.5%). Fatal events included dyspnea (0.6%), pneumonia (0.6%), sepsis (0.6%), completed suicide (0.3%), large intestine perforation (0.3%) and tumor lysis syndrome (0.3%). One patient developed Grade 4 myocarditis after one dose of ROZLYTREK which resolved after discontinuation of ROZLYTREK and administration of high-dose corticosteroids.

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received ROZLYTREK. The most frequent adverse reactions (< 1% each) that resulted in permanent discontinuation were pneumonia, cardio-respiratory arrest, dyspnea, and fatigue.

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Dose interruptions due to adverse reactions occurred in 46% of patients. The most frequent adverse reactions (≥ 2%) that resulted in interruption were increased blood creatinine (4%), fatigue (3.7%), anemia (3.1%), diarrhea (2.8%), pyrexia (2.8%), dizziness (2.5%), dyspnea (2.3%), nausea (2.3%), pneumonia (2.3%), cognitive disorder (2%) and neutropenia (2%).

Dose reductions due to adverse reactions occurred in 29% of patients who received ROZLYTREK. The most frequent adverse reactions resulting in dose reductions (≥ 1%) were dizziness (3.9%), increased blood creatinine (3.1%), fatigue (2.3%), anemia (1.7%), and increased weight (1.4%).

The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia and vision disorders.

Table 7 summarizes the adverse reactions observed in these 355 patients.

Table 7. Adverse Reactions (≥ 10%) in Patients Receiving ROZLYTREK in ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG

Adverse Reactions	ROZLYTREK n = 355	
	All Grades (%)	Grade ≥ 3* (%)
General		
Fatigue[1]	48	5
Edema[2]	40	1.1
Pyrexia	21	0.8
Gastrointestinal		
Constipation	46	0.6
Diarrhea	35	2.0
Nausea	34	0.3
Vomiting	24	0.8
Abdominal pain[3]	16	0.6
Nervous System		
Dysgeusia	44	0.3
Dizziness[4]	38	0.8
Dysesthesia[5]	34	0.3
Cognitive impairment[6]	27	4.5
Peripheral sensory neuropathy[7]	18	1.1
Headache	18	0.3
Ataxia[8]	17	0.8
Sleep[9]	14	0.6
Mood disorders[10]	10	0.6
Respiratory, Thoracic and Mediastinal		
Dyspnea	30	6*
Cough	24	0.3
Musculoskeletal and Connective Tissue		
Myalgia[11]	28	1.1
Arthralgia	21	0.6
Muscular weakness	12	0.8
Back pain	12	1
Pain in extremity	11	0.3
Metabolism and Nutritional		
Increased weight	25	7
Decreased appetite	13	0.3
Dehydration	10	1.1
Eye		
Vision disorders[12]	21	0.8

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Adverse Reactions	ROZLYTREK n = 355	
	All Grades (%)	Grade ≥ 3* (%)
Infections		
Urinary tract infection	13	2.3
Lung infection[13]	10	6*
Vascular		
Hypotension[14]	18	2.8
Skin and Subcutaneous Tissue		
Rash[15]	11	0.8

* Grades 3 – 5, inclusive of fatal adverse reactions, including 2 events of pneumonia and 2 events of dyspnea.
[1]Includes fatigue, asthenia
[2] Includes face edema, fluid retention, generalized edema, localized edema, edema, edema peripheral, peripheral swelling
[3] Includes abdominal pain upper, abdominal pain, lower abdominal discomfort, abdominal tenderness
[4] Includes dizziness, vertigo, dizziness postural
[5] Includes paresthesia, hyperesthesia, hypoesthesia, dysesthesia, oral hypoesthesia, palmar-plantar erythrodysesthesia, oral paresthesia, genital hypoesthesia
[6] Includes amnesia, aphasia, cognitive disorder, confusional state, delirium, disturbance in attention, hallucinations, visual hallucination, memory impairment, mental disorder, mental status changes
[7] Includes neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy
[8] Includes ataxia, balance disorder, gait disturbances
[9] Includes hypersomnia, insomnia, sleep disorder, somnolence
[10] Includes anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation
[11] Includes musculoskeletal pain, musculoskeletal chest pain, myalgia, neck pain
[12] Includes blindness, cataract, cortical cataract, corneal erosion, diplopia, eye disorder, photophobia, photopsia, retinal hemorrhage, vision blurred, visual impairment, vitreous adhesions, vitreous detachment, vitreous floaters
[13] Includes lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection
[14] Includes hypotension, orthostatic hypotension
[15] Includes rash, rash maculopapular, rash pruritic, rash erythematous, rash papular

Clinically relevant adverse reactions occurring in ≤ 10% of patients include dysphagia (10%), fall (8%), pleural effusion (8%), fractures (6%), hypoxia (4.2%), pulmonary embolism (3.9%), syncope (3.9%), congestive heart failure (3.4%), and QT prolongation (3.1%).

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Table 8 summarizes the laboratory abnormalities.

Table 8. Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Receiving ROZLYTREK in ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG

Laboratory Abnormality	ROZLYTREK NCI CTCAE Grade	
	All Grades (%)[1]	Grade 3 or 4 (%)[1]
Chemistry		
Increased creatinine[2]	73	2.1
Hyperuricemia	52	10
Increased AST	44	2.7
Increased ALT	38	2.9
Hypernatremia	35	0.9
Hypocalcemia	34	1.8
Hypophosphatemia	30	7
Increased lipase	28	10
Hypoalbuminemia	28	2.9
Increased amylase	26	5.4
Hyperkalemia	25	1.5
Increased alkaline phosphatase	25	0.9
Hyperglycemia[3]	NE[3]	3.8
Hematology		
Anemia	67	9
Lymphopenia	40	12
Neutropenia	28	7

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase
[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 111 to 346 patients.
[2] Based on NCI CTCAE v5.0
[3] NE = Not evaluable. Grade 1 and 2 could not be determined per NCI CTCAE v5.0, as fasting glucose values were not collected

Safety in Pediatric Patients

The safety of ROZLYTREK was evaluated was evaluated in pediatric patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label clinical trials: STARTRK-NG (n=68), TAPISTRY (n=6) and STARTRK-2 (n=2). Patients received ROZLYTREK 20 mg to 600 mg based on body surface area (BSA) orally or via enteral feeding tube once daily in 4-week cycles until unacceptable toxicity or disease progression. Among patients who received ROZLYTREK, 58% were exposed for 6 months or longer and 38% were exposed for greater than one year.

The median age of patients who received ROZLYTREK was 6 years (range: 0 to 17); 51% were females; 68% were White, 18% Asian, 7% Black or African American, and 7% were other races.

Serious adverse reactions occurred in 45% of patients who received ROZLYTREK. Serious adverse reactions in > 2% of patients included skeletal fractures (12%), pneumonia (5%), pyrexia (5%), hydrocephalus (5%), device related infection (4%), hypoxia (4%), dyspnea (3%), headache (3%), gait disturbance (3%), pain (3%), upper respiratory infection (3%), and sepsis (3%).

Permanent discontinuation of ROZLYTREK due to an adverse reaction occurred in 13% of patients. Adverse reactions which resulted in permanent discontinuation of ROZLYTREK in > 2% of patients included skeletal fracture.

Dosage interruptions of ROZLYTREK due to an adverse reaction occurred in 39% of patients. Adverse reactions which required dosage interruption in > 5% of patients included decreased neutrophil count, pyrexia, vomiting, and diarrhea.

Dose reductions of ROZLYTREK due to an adverse reaction occurred in 21% of patients. Adverse reactions which required dose reductions in > 2% of patients included increased blood creatinine and increased weight.

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Table 9 summarizes the adverse reactions in STARTRK-NG (n=68), TAPISTRY (n=6) and STARTRK-2 (n=2).

Table 9. Adverse Reactions (≥20%) in Pediatric Patients Who Received ROZLYTREK in STARTRK-NG, TAPISTRY and STARTRK-2

Adverse Reaction	ROZLYTREK (n=76)	
	All Grades (%)	Grade 3 or 4 (%)
General Disorders		
Pyrexia	43	1.3
Fatigue[1]	30	2.6
Gastrointestinal Disorders		
Constipation	41	1.3
Vomiting	38	0
Diarrhea	37	0
Nausea	34	0
Abdominal Pain	20	2.6
Investigations		
Increased Weight	39	18
Respiratory, Thoracic And Mediastinal Disorders		
Cough	33	1.3
Nasal Congestion	20	0
Musculoskeletal And Connective Tissue Disorders		
Pain in Extremity	26	2.6
Skeletal Fracture[2]	25	11
Metabolism And Nutrition Disorders		
Decreased Appetite	24	1.3
Nervous System Disorders		
Headache	22	2.6
Infections		
Upper Respiratory Tract Infection	20	1.3
Urinary Tract Infection	20	2.6

[1]Includes fatigue, asthenia

[2]Includes clavicle fracture, tibia fracture, femur fracture, fibula fracture, foot fracture, fracture, pathological fracture, limb fracture, lower limb fracture, pelvic fracture, spinal compression fracture, stress fracture, ulna fracture

Clinically relevant adverse reactions in <20% of patients who received ROZLYTREK included pruritus, rash, urinary incontinence, eye pain and photophobia.

Tables 10 summarizes the laboratory abnormalities in STARTRK-NG (n=68), TAPISTRY (n=6) and STARTRK-2 (n=2).

Table 10. Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Pediatric Patients Who Received ROZLYTREK in STARTRK-NG, TAPISTRY and STARTRK-2

Laboratory Abnormality	ROZLYTREK[1]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased Hemoglobin	53	7
Decreased Neutrophils	53	22
Decreased Leukocytes	46	1.3
Increased Lymphocytes	33	3
Chemistry		
Increased Creatinine	84	5
Increased AST	61	2.7

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Increased ALT	53	2.6
Increased Sodium	38	1.4
Increased Magnesium	32	5
Increased Alkaline Phosphatase	25	0
Decreased Glucose	26	0
Increased Potassium	25	2.7
Decreased Albumin	24	9
Increased Calcium	21	8
Increased Bilirubin	20	8

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase

[1] The denominator used to calculate the rate varied from 67 to 76 based on the number of patients with a baseline value and at least one post-treatment value. All values based on NCI CTCAE v5.0

Other clinically relevant laboratory abnormalities in patients who received ROZLYTREK included decreased phosphorous.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ROZLYTREK

Moderate and Strong CYP3A Inhibitors

Adults and Pediatric Patients 2 Years and Older

Coadministration of ROZLYTREK with a strong or moderate CYP3A inhibitor increases entrectinib plasma concentrations *[see Clinical Pharmacology (12.3)],* which could increase the frequency or severity of adverse reactions. Avoid coadministration of strong or moderate CYP3A inhibitors with ROZLYTREK. If coadministration is unavoidable, reduce the ROZLYTREK dose *[see Dosage and Administration (2.8), Clinical Pharmacology (12.3)]*.

Pediatric Patients less than 2 Years

Avoid coadministration of ROZLYTREK with moderate or strong CYP3A inhibitors *[see Clinical Pharmacology (12.3)]*.

Avoid grapefruit products during treatment with ROZLYTREK, as they contain inhibitors of CYP3A.

Moderate and Strong CYP3A Inducers

Coadministration of ROZLYTREK with a strong or moderate CYP3A inducer decreases entrectinib plasma concentrations *[see Clinical Pharmacology (12.3)],* which may reduce ROZLYTREK efficacy. Avoid coadministration of strong and moderate CYP3A inducers with ROZLYTREK.

7.2 Drugs That Prolong QTc Interval

QTc interval prolongation can occur with ROZLYTREK. Avoid coadministration of ROZLYTREK with other products with a known potential to prolong QT/QTc interval *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on literature reports in humans with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action *[see Clinical Pharmacology (12.1)]*, ROZLYTREK can cause fetal harm when administered to a pregnant woman. There are no available data on ROZLYTREK use in pregnant women. Administration of entrectinib to pregnant rats during the period of organogenesis resulted in malformations at maternal exposures approximately 2.7 times the human exposure at the 600 mg dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Published reports of individuals with congenital mutations in TRK pathway proteins suggest that decreases in TRK-mediated signaling are correlated with obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis.

Animal Data

Entrectinib administration to pregnant rats during the period of organogenesis at a dose of 200 mg/kg [resulting in exposures up to 2.7 times the human exposure (AUC) at the 600 mg dose] resulted in maternal toxicity and fetal malformations including body closure defects (omphalocele and gastroschisis) and malformations of the vertebrae, ribs, and limbs (micromelia and adactyly), but not embryolethality. Lower fetal weights and reduced skeletal ossification occurred at doses ≥ 12.5 and 50 mg/kg [approximately 0.2 and 0.9 times the human exposure (AUC) at the 600 mg dose], respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of entrectinib or its metabolites in human milk or their effects on either the breastfed child or on milk production. Because of the potential serious adverse reactions in breastfed children from ROZLYTREK, advise a lactating woman to discontinue breastfeeding during treatment with ROZLYTREK and for 7 days after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating ROZLYTREK *[see Use in Specific Populations (8.1)]*.

Contraception

ROZLYTREK can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise female patients of reproductive potential to use effective contraception during treatment with ROZLYTREK and for at least 5 weeks following the last dose *[see Use in Specific Populations (8.1)]*.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ROZLYTREK and for 3 months following the last dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ROZLYTREK have been established in pediatric patients older than 1 month of age *[Clinical Studies (14.2)]*. Use of ROZLYTREK in these age groups is supported by evidence from adequate and well-controlled studies of ROZLYTREK in adults and pediatric patients with additional population pharmacokinetic data demonstrating that the exposure of drug substance in pediatric patients greater than 1 month of age is expected to be in the adult range, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients.

The safety and effectiveness of ROZLYTREK have not been established in pediatric patients with *ROS1*-positive NSCLC.

Juvenile Animal Toxicity Data

In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Entrectinib resulted in:

- decreased body weight gain and delayed sexual maturation at doses ≥ 4 mg/kg/day (approximately 0.06 times the human exposure (AUC) at the 600 mg dose),
- deficits in neurobehavioral assessments including functional observational battery and learning and memory (at doses ≥ 8 mg/kg/day, approximately 0.14 times the human exposure at the 600 mg dose), and
- decreased femur length at doses ≥ 16 mg/kg/day (approximately 0.18 times the human exposure at the 600 mg dose).

8.5 Geriatric Use

Of the 355 patients who received ROZLYTREK across clinical trials, 25% were 65 years or older, and 5% were 75 years of age or older. Clinical studies of ROZLYTREK did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger patients.

8.6 Renal Impairment

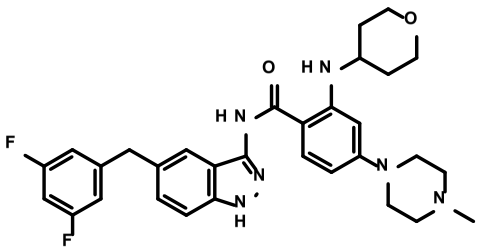
No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr 30 to < 90 mL/min calculated by Cockcroft-Gault equation). ROZLYTREK has not been studied in patients with severe renal impairment (CLcr < 30 mL/min) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The effect of moderate hepatic impairment (total bilirubin > 1.5 – 3.0 times ULN with any aspartate aminotransferase) or severe hepatic impairment (total bilirubin >3.0 times ULN with any aspartate aminotransferase) on the safety of ROZLYTREK at the recommended dosage is unknown. Consider the risk-benefit profile of ROZLYTREK prior to determining whether to administer ROZLYTREK to patients with moderate to severe hepatic impairment. Monitor for ROZLYTREK adverse reactions in patients with hepatic impairment more frequently since these patients may be at increased risk for adverse reactions *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Entrectinib is a kinase inhibitor. The molecular formula for entrectinib is $C_{31}H_{34}F_2N_6O_2$ and the molecular weight is 560.64 Daltons. The chemical name is N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino) benzamide. The chemical structure of entrectinib is as follows:



Entrectinib is white to pale pink powder.

Capsules:

ROZLYTREK (entrectinib) capsules for oral use are supplied as printed hard-shell capsules containing 100 mg (yellow opaque HPMC capsule) or 200 mg of entrectinib (orange opaque HPMC capsule). Inactive ingredients are tartaric acid, lactose anhydrous, hypromellose, crospovidone, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate.

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The yellow opaque capsule shell contains hypromellose, titanium dioxide, and yellow iron oxide. The orange opaque capsule shell contains hypromellose, titanium dioxide, and FD&C yellow #6. The printing ink contains shellac, propylene glycol, strong ammonia solution, and FD&C blue #2 aluminum lake.

Pellets:

ROZLYTREK (entrectinib) oral pellets are supplied as brownish orange or grayish orange, round film-coated pellets in packets. Each packet contains 50 mg of entrectinib and the following inactive ingredients: tartaric acid, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, sodium stearyl fumarate, mannitol, and magnesium stearate.

The film-coating contains polyvinyl alcohol (partially hydrolyzed), titanium dioxide, polyethylene glycol 3350, talc, yellow iron oxide, red iron oxide, and ferrosoferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC (encoded by the neurotrophic tyrosine receptor kinase [*NTRK*] genes *NTRK1, NTRK2,* and *NTRK3*, respectively), proto-oncogene tyrosine-protein kinase ROS1 (ROS1), and anaplastic lymphoma kinase (ALK) with IC_{50} values of 0.1 to 2 nM. Entrectinib also inhibits JAK2 and TNK2 with IC_{50} values > 5 nM. The major active metabolite of entrectinib, M5, showed similar in vitro activity against TRK, ROS1, and ALK.

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. Entrectinib demonstrated in vitro and in vivo inhibition of cancer cell lines derived from multiple tumor types harboring *NTRK*, *ROS1,* and *ALK* fusion genes.

Entrectinib demonstrated steady-state brain-to-plasma concentration ratios of 0.4 – 2.2 in multiple animal species (mice, rats, and dogs) and demonstrated in vivo anti-tumor activity in mice with intracranial implantation of TRKA- and ALK-driven tumor cell lines.

12.2 Pharmacodynamics

Entrectinib exposure-response relationships and the time course of pharmacodynamic responses are unknown.

Cardiac Electrophysiology

Across clinical trials, 3.1% of 355 patients, who received ROZLYTREK at doses ranging from 100 mg to 2600 mg daily under fasting or fed conditions (75% received 600 mg orally once daily) and had at least one post-baseline ECG assessment, experienced QTcF interval prolongation of > 60 ms after starting ROZLYTREK and 0.6% had a QTc interval > 500 ms *[see Warnings and Precautions (5.6)]*.

12.3 Pharmacokinetics

The pharmacokinetics for entrectinib and its pharmacologically active major circulating metabolite M5 were characterized in adult patients with *ROS1*-positive NSCLC, *NTRK* gene fusion-positive solid tumors, and healthy subjects. The pharmacokinetics of entrectinib and M5 are linear and are not dose-dependent or time-dependent. Steady state is achieved within one week for entrectinib and two weeks for M5 following daily administration of ROZLYTREK. The pharmacokinetic parameters for entrectinib and M5 are described in Table 11.

Table 11. Pharmacokinetic Parameters for Entrectinib and Metabolite M5

Parameter	Entrectinib Mean* (% CV)	M5 Mean* (% CV)
AUC_{D1} (nM*h)	31800 (48%)	10200 (82%)
AUC_{ss} (nM*h)	48000 (77%)	24000 (97%)
C_{maxD1} (nM)	2250 (58%)	622 (79%)

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C_{maxss} (nM)	3130 (80%)	1250 (90%)
$R_{acc(AUC)}$	1.55 (49%)	2.84 (93%)

* Geometric mean

Absorption

The maximum entrectinib plasma concentration was reached 4 – 6 hours after oral administration of a 600 mg dose.

Entrectinib exposure following a single oral dose (600 mg) of ROZLYTREK oral pellets was not clinically significant compared to ROZLYTREK capsule administered with a light meal (250 calories: 25% fat) in healthy subjects. In STARTRK-2, STARTRK-NG and TAPISTRY studies, ROZLYTREK was administered without regard to food in patients.

Entrectinib exposure of a single dose (600 mg) of ROZLYTREK capsules as a suspension with water or milk, administered orally or through a nasogastric or gastric tube, was not clinically significant compared to administration of intact ROZLYTREK capsules in healthy subjects under fasted conditions.

Effect of Food

A high-fat (approximately 50% of total caloric content), high-calorie (approximately 800 to 1000 calories) meal did not have a significant effect on entrectinib exposure of ROZLYTREK capsules.

Distribution

Entrectinib and its active major metabolite M5 are both > 99% bound to human plasma proteins in vitro.

The estimated apparent volume of distribution (V/F) was 551 L and 81.1 L for entrectinib and M5, respectively.

Elimination

The estimated apparent clearance (CL/F) was 19.6 L/h and 52.4 L/h for entrectinib and M5, respectively. The elimination half-lives of entrectinib and M5 were estimated to be 20 and 40 hours, respectively.

Metabolism

Entrectinib is metabolized primarily by CYP3A4 (~76%). The active metabolite M5 (formed by CYP3A4) is the only major active circulating metabolite identified. M5 has similar pharmacological potency to entrectinib in vitro and circulating M5 exposures at steady-state in patients were 40% of the corresponding entrectinib exposure.

Excretion

Following oral administration of a single oral dose of [^{14}C]-labeled entrectinib, 83% of radioactivity was excreted in feces (36% of the dose as unchanged entrectinib and 22% as M5) with minimal excretion in urine (3%).

Specific Populations

No clinically significant differences in the pharmacokinetics of entrectinib were observed based on sex, race (White, Asian and Black), mild to moderate renal impairment (CLcr 30 to < 90 mL/min) and mild hepatic impairment (total bilirubin ≤ ULN with aspartate aminotransferase > ULN or total bilirubin > 1.0 – 1.5 times ULN with any aspartate aminotransferase). The impact of severe renal impairment on the pharmacokinetics of entrectinib is unknown.

Hepatic Impairment

Following administration of a single oral dose of ROZLYTREK 100 mg (1/6 of the recommended dose), the entrectinib AUC_{INF} was increased by 39% for the mild, 39% for the moderate, and 23% for the severe hepatic impairment groups compared to the normal hepatic function group. The combined AUC_{last} of entrectinib and M5 was increased by 16% for the mild, 16% for the moderate, and 4% for the severe hepatic impairment groups

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compared to the normal hepatic function group. Large variability in systemic exposure of entrectinib was observed in the hepatic impairment groups.

Pediatric Patients > 6 months

In pediatric patients older than 6 months administered 300 mg/m^2 (based on BSA) of ROZLYTREK once daily, systemic exposure of the sum of entrectinib and M5 in pediatric patients receiving 300 mg/m^2 of ROZLYTREK once daily is within the range of the adults treated with 600 mg of ROZLYTREK once daily.

The available efficacy and safety data also confirm the adequacy of the recommended doses *[see Use in Specific Populations (8.4)]*.

Pediatric Patients > 1 to ≤ 6 months

In pediatric patients > 1 to ≤ 6 months administered 250 mg/m^2 (based on BSA) of ROZLYTREK once daily, systemic exposure of the sum of entrectinib and M5 in pediatric patients was at the lower range of the adults administered 600 mg of ROZLYTREK once daily.

The available efficacy and safety data also confirm the adequacy of the recommended doses *[see Use in Specific Populations (8.4)]*.

Drug Interaction Studies

Clinical Studies

Effect of CYP3A Inhibitors on Entrectinib: Coadministration of itraconazole (a strong CYP3A inhibitor) with a single 100 mg dose of ROZLYTREK capsule increased entrectinib $AUC_{0\text{-}INF}$ by 6-fold and C_{max} by 1.7-fold *[see Drug Interactions (7.1)]*. Coadministration of a moderate CYP3A inhibitor with ROZLYTREK capsule is predicted to increase entrectinib $AUC_{0\text{-}Tau}$ by 3-fold and C_{max} by 2.9-fold. Based on physiologically based pharmacokinetic (PBPK) modelling, a similar magnitude of the effect is expected in children as young as 2 years old.

Effect of CYP3A Inducers on Entrectinib: Coadministration of rifampin (a strong CYP3A inducer) with a single 600 mg dose of ROZLYTREK capsule reduced entrectinib $AUC_{0\text{-}INF}$ by 77% and C_{max} by 56% *[see Drug Interactions (7.1)]*. Coadministration of a moderate CYP3A inducer with ROZLYTREK capsule is predicted to reduce entrectinib $AUC_{0\text{-}Tau}$ by 56% and C_{max} by 43%.

Effect of Gastric Acid Reducing Drugs on Entrectinib: Coadministration of a proton pump inhibitor (PPI), lansoprazole with a single 600 mg dose of ROZLYTREK capsule reduced entrectinib AUC by 25% and C_{max} by 23%.

Coadministration of lansoprazole, with a single 600 mg dose of ROZLYTREK capsule as oral suspension in water increased entrectinib AUC by 25% and C_{max} by 17%. These changes are not likely to be clinically significant.

Effect of Entrectinib on CYP Substrates: Coadministration of 600 mg dose of ROZLYTREK capsule once daily with oral midazolam (a sensitive CYP3A substrate) in patients increased the midazolam AUC by 50% but reduced midazolam C_{max} by 21% *[see Drug Interactions (7.1)]*.

Effect of Entrectinib on Transporters: Coadministration of a single 600 mg dose of ROZLYTREK capsule with digoxin [a sensitive P-glycoprotein (P-gp) substrate] increased digoxin C_{max} by 28% and AUC by 18%.

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In Vitro Studies

Entrectinib is not a substrate of P-gp or BCRP, but M5 is a substrate of P-gp and BCRP. Entrectinib and M5 are not substrates of OATP1B1 or OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not conducted with entrectinib. Entrectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay; however, an in vitro assay in cultured human peripheral blood lymphocytes did demonstrate a potential for abnormal chromosome segregation (aneugenicity). Entrectinib was not clastogenic or aneugenic in the in vivo micronucleus assay in rats and did not induce DNA damage in a comet assay in rats.

Dedicated fertility studies were not conducted with entrectinib. With the exception of dose-dependent decreases in prostate weight in male dogs, there were no effects on male and female reproductive organs observed in general toxicology studies conducted in rats and dogs at doses resulting in exposures of up to approximately 3.2-fold the human exposure (AUC) at the 600 mg dose.

14 CLINICAL STUDIES

14.1 *ROS1*-Positive Non-Small Cell Lung Cancer

The efficacy of ROZLYTREK was evaluated in a pooled subgroup of patients with *ROS1*-positive metastatic NSCLC who received ROZLYTREK at various doses and schedules (90% received ROZLYTREK 600 mg orally once daily) and were enrolled in one of three multicenter, single-arm, open-label clinical trials: ALKA, STARTRK-1 (NCT02097810) and STARTRK-2 (NCT02568267). To be included in this pooled subgroup, patients were required to have histologically confirmed, recurrent or metastatic, *ROS1*-positive NSCLC, ECOG performance status ≤ 2, measurable disease per RECIST v 1.1, ≥ 18 months of follow-up from first post-treatment tumor assessment, and no prior therapy with a ROS1 inhibitor. Identification of *ROS1* gene fusion in tumor specimens was prospectively determined in local laboratories using either a fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), or polymerase chain reaction (PCR) laboratory-developed tests. All patients were assessed for CNS lesions at baseline. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR). Intracranial response according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) was assessed by BICR. Tumor assessments with imaging were performed every 8 weeks.

Efficacy was assessed in 92 patients with *ROS1*-positive NSCLC. The median age was 53 years (range: 27 to 86); female (65%); White (48%), Asian (45%), and Black (5%); and Hispanic or Latino (2.4%); never smoked (59%); and ECOG performance status 0 or 1 (88%). Ninety-nine percent of patients had metastatic disease, including 42% with CNS metastases; 96% had adenocarcinoma; 65% received prior platinum-based chemotherapy for metastatic or recurrent disease and no patient had progressed in less than 6 months following platinum-based adjuvant or neoadjuvant therapy. *ROS1* positivity was determined by NGS in 79%, FISH in 16%, and PCR in 4%. Twenty-five percent had central laboratory confirmation of *ROS1* positivity using an analytically validated NGS test.

Efficacy results are summarized in Table 12.

Table 12. Efficacy Results in *ROS1*-Positive NSCLC Patients per BICR Assessment

Efficacy Parameters	**ROZLYTREK n = 92**
Overall Response Rate (95% CI)	74% (64, 83)
Complete Response	15%
Partial Response	59%
Duration of Response (DOR)*	**n = 68**
Range (months)	2.4, 55.2+

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% DOR ≥ 9 months	75%
% DOR ≥ 12 months	57%
% DOR ≥ 18 months	38%

Confidence Interval (CI) calculated using the Clopper-Pearson method.
* Observed DOR
+ denotes ongoing response

Among the 92 patients, 10 had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 7 of these 10 patients.

14.2 *NTRK* Gene Fusion-Positive Solid Tumors

Efficacy in Adult Patients

The efficacy of ROZLYTREK was evaluated in a pooled subgroup of adult patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled in one of three multicenter, single-arm, open-label clinical trials: ALKA, STARTRK-1 (NCT02097810) and STARTRK-2 (NCT02568267). To be included in this pooled subgroup, patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery causing significant morbidity for locally advanced disease; measurable disease per RECIST v1.1; at least 2 years of follow-up from first post-treatment tumor assessment; and no prior therapy with a TRK inhibitor. Patients received ROZLYTREK at various doses and schedules (94% received ROZLYTREK 600 mg orally once daily) until unacceptable toxicity or disease progression. Identification of positive *NTRK* gene fusion status was prospectively determined in local laboratories or a central laboratory using various nucleic acid-based tests. The major efficacy outcome measures were ORR and DOR, as determined by a BICR according to RECIST v1.1. Intracranial response according to RECIST v1.1 as evaluated by BICR. Tumor assessments with imaging were performed every 8 weeks.

Efficacy was assessed in the first 54 adult patients with solid tumors with an *NTRK* gene fusion enrolled into these trials. The median age was 58 years (range: 21 to 83); female (59%); White (80%), Asian (13%) and Hispanic or Latino (7%); and ECOG performance status 0 (43%) or 1 (46%). Ninety-six percent of patients had metastatic disease, including 22% with CNS metastases, and 4% had locally advanced, unresectable disease. All patients had received prior treatment for their cancer including surgery (n = 43), radiotherapy (n = 36), or systemic therapy (n = 48). Forty patients (74%) received prior systemic therapy for metastatic disease with a median of 1 prior systemic regimen and 17% (n = 9) received 3 or more prior systemic regimens. The most common cancers were sarcoma (24%), lung cancer (19%), salivary gland tumors (13%), breast cancer (11%), thyroid cancer (9%), and colorectal cancer (7%). A total of 52 (96%) patients had an *NTRK* gene fusion detected by NGS and 2 (4%) had an *NTRK* gene fusion detected by other nucleic acid-based tests. Eighty-three percent of patients had central laboratory confirmation of *NTRK* gene fusion using an analytically validated NGS test.

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Efficacy results are summarized in Tables 13, 14, and 15.

Table 13. Efficacy Results for Adult Patients with Solid Tumors Harboring *NTRK* Gene Fusions

Efficacy Parameter	**ROZLYTREK n = 54**
Overall Response Rate (95% CI)	59% (45, 72)
Complete Response	13%
Partial Response	46%
Duration of Response*	**n = 32**
Range (months)	2.8, 47.8+
% with duration ≥ 6 months	72%
% with duration ≥ 9 months	66%
% with duration ≥ 12 months	56%

* Observed DOR
\+ denotes ongoing response

Table 14. Efficacy by Tumor Type

Tumor Type	**Patients n = 54**	**ORR**		**DOR**
		%	**95% CI**	**Range (months)**
Sarcoma	13	46%	19%, 75%	2.8, 33.6+
Non-small cell lung cancer	10	60%	26%, 88%	3.7, 47.8+
Salivary (MASC)	7	86%	42%, 100%	2.8, 38.5+
Breast cancer	6	83%	36%, 100%	4.2, 42.3+
Thyroid cancer	5	60%	NA	7.9, 31.5+
Colorectal cancer	4	25%	NA	15.1
Neuroendocrine cancers	3	CR	NA	32.9+
Pancreatic cancer	3	PR, PR	NA	7.1, 12.9
Gynecological cancers	2	PR	NA	38.2
Cholangiocarcinoma	1	PR	NA	9.3

\+ denotes ongoing response
MASC: mammary analogue secretory carcinoma; NA = not applicable due to small numbers or lack of response; PR = partial response.

Table 15. Efficacy Results by *NTRK* Gene Fusion Partner

***NTRK* Partner**	**Patients n = 54**	**ORR**		**DOR**
		%	**95% CI**	**Range (months)**
ETV6 – NTRK3	25	72%	51%, 88%	2.8, 47.8+
TPM3 – NTRK1	4	50%	7%, 93%	2.8, 15.1
TPR – NTRK1	4	100%	40%, 100%	5.6, 33.6+
LMNA – NTRK1	2	PR, PD	NA	4.2
SQSTM1 – NTRK1	2	PR, PD	NA	18.8+
PEAR1 – NTRK1	2	SD, NE	NA	NA
EML4 – NTRK3	2	PR, NE	NA	13.2
CD74 – NTRK1	1	PR	NA	10.4
PLEKHA6 – NTRK1	1	PR	NA	9.3
CDC42BPA – NTRK1	1	PR	NA	29.4
EPS15L1 – NTRK1	1	PR	NA	3.7
RBPMS – NTRK3	1	PR	NA	4.6
ERC1 – NTRK1	1	SD	NA	NA
PDIA3 – NTRK1	1	SD	NA	NA
TRIM33 – NTRK1	1	SD	NA	NA
AKAP13 – NTRK3	1	SD	NA	NA
KIF7 – NTRK3	1	SD	NA	NA

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FAM19A2 – NTRK3	1	PD	NA	NA
CGN – NTRK1	1	NE	NA	NA
SQSTM1 – NTRK2	1	NE	NA	NA

+ denotes ongoing response
PR = partial response; PD = progressive disease; SD = stable disease; NA = not applicable due to small numbers or lack of response; NE = not evaluable.

Among the subset of patients who received prior systemic therapy for metastatic disease, the ORR was 53%, similar to that seen in the overall population. Among the 54 adult patients, 4 had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months of study entry. Responses in intracranial lesions were observed in 3 of these 4 patients.

Efficacy in Pediatric Patients

The efficacy of ROZLYTREK was evaluated in pediatric patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled in one of two multicenter, open-label clinical trials: STARTRK-NG (NCT02650401) and TAPISTRY (NCT04589845). To be included in the analysis, patients were required to have received at least 1 dose of ROZLYTREK; measurable or evaluable disease at baseline; at least 6 months of follow-up; and no prior therapy with a TRK inhibitor. Patients received ROZLYTREK 20 mg to 600 mg based on body surface area (BSA) orally or via enteral feeding tube once daily in 4-week cycles until unacceptable toxicity or disease progression. The major efficacy outcome measure was overall response rate (ORR) as assessed by BICR according to RECIST v1.1 for extracranial tumors and according to Response Assessment in Neuro-Oncology (RANO) for primary central nervous system (CNS) tumors. An additional efficacy outcome measure was DOR as evaluated by BICR.

Efficacy was assessed in 33 pediatric patients with *NTRK* fusion-positive solid tumors treated with ROZLYTREK. The median age was 4 years (range: 2 months to 15 years); male (52%); White (58%), Asian (30%), other races (9%), Black or African American (3.0%), and Hispanic or Latino (9%). Seventy-one percent of patients had locally advanced disease and 29% had metastatic disease. Eighty-five percent of patients had received prior treatment for their cancer including surgery (n=20), radiotherapy (n=7) and/or systemic therapy (n=22). The sites for metastatic disease included other (4 patients), brain (3 patients) and lung (2 patients).

Efficacy results are summarized in Tables 16 and 17.

Table 16. Efficacy Results for Pediatric Patients with Solid Tumors Harboring *NTRK* Gene Fusions

Efficacy Parameter*	**ROZLYTREK n = 33**
Overall Response Rate (95% CI)	70% (51, 84)
Complete Response	42%
Partial Response	27%
Duration of Response**	**n = 23**
Median in months (95% CI)	25.4 (14.3, NE)
% with duration ≥ 12 months	43%

* Includes patients with measurable and evaluable disease. BICR analysis by RECIST v1.1 for solid tumors (16 patients) and by RANO criteria for primary CNS tumors (17 patients)
** Observed DOR
NE = not estimable

Table 17. Efficacy Results for Pediatric Patients with Solid Tumors Harboring *NTRK* Gene Fusions by Tumor Type

Tumor Type	**Patients n = 33**	**ORR**		**DOR**
		%	**95% CI**	**Range (months)**
Primary CNS*	17	53%	28%, 77%	5.5, 30.4+
Infantile fibrosarcoma	8	88%	47%, 100%	3.7+, 24+
Spindle Cell	6	100%	54%, 100%	3.7+, 12.9+
Sarcoma (other)	1	0%**	NA	NA

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Melanoma	1	100%	NA	42.4+

*Median time to first objective response for patients with primary CNS tumors was 1.9 months
+ denotes ongoing response
** Patient with evaluable but non-measurable disease at baseline
NA = not applicable due to small numbers or lack of response

Table 18. Efficacy Results for Pediatric Patients with Solid Tumors Harboring *NTRK* by Gene Fusion Partner

***NTRK* Partner**	**Patients n = 33**	**ORR**		**DOR**
		%	**95% CI**	**Range (months)**
ETV6 – NTRK3	7	86%	42%, 100%	11.9+ - 42.4+
LMNA – NTRK1	5	80%	28%, 99%	7.4+ - 12.9+
TPM3 – NTRK1	3	100%	29%, 100%	3.7+ - 24.0+
TPR – NTRK1	3	67%	9%, 99%	8.1+ - 14.3
EML4-NTRK3	2	50%	1.3%, 99%	13.8+
BCAN-NTRK1	1	CR	NA	11.8+
EML1-NTRK2	1	CR	NA	11.8
QKI-NTRK2	1	CR	NA	11.1+
TFG-NTRK3	1	CR	NA	3.7+
KANK1-NTRK2	1	PR	NA	5.5
KIF5B-NTRK2	1	PR	NA	12.9+
TNS3-NRTK2	1	PR	NA	9.5
ARHGEF2-NTRK1	1	SD	NA	NA
KIF21B-NTRK1	1	SD	NA	NA
BCR-NTRK2	1	SD	NA	NA
GKAP1-NTRK2	1	SD	NA	NA
DNM3-NTRK2	1	PD	NA	NA
PARP6-NTRK3	1	PD	NA	NA

+ denotes ongoing response
PR = partial response; PD = progressive disease; SD = stable disease; NA = not applicable due to small numbers or lack of response

16 HOW SUPPLIED/STORAGE AND HANDLING

Capsules

How Supplied

- 100 mg hard capsules: Size 2 yellow opaque, with “ENT 100” printed in blue ink; available in HDPE bottles of 30 capsules: NDC 50242-091-30
- 200 mg hard capsules: Size 0 orange opaque, with “ENT 200” printed in blue ink; available in HDPE bottles of 90 capsules: NDC 50242-094-90

Storage:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Store ROZLYTREK capsules in the original container and keep the bottle tightly closed in order to protect from moisture.

Storage time should not exceed 2 hours (below 30°C (86°F)) if capsules are prepared as an oral suspension using drinking water or milk. Discard any unused suspension if not used within 2 hours of preparation.

Pellets

How Supplied

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- ROZLYTREK oral pellets are supplied as brownish orange to grayish orange, round pellets, available in: 42-count carton (each packet contains 50 mg entrectinib): NDC 50242-623-42

Storage:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Store ROZLYTREK oral pellets in the original container in order to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Congestive Heart Failure

- Inform patients of the risks of CHF and advise patients to contact their healthcare provider immediately for any new or worsening signs or symptoms of CHF *[see Warnings and Precautions (5.1)]*.

Central Nervous System Effects

- Advise patients to inform their healthcare provider if they experience new or worsening central nervous system symptoms. Instruct patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions *[see Warnings and Precautions (5.2)]*.

Skeletal Fractures

- Inform patients that bone fractures have been reported in patients taking ROZLYTREK. Advise patients to report symptoms such as pain, changes in mobility, or deformity to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

- Advise patients that they will need to undergo laboratory tests to monitor liver function and to immediately report symptoms of hepatotoxicity *[see Warnings and Precautions (5.4)]*.

Hyperuricemia

- Advise patients to inform their healthcare provider if they experience signs or symptoms associated with hyperuricemia *[see Warnings and Precautions (5.5)]*.

QT Interval Prolongation

- Inform patients of the risks of QT interval prolongation and to advise patients to contact their healthcare provider immediately for any symptoms of QT interval prolongation *[see Warnings and Precautions (5.6)]*.

Vision Disorders

- Advise patients to inform their healthcare provider if they experience visual changes *[see Warnings and Precautions (5.7)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1, 8.3)]*.
- Advise females of reproductive potential to use effective contraception during treatment with ROZLYTREK and for 5 weeks after the last dose.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose.

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Lactation

- Advise females not to breastfeed during treatment with ROZLYTREK and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

- Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Advise patients to avoid grapefruit juice while taking ROZLYTREK *[see Drug Interactions (7)]*.

Administration

- Instruct patients and caregivers to read the Instructions for Use before the patient starts using ROZLYTREK, and each time the patient gets a refill as there may be new information they need to know.
- For capsules taken as an oral suspension or for administration by enteral tube: Provide patients and caregivers with a measuring device (e.g., oral syringe, measuring cup) to prepare and measure their prescribed dose if taking ROZLYTREK capsules as an oral suspension. Instruct patients and/or caregivers how to use the measuring device provided and inform patients they may need to measure out a portion of oral suspension prepared to receive the prescribed dosage. If not taken immediately after preparation, store no longer than 2 hours at room temperature below 30°C (86°F) *[see Dosage and Administration (2.9)]*.
- For pellets: Instruct patients and caregivers that ROZLYTREK oral pellets should be sprinkled on one or more spoonfuls of a soft food (e.g., applesauce, yogurt, or pudding) and must be taken within 20 minutes of preparation. Oral pellets are not suitable for enteral administration due to potential for clogging in tubing *[see Dosage and Administration (2.9)]*.
- Instruct patients if they miss a dose to make up that dose unless the next dose is due within 12 hours.
- Instruct patients if they vomit immediately after taking a dose of ROZLYTREK to take a dose as soon as possible *[Dosage and Administration (2.4)]*.

ROZLYTREK (entrectinib)

Distributed by:
Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

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PATIENT INFORMATION

ROZLYTREK® (roz lye' trek)
(entrectinib)
capsules

ROZLYTREK® (roz lye' trek)
(entrectinib)
oral pellets

What is the most important information I should know about ROZLYTREK?

ROZLYTREK may cause serious side effects, including:

- **Congestive heart failure.** ROZLYTREK may cause congestive heart failure or make the congestive heart failure that you already have worse. Tell your healthcare provider right away if you have any of the following signs and symptoms of congestive heart failure:
  - persistent coughing or wheezing
  - trouble breathing when lying down
  - sudden weight gain
  - increasing shortness of breath
  - tiredness, weakness, or fatigue
  - swelling in ankles, feet, or legs
- **Central nervous system (CNS) effects.** ROZLYTREK may cause dizziness, changes in your mood, or may affect how you think and cause confusion, hallucinations, and problems with concentration, attention, memory, speaking, understanding what your hear or read, and sleep. Tell your healthcare provider right away if you have any of these symptoms.
- **Bone fractures.** ROZLYTREK may increase your risk for bone fractures. Bone fractures may happen with or without a fall or other injury. Tell your healthcare provider if you develop pain, changes in movement, or bone abnormalities.
- **Liver problems (hepatotoxicity).** Your healthcare provider will do blood tests to check your liver function during treatment with ROZLYTREK. Tell your healthcare provider right away if you develop any of the following symptoms of liver problems:
  - loss of appetite
  - nausea or vomiting
  - pain in your upper right stomach area
  - yellowing of your skin or the white part of your eyes
  - dark urine
- **Increased uric acid level in your blood (hyperuricemia).** ROZLYTREK may cause too much uric acid in your blood. Your healthcare provider may do tests before and during your treatment with ROZLYTREK to check the uric acid level in your blood. Your healthcare provider may prescribe medications if you have high blood uric acid levels. Tell your healthcare provider if you develop any of the following symptoms of hyperuricemia:
  - red, hot, tender, or swollen joints, especially in your big toe
  - pain in your stomach-area or sides
  - nausea or vomiting
  - pink or brown urine
- **Changes in the electrical activity of your heart called QT prolongation**. QT prolongation can cause irregular heartbeats that can be life-threatening. Your healthcare provider will do tests before and during your treatment with ROZLYTREK to check the electrical activity of your heart and your body salts (electrolytes). Tell your healthcare provider right away if you feel faint, lightheaded, dizzy, or feel your heart beating irregularly or fast during your treatment with ROZLYTREK. These may be symptoms related to QT prolongation.
- **Vision problems.** ROZLYTREK may cause vision problems. Your healthcare provider may stop ROZLYTREK and refer you to an eye specialist if you develop severe vision problems during treatment with ROZLYTREK. Tell your healthcare provider right away if you have any loss of vision or any change in vision, including:
  - double vision
  - blurry vision
  - new or increased floaters
  - seeing flashes of light
  - light hurting your eyes

Your healthcare provider may temporarily stop treatment, decrease your dose, or permanently stop ROZLYTREK if you develop certain side effects during treatment with ROZLYTREK.

What is ROZLYTREK?

ROZLYTREK is a prescription medicine used to treat:

- Adults with non-small cell lung cancer (NSCLC) that has spread to other parts of the body and is caused by an abnormal *ROS1* gene.
- Adults and children 1 month of age and older with solid tumors (cancer) that:
  - are caused by certain abnormal *NTRK* genes, **and**
  - have spread or if surgery to remove their cancer is likely to cause severe complications, **and**
  - there is no satisfactory alternative treatment option or the cancer grew or spread on other treatment.

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It is not known if ROZLYTREK is safe and effective in children with *ROS1* NSCLC or in children under 1 month of age with *NTRK* solid tumors.

Before taking ROZLYTREK, tell your healthcare provider about all your medical conditions, including if you:

- have liver or kidney problems
- have any heart problems, including a condition called long QT syndrome
- have nervous system (neurological) problems
- have or have had eye or vision problems
- are pregnant or plan to become pregnant. ROZLYTREK can cause harm to your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with ROZLYTREK.

  Females who can become pregnant:
  - Your healthcare provider will do a pregnancy test before you start treatment with ROZLYTREK.
  - Use effective birth control (contraception) during treatment with ROZLYTREK and for at least 5 weeks after the last dose.

  Males with female partners that can become pregnant:
  - Use effective birth control (contraception) during treatment with ROZLYTREK and for 3 months after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if ROZLYTREK passes into your breast milk. Do not breastfeed during treatment with ROZLYTREK and for 7 days (1 week) after the last dose of ROZLYTREK. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

Taking ROZLYTREK with certain other medicines may affect the amount of ROZLYTREK or other medicine in your blood and may cause side effects or affect the way that ROZLYTREK or the other medicine work. Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ROZLYTREK?

- Take ROZLYTREK exactly as your healthcare provider tells you. Do not change your dose or stop taking ROZLYTREK unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with ROZLYTREK if you develop certain side effects.
- Take ROZLYTREK 1 time each day with or without food.
- Your healthcare provider will either prescribe:
  - ROZLYTREK capsules to be swallowed whole or prepared and taken or given as a suspension **or**
  - ROZLYTREK oral pellets to be sprinkled on 1 or more spoonfuls of soft food before taking.
- If you miss a dose of ROZLYTREK, take it as soon as you remember. If your next dose is due within 12 hours, skip the missed dose and take your next dose at your regular time.
- If you vomit right after taking a dose of ROZLYTREK, you may take the dose again.

See the detailed Instructions for Use for information on how to give or take a dose of ROZLYTREK capsules or oral pellets.

If you are taking whole ROZLYTREK capsules:

- Swallow whole capsules with drinking water, as directed by your healthcare provider.
- Do not crush or chew the capsule.

If you are taking ROZLYTREK capsules prepared as a suspension:

- Carefully open the prescribed number of capsules and pour the contents into room temperature drinking water or milk. Your healthcare provider will tell you how much water or milk to use, how much suspension to take or give, and provide you with a measuring device like an oral syringe or measuring cup.
- Let the suspension sit for 15 minutes before taking.
- You may need to take less suspension than you prepared depending on your prescribed dose.
- Drink water after taking the suspension to make sure you have swallowed all the medicine.
- If you do not take the suspension right away, you can store it for up to 2 hours at room temperature below 86°F (30°C). Throw away (discard) the unused suspension if it is not used within 2 hours of preparation.

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- If you cannot swallow and have a gastric or nasogastric tube, the suspension can be given through the feeding tube.

If you are taking ROZLYTREK oral pellets:

- Sprinkle the prescribed number of packets of pellets on 1 or more spoonfuls of a soft food like applesauce, yogurt, or pudding, and take within 20 minutes of sprinkling the pellets on the soft food.
- **Do not** crush or chew the pellets to avoid a bitter taste.
- Drink water after taking the prescribed dose to make sure you have swallowed all the medicine.
- Use the whole packet of pellets. **Do not** use part of the packet to try to prepare a dose.
- **Do not** use the pellets to make a suspension.
- **Do not** give the pellets through a gastric or nasogastric tube because the pellets may clog the feeding tube.

What should I avoid while taking ROZLYTREK?

- You should not drink grapefruit juice or eat grapefruit during your treatment with ROZLYTREK. It may increase the amount of entrectinib in your blood to a harmful level and increase your chance of getting side effects.
- Do not drive or operate heavy machinery until you know how ROZLYTREK affects you. If you experience dizziness, fainting, tiredness, blurred vision, memory loss, changes in mental status, confusion, or hallucinations, do not drive or operate heavy machines until your symptoms resolve.

What are the possible side effects of ROZLYTREK?

ROZLYTREK may cause serious side effects, including:

- See **"What is the most important information I should know about ROZLYTREK?"**

The most common side effects of ROZLYTREK include:

- tiredness
- constipation
- change in taste
- swelling
- dizziness
- diarrhea
- nausea
- abnormal touch sensation
- shortness of breath
- muscle pain
- confusion, mental status changes, memory problems, and hallucinations
- weight gain
- cough
- vomiting
- fever
- joint pain
- vision changes

These are not all the possible side effects of ROZLYTREK.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ROZLYTREK?

ROZLYTREK capsules

- Store ROZLYTREK at room temperature between 68°F to 77°F (20°C to 25°C).
- Store ROZLYTREK capsules in the original container and keep the bottle tightly closed to protect from moisture.

ROZLYTREK oral pellets

- Store ROZLYTREK oral pellets at room temperature between 68°F to 77°F (20°C to 25°C).
- Store ROZLYTREK oral pellets in the original container to protect from moisture.

Keep ROZLYTREK and all medicines out of the reach of children.

General information about the safe and effective use of ROZLYTREK.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ROZLYTREK for a condition for which it was not prescribed. Do not give ROZLYTREK to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ROZLYTREK that is written for health professionals.

What are the ingredients in ROZLYTREK?

Active ingredient: entrectinib

Inactive ingredients:

Capsules: tartaric acid, lactose anhydrous, hypromellose, crospovidone, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate.

- Yellow opaque capsule shell: hypromellose, titanium dioxide, and yellow iron oxide
- Orange opaque capsule shell: hypromellose, titanium dioxide, and FD&C Yellow No. 6
- Printing ink: shellac, propylene glycol, strong ammonia solution, and FD&C Blue No. 2 aluminum lake

Pellets: tartaric acid, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, sodium stearyl fumarate, mannitol, and magnesium stearate

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- Film-coating: polyvinyl alcohol (partially hydrolyzed), titanium dioxide, polyethylene glycol 3350, talc, yellow iron oxide, red iron oxide, and ferrosoferric oxide

Distributed by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

ROZLYTREK® is a registered trademark of Genentech, Inc. ©2023 Genentech, Inc.

For more information, go to www.ROZLYTREK.com or call 1-877-436-3683.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 10/2023

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PREPRESS - INFORMATION

Format 95 x 35 mm
Register Nr. 98.4.3650
NP 9706
10.10.2023 12:16:42
Grundschrift 5.75 Punkt

PREPRESS - ROCHE BASEL

Control Proof

Date: .....

New Proof

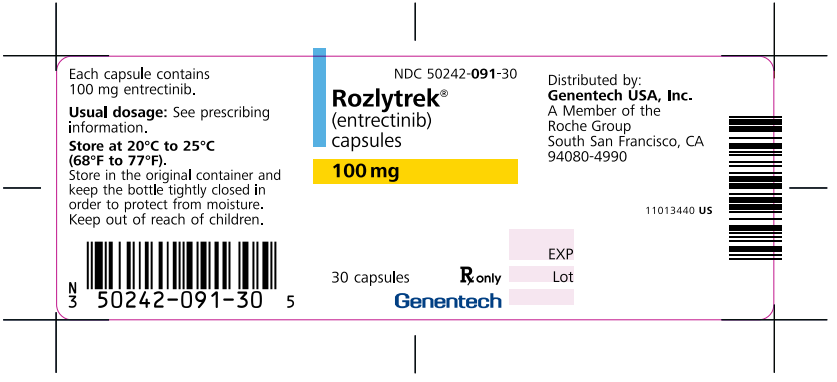
Date: .....

11013440 US
FILM 1 VON 4
Pantone Black
10.10.23

11013440 US
FILM 2 VON 4
PMS 294
10.10.23

11013440 US
FILM 3 VON 4
PMS 284
10.10.23

11013440 US
FILM 4 VON 4
PMS 109
10.10.23



This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

PREPRESS - INFORMATION

Format 48 x 61 x 82 mm
Register Nr. 10.400
NP 93
10.10.2023 09:21:32
Grundschrift 7.25 Punkt

PREPRESS - ROCHE BASEL

Control Proof

Date: .....

New Proof

Date: .....

11013439 US
FILM 1 VON 4
Pantone Black
10.10.23

11013439 US
FILM 2 VON 4
PMS 294
10.10.23

11013439 US
FILM 3 VON 4
PMS 284
10.10.23

11013439 US
FILM 4 VON 4
PMS 109
10.10.23

NDC 50242-**091**-30

Rozlytrek®
(entrectinib)
capsules

100 mg

PHARMACIST: Dispense with the included Instructions for Use

30 capsules

℞only

Genentech

11013439

Rozlytrek®
(entrectinib)
capsules

100 mg

30 capsules

Genentech

11013439
US
93

Each capsule contains 100 mg entrectinib.

Usual dosage: See prescribing information.

Capsules may be administered whole or may be used to prepare an oral suspension.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Store in the original container and keep the bottle tightly closed in order to protect from moisture.
Keep out of reach of children.

Product of Switzerland

Distributed by:
Genentech USA, Inc.
A Member of the Roche Group
South San Francisco, CA 94080-4990

GTIN 00350242091305

S/N
EXP
Lot

30 capsules Genentech

100 mg

Rozlytrek®
(entrectinib)
capsules

Reference ID: 5264688

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

PREPRESS - INFORMATION

Format 115 x 53 mm
Register Nr. 98.4.3650
NP 9707
10.10.2023 08:27:46
Grundschrift 6.5 Punkt

PREPRESS - ROCHE BASEL

Control Proof

Date: .....

New Proof

Date: .....

11013452 US
FILM 1 VON 4
Pantone Black
10.10.23

11013452 US
FILM 2 VON 4
PMS 294
10.10.23

11013452 US
FILM 3 VON 4
PMS 284
10.10.23

11013452 US
FILM 4 VON 4
PMS 2695
10.10.23

Each capsule contains
200 mg entrectinib.

Usual dosage: See prescribing information.

Store at 20°C to 25°C (68°F to 77°F).
Store in the original container and keep the bottle tightly closed in order to protect from moisture.
Keep out of reach of children.

NDC 50242-**094**-90

Rozlytrek®
(entrectinib)
capsules

200 mg

Distributed by:
Genentech USA, Inc.
A Member of the
Roche Group
South San Francisco, CA
94080-4990

11013452 US

N 3 50242-094-90 0

90 capsules

℞ only

Genentech

EXP
Lot

Reference ID: 5264688

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

PREPRESS - INFORMATION

Format 62 x 72 x 118 mm
Register Nr. 10.427
NP 94
10.10.2023 09:28:34
Grundschrift 9 Punkt

PREPRESS - ROCHE BASEL

Control Proof

Date: .....

New Proof

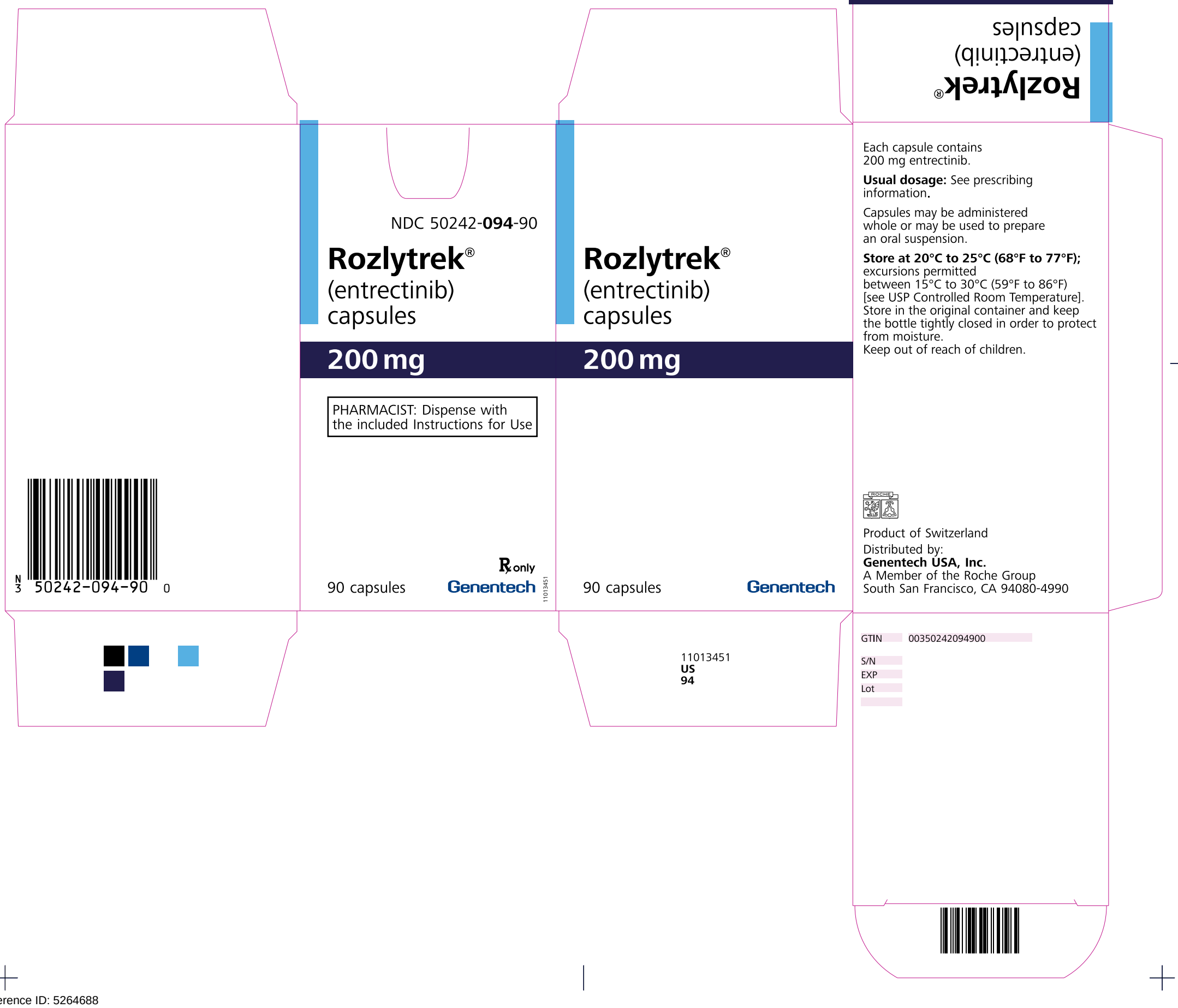
Date: .....

11013451 US
FILM 1 VON 4
Pantone Black
10.10.23

11013451 US
FILM 2 VON 4
PMS 294
10.10.23

11013451 US
FILM 3 VON 4
PMS 284
10.10.23

11013451 US
FILM 4 VON 4
PMS 2695
10.10.23



Reference ID: 5264688