Entrectinib

10:00 • ANTINEOPLASTIC AGENTS

- Entrectinib, a potent inhibitor of multiple receptor tyrosine kinases including tropomyosin receptor kinases (Trk) A, TrkB, TrkC, c-ros oncogene-1 (*ROS-1*), and anaplastic lymphoma kinase (ALK), is an antineoplastic agent.

USES

Non-small Cell Lung Cancer

Entrectinib is used for the treatment of c-ros oncogene-1 (*ROS-1*)-positive metastatic non-small cell lung cancer (NSCLC). The presence of *ROS-1* fusion should be confirmed prior to initiation of therapy. An FDA-approved diagnostic test for the detection of *ROS-1* fusion is not currently available; however, in clinical studies, presence of *ROS-1* fusion was determined by fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS). Entrectinib has been designated an orphan drug by FDA for the treatment of tropomyosin receptor kinase (Trk) A-positive, TrkB-positive, TrkC-positive, *ROS-1*-positive, and anaplastic lymphoma kinase (ALK)-positive NSCLC. The current indication for entrectinib is based on an objective response rate of 78% in a cohort of patients with *ROS-1*-positive locally advanced or metastatic NSCLC.

The current indication for entrectinib in the treatment of *ROS-1*-positive metastatic NSCLC is based principally on pooled results for a cohort of 51 adults with previously untreated or recurrent locally advanced or metastatic NSCLC harboring a *ROS-1* fusion in 3 multicenter, open-label, noncomparative phase 1 and 2 studies (ALKA-372-001, STARTRK-1, and STARTRK-2). Patients who previously received a *ROS-1* inhibitor were excluded from the primary efficacy analysis. *ROS-1* fusion was determined using FISH or NGS and was confirmed by a central laboratory using a validated NGS test in 55% of patients. Patients enrolled in the NSCLC cohort received varying dosages of entrectinib; however, 90% of patients received entrectinib 600 mg orally once daily. The primary efficacy end points were objective response rate (as evaluated by a blinded independent review committee) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response; an additional outcome measure was intracranial response. The median age of patients included in the NSCLC cohort was 53 years; 94% had adenocarcinoma histology, 88% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 57% were white, 37% were Asian, 67% were female, and 69% had received prior platinum-containing therapy for metastatic or recurrent disease or had progressed within 6 months of adjuvant or neoadjuvant therapy. Most patients (94%) had metastatic disease; CNS metastases were present in 43% of patients.

At a median follow-up of 16.6 months, the objective response rate for patients receiving entrectinib for the treatment of locally advanced or metastatic *ROS-1*-positive NSCLC was 78%; complete response was achieved in 6% of patients. At the time of analysis, 70, 55, or 30% of patients had durable responses of at least 9, 12, or 18 months, respectively. Intracranial response was achieved in 5 of 7 patients with measurable CNS metastases at baseline (as assessed by a blinded independent review committee) who had not received prior radiation therapy to the brain within 2 months of receiving entrectinib. The most common *ROS-1* fusion was *CD74-ROS-1*. The objective response rate in patients with tumors harboring *CD74-ROS-1*, *SLC34A2-ROS-1*, *SDC4-ROS-1*, *EZR-ROS-1*, or *TPM3-ROS-1* was 85, 57, 67, 100, or 50%, respectively. Among patients with tumors harboring an unknown *ROS-1* fusion, the objective response rate was 83%.

Solid Tumors with Neurotrophic Receptor Tyrosine Kinase Gene Fusion

Entrectinib is used for the treatment of solid tumors harboring a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion (without a known acquired mutation for resistance) in patients who have metastatic disease or may experience severe morbidity following surgical resection and whose disease progressed following prior therapy or those who are not candidates for other treatment options. The presence of *NTRK* fusion should be confirmed prior to initiation of therapy. An FDA-approved diagnostic test for detection of *NTRK* fusion is not currently available; however, in clinical studies, presence of *NTRK* fusion was determined by NGS or other nucleic acid-based tests. Entrectinib has been designated an orphan drug by FDA for the treatment of these cancers. The accelerated approval of entrectinib for this indication is based on objective response rate and duration of response. Continued approval for this indication may be contingent on verification and description of clinical benefit of entrectinib in confirmatory studies.

The incidence of solid tumors harboring activating *NTRK* fusions has not been fully characterized; however, 1500–5000 cases are estimated per year in the US. Although a relatively small subset (less than 1%) of patients with common solid tumors (e.g., cancers of the lung, colon, or prostate) harbor *NTRK* fusions, such fusions have been frequently reported in certain rare cancers (i.e., 91–100% of mammary analogue secretory carcinomas, secretory breast carcinomas, or infantile fibrosarcomas; 61% of congenital mesoblastic nephromas; 12–15% of papillary thyroid cancers).

The current indication for entrectinib in the treatment of solid tumors harboring a *NTRK* fusion is based principally on pooled results for a cohort of patients with unresectable or metastatic solid tumors harboring a *NTRK* fusion in 3 multicenter, open-label, noncomparative phase 1 and 2 studies (ALKA-372-001, STARTRK-1, and STARTRK-2). This cohort of patients included the initial 54 adults enrolled in the ALKA-372-001, STARTRK-1, and STARTRK-2 studies with solid tumors harboring a *NTRK* fusion. Patients were included in the *NTRK* fusion-positive solid tumor cohort if they experienced disease progression following prior systemic therapy, if available, or if severe morbidity following surgical resection for locally advanced disease was expected. Patients who previously received a tropomyosin receptor kinase (Trk) inhibitor were excluded from the primary efficacy analysis. *NTRK* fusion was detected using NGS or other nucleic acid-based tests; confirmation of *NTRK* fusion was detected by a validated NGS test in a central laboratory in 83% of patients. Patients enrolled in the *NTRK* fusion-positive solid tumor cohort received varying dosages of entrectinib; however, 94% of patients received entrectinib 600 mg orally once daily. Treatment was continued until disease progression or unacceptable toxicity occurred. The primary efficacy end points were objective response rate according to RECIST 1.1 (as evaluated by a blinded independent review committee) and duration of response; an additional outcome measure was intracranial response. The median age of patients included in the *NTRK* fusion-positive solid tumor cohort was 57 years, 89% had an ECOG performance status of 0 or 1, 80% were white, and 59% were female. Most patients (96%) had metastatic disease and 4% had unresectable locally advanced disease. All patients in the *NTRK* fusion-positive solid tumor cohort had received prior therapy for their disease (i.e., surgery, radiation therapy, systemic therapy); 63 or 17% of patients had received a median of 1 or at least 3 prior systemic therapies for metastatic disease, respectively. CNS metastases were present in 22% of patients. The most common cancers in the *NTRK* fusion-positive solid tumor cohort were sarcoma (24%), lung cancer (19%), salivary gland tumors (13%), breast cancer (11%), thyroid cancer (9%), and colorectal cancer (7%).

At a median follow-up of 12.9 months, the objective response rate in the *NTRK* fusion-positive solid tumor cohort was 57%; complete response was achieved in 7.4% of patients. At the time of analysis, 68, 61, or 45% of patients had durable responses of at least 6, 9, or 12 months, respectively. Intracranial response was achieved in 3 of 4 patients with measurable CNS metastases at baseline (as assessed by a blinded independent review committee) who had not received prior radiation therapy to the brain within 2 months of receiving entrectinib. Among patients with previously treated metastatic disease, the objective response rate was 53%. The objective response rate in patients with mammary analogue secretory carcinoma, breast cancer, NSCLC, sarcoma, colorectal cancer, or thyroid cancer was 86, 83, 70, 46, 25, or 20%, respectively. All patients with neuroendocrine cancers, pancreatic cancer, gynecologic cancers, or cholangiocarcinoma achieved partial responses. The most common documented *NTRK* fusion was *ETV6-NTRK3*. The objective response rate in patients with tumors harboring *TPR-NTRK1*, *ETV6-NTRK3*, or *TPM3-NTRK1* was 100, 68, or 50%, respectively. Although *SQSTM1-NTRK1* fusion was detected in 2 patients and *CD74-NTRK1*, *PLEKHA6-NTRK1*, *CDC42BPA-NTRK1*, *EPS15L1-NTRK1*, and *RBPMS-NTRK3* fusions were detected in one patient each, all patients with tumors harboring these *NTRK* fusions achieved partial responses.

DOSAGE AND ADMINISTRATION

General

Confirmation of the presence of c-ros oncogene-1 (*ROS-1*) fusion in tumor specimens of patients with metastatic non-small cell lung cancer (NSCLC) is necessary prior to initiating therapy with entrectinib. (See Uses: Non-small Cell Lung Cancer.)

Presence of a neurotrophic receptor tyrosine kinase (*NTRK*) fusion must be confirmed prior to initiation of therapy with entrectinib for the treatment of

locally advanced or metastatic solid tumors. (See Uses: Solid Tumors with Neurotrophic Receptor Tyrosine Kinase Gene Fusion.)

Restricted Distribution

Entrectinib is available only from designated specialty pharmacies and distributors. The manufacturer should be contacted for additional information.

● *Administration*

Entrectinib is administered orally once daily without regard to food. The capsules should be swallowed whole and should *not* be opened, crushed, chewed, or dissolved.

If a dose of entrectinib is missed, the missed dose should be taken as soon as it is remembered unless the next dose is due within 12 hours. If a dose is vomited immediately after administration, an additional dose should be administered to make up for the vomited dose.

● *Dosage*

Non-small Cell Lung Cancer

For the treatment of *ROS-1*-positive metastatic NSCLC, the recommended adult dosage of entrectinib is 600 mg orally once daily. Treatment should be continued until disease progression or unacceptable toxicity occurs.

Solid Tumors with Neurotrophic Receptor Tyrosine Kinase Gene Fusion

For the treatment of solid tumors harboring a *NTRK* fusion (without a known acquired mutation for resistance) in patients who have metastatic disease or may experience severe morbidity following surgical resection and whose disease progressed following prior therapy or those who are not candidates for other treatment options, the recommended dosage of entrectinib in *adults* is 600 mg once daily. The recommended dosage in *pediatric patients 12 years of age or older* is based on body surface area (BSA) as described in Table 1. Treatment should be continued until disease progression or unacceptable toxicity occurs.

TABLE 1. Recommended Dosage of Entrectinib in Pediatric Patients 12 Years of Age or Older.

BSA	Recommended Dosage
>1.5 m^2	600 mg once daily
1.11–1.5 m^2	500 mg once daily
0.91–1.1 m^2	400 mg once daily

Dosage Modification for Toxicity

Temporary interruption of therapy, dosage reduction, and/or permanent discontinuance of entrectinib may be necessary in patients experiencing certain adverse effects (see Table 3). When dosage modification of entrectinib is necessary, the dosage of entrectinib should be reduced as described in Table 2.

TABLE 2. Dosage Reduction for Entrectinib Toxicity.

	Dosage Reduction after Recovery from Toxicity		
Dose Reduction Level	Adults and Pediatric Patients ≥12 Years of Age with BSA >1.5 m^2 (Initial Dosage = 600 mg once daily)	Pediatric Patients ≥12 Years of Age with BSA of 1.11–1.5 m^2 (Initial Dosage = 500 mg once daily)	Pediatric Patients ≥12 Years of Age with BSA of 0.91–1.1 m^2 (Initial Dosage = 400 mg once daily)
First	Restart at 400 mg once daily	Restart at 400 mg once daily	Restart at 300 mg once daily
Second	Restart at 200 mg once daily	Restart at 200 mg once daily	Restart at 200 mg once daily
Third	Permanently discontinue entrectinib	Permanently discontinue entrectinib	Permanently discontinue entrectinib

The following Dosage Modification for Entrectinib Toxicity table indicates the recommended dosage modification (i.e., temporary interruption of therapy, dosage reduction, discontinuance of therapy) for certain adverse effects according to severity.

TABLE 3. Dosage Modification for Entrectinib Toxicity

Adverse Reaction and Severity	Modification
Heart Failure	
Grade 2 or 3	Withhold therapy; when toxicity resolves to grade 1 or less, resume at reduced dosage (see Table 2)
Grade 4	Permanently discontinue therapy
CNS Effects	
Grade 2 (intolerable)	Withhold therapy; when toxicity resolves to baseline or grade 1 or less, resume at same or reduced dosage (see Table 2)
Grade 3	Withhold therapy; when toxicity resolves to baseline or grade 1 or less, resume at reduced dosage (see Table 2)
Grade 4	Permanently discontinue therapy
Hepatotoxicity	
Grade 3	Withhold therapy If toxicity resolves to baseline or grade 1 or less within 4 weeks, resume at same dosage (see Table 2)
If toxicity does *not* resolve within 4 weeks, permanently discontinue therapy	Grade 3 (recurrent)
Withhold therapy; if toxicity resolves to baseline or grade 1 or less within 4 weeks, resume at reduced dosage (see Table 2)	Grade 4
Withhold therapy	
If toxicity resolves to baseline or grade 1 or less within 4 weeks, resume at reduced dosage (see Table 2)	If toxicity does *not* resolve within 4 weeks, permanently discontinue therapy
Grade 4 (recurrent)	Permanently discontinue therapy
Elevated ALT or AST concentrations >3 times the ULN with concomitant total bilirubin concentrations >1.5 times the ULN in absence of cholestasis or hemolysis	Permanently discontinue therapy
Hyperuricemia	
Symptomatic	Withhold therapy and initiate urate-lowering therapy; when toxicity improves, resume at same or reduced dosage (see Table 2)
Grade 4	Withhold therapy and initiate urate-lowering therapy; when toxicity improves, resume at same or reduced dosage (see Table 2)
Prolongation of QT Interval	
QT_c interval >500 msec	If other etiology of QT-interval prolongation is present: Withhold therapy and correct other causes of QT-interval prolongation; resume at same dosage when toxicity resolves to baseline

TABLE 3. Continued

Adverse Reaction and Severity	Modification
Prolongation of QT Interval, continued	
If no other etiology of QT-interval prolongation is present: Withhold therapy; resume at reduced dosage (see Table 2) when toxicity resolves to baseline	Torsades de pointes, polymorphic ventricular tachycardia, or signs and/or symptoms of serious arrhythmia
Permanently discontinue therapy	**Visual Disturbances**
New visual symptoms, including changes that interfere with activities of daily living	Withhold therapy; when toxicity improves or stabilizes, resume at same or reduced dosage (see Table 2)
Grade 2 or greater	Withhold therapy; when toxicity improves or stabilizes, resume at same or reduced dosage (see Table 2)
Hematologic Toxicity	
Grade 3 or 4 anemia or neutropenia	Withhold therapy; when toxicity improves to grade 2 or less, resume at same or reduced dosage (see Table 2)
Other Toxicity	
Grade 3 or 4 (clinically significant)	Withhold therapy If toxicity resolves to baseline or grade 1 within 4 weeks, resume at same or reduced dosage (see Table 2)
If toxicity does *not* resolve within 4 weeks, permanently discontinue therapy	Grade 4 (recurrent)
Permanently discontinue therapy	

Concomitant Use with CYP3A Inhibitors

Concomitant use of entrectinib with moderate and potent inhibitors of cytochrome P-450 (CYP) isoenzyme 3A should be avoided. If concomitant use of a *potent* CYP3A inhibitor cannot be avoided in adults and pediatric patients 12 years of age or older with BSA more than 1.5 m^2, the manufacturer recommends reducing the dosage of entrectinib to 100 mg once daily. If concomitant use of a *moderate* CYP3A inhibitor cannot be avoided in adults and pediatric patients 12 years of age or older with BSA more than 1.5 m^2, the manufacturer recommends reducing the dosage of entrectinib to 200 mg once daily. If concomitant use of the moderate or potent CYP3A inhibitor is discontinued, the entrectinib dosage should be returned (after 3–5 elimination half-lives of the CYP3A inhibitor) to the dosage used prior to initiation of the moderate or potent CYP3A inhibitor.

The manufacturer states that concomitant use of moderate or potent inhibitors of CYP3A should be avoided in pediatric patients 12 years of age or older with BSA of 1.5 m^2 or less.

● *Special Populations*

No dosage adjustment is necessary in patients with mild hepatic impairment (total bilirubin concentration 1.5 times or less the ULN). (See Hepatic Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

No dosage adjustment is necessary in patients with mild or moderate renal impairment (creatinine clearance of 30 to less than 90 mL/minute). (See Renal Impairment under Warnings/ Precautions: Specific Populations, in Cautions.)

The manufacturer makes no specific dosage recommendations for geriatric patients. (See Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

CAUTIONS

● *Contraindications*

The manufacturer states that there are no known contraindications to the use of entrectinib.

● *Warnings/Precautions*

Heart Failure

Heart failure has been reported in patients receiving entrectinib. In clinical trials, heart failure occurred in 3.4% of 355 patients receiving the drug and was grade 3 in 2.3% of patients. The median time to onset of heart failure was 2 months (range: 11 days to 12 months). Heart failure was managed with appropriate treatment for heart failure and treatment delays or drug discontinuance in 50 or 17%, respectively, of patients receiving the drug; heart failure resolved in 75% of patients who experienced treatment delays or drug discontinuance. Myocarditis in the absence of heart failure also was reported in 0.3% of patients receiving the drug. Routine cardiac function assessment (except electrocardiograms [ECGs]) prior to and during therapy was not performed during these studies.

Patients with symptomatic heart failure, myocardial infarction (MI), unstable angina, or those who underwent coronary artery bypass graft (CABG) within 3 months were excluded from clinical trials.

In patients with symptoms or known risk factors for heart failure, left ventricular ejection fraction (LVEF) should be assessed prior to initiation of entrectinib. Patients should be monitored for signs and symptoms of heart failure (e.g., dyspnea, edema). For patients with myocarditis with or without decreased ejection fraction, magnetic resonance imaging (MRI) or cardiac biopsy may be necessary to confirm the diagnosis of myocarditis. If new onset or worsening heart failure occurs, appropriate therapy for heart failure should be initiated and assessment of left ventricular function should be repeated. Dosage reduction or permanent discontinuance of therapy may be necessary depending on the severity of heart failure or left ventricular dysfunction. (See Dosage Modification for Toxicity under Dosage and Administration: Dosage.)

CNS Effects

Entrectinib can cause a wide variety of adverse CNS effects, including cognitive impairment, mood disorder, dizziness, and sleep disturbance. The overall incidence of adverse CNS effects was similar in patients with or without CNS metastases; however, the incidence of dizziness, headache, paresthesia, balance disorder, and confusional state appeared to be higher in patients who received prior radiation therapy to the brain for the treatment of CNS metastases compared with those who had not received prior radiation therapy to the brain.

In clinical trials, 27% of 355 patients receiving entrectinib experienced cognitive impairment, which was grade 3 in 4.5% of patients. Most patients (77%) experienced cognitive impairment within 3 months of initiating the drug. Cognitive impairment included cognitive disorders, confusional state, disturbance in attention, memory impairment, amnesia, aphasia, mental status change, hallucination, and delirium. Dosage interruption, dosage reduction, or drug discontinuance was required in 18, 13, or 1%, respectively, of entrectinib-treated patients experiencing cognitive impairment.

In clinical trials, 10% of 355 patients receiving entrectinib experienced mood disorders, which were grade 3 in 0.6% of patients. The median time to onset of mood disorders was 1 month (range: 1 day to 9 months). Mood disorders included anxiety, depression, and agitation. Suicidality (i.e., completed suicide) was reported in one patient 11 days following discontinuance of entrectinib. Among patients experiencing mood disorders, 6% required dosage reduction and 6% required interruption of therapy. Discontinuance of entrectinib therapy was not required in patients who experienced mood disorders.

In clinical trials, 38% of 355 patients receiving entrectinib experienced dizziness, which was grade 3 in 2.2% of patients. Dosage reduction, dosage interruption, or drug discontinuance was required in 10, 7, or 0.7%, respectively, of entrectinib-treated patients experiencing dizziness.

In clinical trials, 14% of 355 patients receiving entrectinib experienced sleep disturbances and was grade 3 in 0.6% of patients. Sleep disturbances included insomnia, somnolence, hypersomnia, and sleep disorder. Dosage reduction was required in 6% of entrectinib-treated patients experiencing sleep disturbance. Discontinuance of entrectinib therapy was not required in patients who experienced sleep disturbance.

Patients and their caregivers should be informed of the risk of adverse CNS effects associated with entrectinib therapy. Temporary interruption of entrectinib therapy, dosage reduction, or permanent discontinuance of therapy may be necessary in patients experiencing adverse CNS effects during therapy with the drug, and such patients should be advised not to drive or operate machinery. (See Dosage Modification for Toxicity under Dosage and Administration: Dosage.)

Fractures

Fractures have been reported in patients receiving entrectinib. In an expanded safety population, fracture occurred in 5% of 338 adults and 23% of 30 pediatric patients receiving the drug; the median time to onset of fracture was 3.8 months (range: 0.3–18.5 months) in adults and 4 months (range: 1.8–7.4 months) in pediatric patients. Most fractures involved the lower extremity (e.g., hip, femoral or tibial shaft) and, less frequently, the bilateral femoral neck. In adults, fractures were sometimes associated with trauma (e.g., fall) whereas fractures were associated with minimal or no trauma in pediatric patients. Assessment of bone metastases generally was inadequate; however, radiographic abnormalities potentially indicating bone metastases were reported in some patients. Entrectinib therapy was interrupted because of fractures in 41% of adults and 43% of pediatric patients. Discontinuance of entrectinib therapy was not required in patients who developed fracture.

Patients experiencing signs or symptoms of fracture (e.g., pain, changes in mobility, deformity) should be promptly evaluated. Effect of entrectinib on healing of known fractures or long-term fracture risk is unknown.

Hepatotoxicity

Hepatotoxicity has been reported in patients receiving entrectinib. In clinical trials, elevations of serum AST or ALT concentrations were reported in 42 or 36%, respectively, of 355 patients receiving entrectinib; grade 3–4 elevations in AST or ALT concentrations occurred in 2.5 or 2.8%, respectively, of patients. Because posttreatment liver function tests were not available for 4.5% of patients, the reported frequency may underestimate the drug's potential to cause elevated aminotransferase concentrations. The median time to onset of elevated ALT or AST concentrations was 2 weeks (range: 1 day to 29.5 months). Dosage interruption, dosage reduction, or drug discontinuance was required in 0.8, 0.8, or 0.8%, respectively, of entrectinib-treated patients who developed elevated ALT or AST concentrations.

Liver function tests (e.g., ALT and AST concentrations) should be monitored every 2 weeks during the first month of therapy, monthly thereafter, and as clinically indicated. Temporary interruption of entrectinib therapy, dosage reduction, or permanent discontinuance of therapy may be necessary in patients experiencing hepatotoxicity. (See Dosage Modification for Toxicity under Dosage and Administration: Dosage.)

Hyperuricemia

Hyperuricemia has been reported in patients receiving entrectinib. In clinical trials, 9% of 355 patients receiving entrectinib experienced symptomatic hyperuricemia-associated adverse reactions. Grade 4 hyperuricemia occurred in 1.7% of patients receiving the drug, including one fatal case of tumor lysis syndrome. Urate-lowering therapy, dosage reduction, and interruption of therapy were required in 34, 6, and 6%, respectively, of patients who experienced symptomatic hyperuricemia. Hyperuricemia resolved in 73% of patients following initiation of urate-lowering therapy without interruption of therapy or dosage reduction. Discontinuance of entrectinib therapy was not required in patients experiencing hyperuricemia.

Serum uric acid levels should be assessed prior to initiating entrectinib and periodically during treatment. Patients should be monitored for signs and symptoms of hyperuricemia. In patients who develop signs or symptoms of hyperuricemia, urate-lowering therapy should be initiated as clinically indicated. Temporary interruption of therapy or dosage reduction may be necessary. (See Dosage Modification for Toxicity under Dosage and Administration: Dosage.)

Prolongation of QT Interval

Prolongation of the corrected QT (QT_c) interval has been reported in patients receiving entrectinib. In clinical trials, an increase in the QT_c interval (corrected for heart rate using Fridericia's formula [QT_cF]) exceeding 60 msec from baseline occurred in 3.1% of entrectinib-treated patients, and QT_cF intervals exceeding 500 msec occurred in 0.6% of entrectinib-treated patients.

QT interval and electrolyte concentrations should be monitored at baseline and periodically during therapy. More frequent monitoring may be necessary in patients with preexisting QT_c-interval prolongation and those with risk factors for developing QT_c-interval prolongation (e.g., long QT syndromes, clinically important bradyarrhythmia, severe or uncontrolled heart failure, electrolyte abnormalities, concomitant use of drugs known to prolong the QT_c interval). Temporary interruption of entrectinib therapy, dosage reduction, or permanent discontinuance of therapy may be necessary in patients experiencing QT_c-interval prolongation. (See Dosage Modification for Toxicity under Dosage and Administration: Dosage.)

Visual Disturbances

Visual disturbances (i.e., blurring, photophobia, diplopia, visual impairment, photopsia, cataract, vitreous floaters), generally mild in severity, have been reported in patients receiving entrectinib. In clinical trials, vision changes occurred in 21% of 355 patients receiving the drug.

In patients who report new visual symptoms, including changes that interfere with activities of daily living, an ophthalmologic evaluation should be performed as clinically appropriate. Temporary interruption of therapy or dosage reduction may be necessary depending on the severity of the visual disturbance. (See Dosage Modification for Toxicity under Dosage and Administration: Dosage.)

Fetal/Neonatal Morbidity and Mortality

Entrectinib may cause fetal harm in humans based on its mechanism of action and animal findings; embryofetal toxicity and teratogenicity have been demonstrated in animals. There are no available data regarding use of entrectinib in pregnant women. In animal reproduction studies, body closure defects (omphalocele, gastroschisis) and malformations of vertebrae, ribs, and limbs (micromelia, adactyly) were observed in rats receiving entrectinib at exposure levels up to 2.7 times the human exposure at the recommended dosage; reduced fetal weight and reduced skeletal ossification were observed in rats receiving the drug at exposure levels approximately 0.2 and 0.9 times the human exposure, respectively, at the recommended dosage. Literature reports in individuals with congenital mutations in the tropomyosin receptor kinase (Trk) pathway suggest an association between decreased Trk-mediated signaling and obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis.

Pregnancy should be avoided during entrectinib therapy. The manufacturer states that a pregnancy test should be performed prior to initiation of entrectinib therapy in women of reproductive potential and states that such women should be advised to use effective contraceptive methods while receiving entrectinib and for at least 5 weeks after the last dose. Men who are partners of such women should use effective methods of contraception while receiving entrectinib and for 3 months after the last dose. Patients should be apprised of the potential hazard to the fetus if entrectinib is used during pregnancy.

Specific Populations

Pregnancy

Entrectinib may cause fetal harm if administered to pregnant women based on its mechanism of action and animal findings. (See Fetal/Neonatal Morbidity and Mortality under Cautions: Warnings/Precautions.)

Lactation

It is not known whether entrectinib or its metabolites are distributed into human milk. The effects of the drug on nursing infants or on the production of milk are unknown. Because of the potential for adverse reactions to entrectinib in nursing infants, women should be advised not to nurse while receiving the drug and for 1 week after the last dose.

Pediatric Use

Safety and efficacy of entrectinib for the treatment of c-ros oncogene-1 (*ROS-1*)-positive non-small cell lung cancer (NSCLC) have not been established in pediatric patients.

Safety and efficacy of entrectinib have not been established in pediatric patients less than 12 years of age with solid tumors harboring a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion. Efficacy of entrectinib for the treatment of solid tumors harboring *NTRK* fusion in pediatric patients 12 years of age or older is supported by extrapolation of data from 3 noncomparative studies evaluating entrectinib in adults; safety of entrectinib in such patients is supported by extrapolation of data from adults and a clinical study that included 30 pediatric patients (2 infants, 23 children, 5 adolescents). Some grade 3 or 4 adverse effects and laboratory abnormalities (i.e., neutropenia, fractures, weight gain, thrombocytopenia, lymphopenia, elevations in γ-glutamyltransferase [GGT, γ-glutamyltranspeptidase, GGTP] concentrations, device-related infection) occurred more frequently in pediatric patients compared with adults; however, because the studies were

uncontrolled, it is unclear whether this effect was related to entrectinib or to other confounding factors (e.g., differences in susceptibility to infection).

In a phase 1 study, no difference in systemic exposure was observed between pediatric patients and adults.

Geriatric Use

In clinical trials, 25% of patients receiving entrectinib were 65 years of age or older, while 5% were 75 years of age or older. There is insufficient experience in patients 65 years of age or older to determine whether geriatric patients respond differently than younger adults.

Hepatic Impairment

Population pharmacokinetic analysis suggests that the pharmacokinetics of entrectinib are not substantially altered in patients with mild hepatic impairment (total bilirubin concentration 1.5 times or less the upper limit of normal [ULN]).

The effect of moderate to severe hepatic impairment (total bilirubin concentration exceeding 1.5 times the ULN) on the pharmacokinetics of entrectinib has not been established.

Renal Impairment

Population pharmacokinetic analysis suggests that the pharmacokinetics of entrectinib are not substantially altered in patients with mild to moderate renal impairment (creatinine clearance of 30 to less than 90 mL/minute).

The effect of severe renal impairment (creatinine clearance less than 30 mL/minute) on the pharmacokinetics of entrectinib has not been established.

● *Common Adverse Effects*

Adverse effects reported in at least 20% of patients receiving entrectinib include fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders.

DRUG INTERACTIONS

Entrectinib is metabolized principally by cytochrome P-450 (CYP) isoenzyme 3A4 and to a lesser extent by CYP isoenzymes 2C9 and 1C19.

In vitro, entrectinib is not a substrate of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), but its major active metabolite M5 is a substrate of both P-gp and BCRP. Neither entrectinib nor M5 is a substrate of organic anion transport protein (OATP) 1B1 or 1B3.

● *Drugs and Foods Affecting Hepatic Microsomal Enzymes*

Inhibitors of CYP3A

Concomitant use of entrectinib with moderate and potent inhibitors of CYP isoenzyme 3A may increase systemic exposure to entrectinib and possible toxicity. When the potent CYP3A inhibitor itraconazole was administered concomitantly with entrectinib (single 100-mg dose), peak plasma concentration and area under the concentration-time curve (AUC) of entrectinib were increased 1.7- and 6-fold, respectively. Simulations using physiologically based pharmacokinetic models suggest that concomitant use of the moderate CYP3A inhibitor erythromycin (500 mg three times daily) and entrectinib (200 mg once daily) may increase steady-state peak plasma concentration and AUC of entrectinib 2.9- and 3.4-fold, respectively.

In *adults and pediatric patients 12 years of age or older with body surface area (BSA) more than 1.5 m²*, concomitant use of entrectinib with moderate and potent CYP3A inhibitors (e.g., itraconazole, grapefruit juice) should be avoided. If concomitant use of a *potent* CYP3A inhibitor cannot be avoided, the manufacturer recommends reducing the dosage of entrectinib from 600 mg once daily to 100 mg once daily. If concomitant use of a *moderate* CYP3A inhibitor cannot be avoided, the manufacturer recommends reducing the dosage of entrectinib from 600 mg once daily to 200 mg once daily. When concomitant use of the moderate or potent CYP3A inhibitor is discontinued, the entrectinib dosage should be returned (after 3–5 elimination half-lives of the CYP3A inhibitor) to the dosage used prior to initiation of the moderate or potent CYP3A inhibitor.

In *pediatric patients 12 years or age or older with BSA of 1.5 m² or less*, concomitant use of moderate or potent inhibitors of CYP3A should be avoided.

Inducers of CYP3A

Concomitant use of entrectinib with moderate and potent inducers of CYP3A may decrease systemic exposure to entrectinib and reduce entrectinib efficacy. When the potent CYP3A inducer rifampin (600 mg once daily for 14 days) was administered concomitantly with entrectinib (single 600-mg dose), peak plasma concentration and AUC of entrectinib were decreased by 56 and 77%, respectively. Simulations using physiologically-based pharmacokinetic models suggest that concomitant use of the moderate CYP3A inducer efavirenz (600 mg once daily) and entrectinib (600 mg once daily) may decrease the steady-state peak plasma concentration and AUC of entrectinib by 43 and 56%, respectively.

Concomitant use of entrectinib with moderate and potent CYP3A inducers should be avoided.

● *Drugs Metabolized by Hepatic Microsomal Enzymes*

Substrates of CYP3A

When the sensitive CYP3A substrate midazolam was administered concomitantly with entrectinib (600 mg once daily), peak plasma concentration of midazolam was decreased by 21% and AUC of midazolam was increased by 50%.

● *Substrates of P-glycoprotein Transport Systems*

When the sensitive P-gp substrate digoxin was administered concomitantly with entrectinib (single 600-mg dose), peak plasma concentration and AUC of digoxin were increased by 28 and 18%, respectively.

● *Drugs Affecting Gastric Acidity*

When the proton-pump inhibitor lansoprazole was administered concomitantly with entrectinib (single 600-mg dose), peak plasma concentration and AUC of entrectinib were decreased by 23 and 25%, respectively.

● *Drugs that Prolong the QT Interval*

Concomitant use of entrectinib with other drugs with known potential to prolong the QT interval should be avoided. (See Prolongation of QT Interval under Cautions: Warnings/Precautions.)

DESCRIPTION

Entrectinib, a potent inhibitor of multiple receptor tyrosine kinases, including tropomyosin receptor kinases (Trk) A, TrkB, TrkC, c-ros oncogene-1 (*ROS-1*), and anaplastic lymphoma kinase (ALK), is an antineoplastic agent. The Trk family of tyrosine kinases (encoded by the neurotrophic receptor tyrosine kinase genes *NTRK1*, *NTRK2*, and *NTRK3*) are involved in the initiation of various cascades of intracellular signaling events (i.e., Ras/MAPK/ERK, PI3K/Akt, and PLCγ1/Pkc signal transduction pathways), which leads to cell proliferation, differentiation, apoptosis, and regulation of processes critical to neuron survival in the central and peripheral nervous systems. Chromosomal rearrangements of the *NTRK1*, *NTRK2*, and *NTRK3* genes result in fusions with an unrelated gene. These *NTRK* gene fusions encode a constitutively active chimeric Trk oncogenic fusion protein resulting in dysregulation of Trk signaling and subsequent tumorigenesis. Similarly, fusion proteins, including *ROS-1* or ALK kinase domains, activate tumorigenesis through hyperactivation of downstream signaling pathways. In vitro and in vivo, entrectinib has demonstrated inhibition of cancer cell lines derived from multiple tumor types harboring *NTRK*, *ROS-1*, and *ALK* fusion genes. In vitro, entrectinib is 10- to 100-fold more potent than crizotinib in its activity against *ROS-1*, and 7- to 8-fold more potent than crizotinib in its activity against ALK. Entrectinib also has demonstrated inhibition of Janus kinase 2 (JAK2) and tyrosine kinase nonreceptor 2 (TNK2).

Based on limited data, clinical resistance to entrectinib has been attributed to secondary point mutations of the NTRK kinase domain (i.e., G595R and G667C point mutations in the TrkA kinase domain; G623R point mutation in the TrkC kinase domain).

Entrectinib and its active metabolite exhibit linear and time-independent pharmacokinetics over the oral dosage range of 100–400 mg/m² when coadministered with food. Following oral administration of a single 600-mg dose, peak plasma concentration of the drug is achieved in 4–6 hours. A high-fat, high-calorie meal did not affect the systemic exposure of entrectinib. Steady-state concentrations of entrectinib and its active metabolite are achieved within 1 and 2 weeks, respectively, of daily dosing; systemic accumulation of entrectinib and

its active metabolite is approximately 2- and 1.6-fold, respectively. Entrectinib crosses the blood-brain barrier in preclinical models. Entrectinib is metabolized principally by cytochrome P-450 (CYP) isoenzyme 3A4 to form its major active metabolite, M5, which exhibits similar inhibitory activity for TrkA, TrkB, TrkC, *ROS-1*, and ALK to that of the parent drug in vitro. Entrectinib and M5 are more than 99% bound to plasma proteins. Following oral administration of a single radiolabeled dose of entrectinib, 83% of the dose was recovered in feces (36% as unchanged drug and 22% as M5) and 3% of the dose was recovered in urine. The elimination half-lives of entrectinib and M5 are 20 and 40 hours, respectively.

The pharmacokinetics of entrectinib do not appear to be affected by age (12–86 years), sex, race (white, Asian, or black), or body weight (32–130 kg).

ADVICE TO PATIENTS

Importance of advising patients to read the FDA-approved patient information.

Importance of advising patients to swallow entrectinib capsules whole and to avoid grapefruit juice while taking entrectinib. If a dose is missed, importance of taking the missed dose as soon as it is remembered unless the next dose is due within 12 hours. If a dose is vomited immediately after administration, an additional dose should be administered to make up for the vomited dose.

Risk of heart failure. Importance of informing clinician promptly if new or worsening signs or symptoms of heart failure (e.g., dyspnea, edema) occur.

Risk of CNS effects. Importance of informing clinician if new or worsening CNS effects (i.e., cognitive impairment, mood disorders, dizziness, sleep disturbance) occur. Necessity of advising patients to avoid driving or operating hazardous machinery if they experience CNS effects.

Risk of hepatotoxicity and importance of monitoring liver function. Importance of informing clinician promptly if symptoms of hepatotoxicity (e.g., loss of appetite, nausea, vomiting, upper right abdominal pain) occur.

Risk of fractures. Importance of informing clinician if symptoms such as pain, changes in mobility, or deformity occur.

Risk of hyperuricemia. Importance of informing clinician if signs or symptoms associated with hyperuricemia occur.

Risk of QT-interval prolongation. Importance of informing clinician promptly if abnormal heartbeat or feelings of faintness, lightheadedness, or dizziness occur.

Risk of visual disturbances. Importance of informing clinician if visual disturbances (e.g., blurring, photophobia, diplopia, photopsia, light sensitivity, new or increased floaters) occur.

Risk of fetal harm. Necessity of advising women of reproductive potential to use effective methods of contraception while receiving entrectinib and for at least 5 weeks after the last dose. Importance of advising men with female partners of reproductive potential to use effective methods of contraception while receiving the drug and for 3 months after the last dose. Importance of women informing clinicians if they are or plan to be pregnant. If pregnancy occurs, advise pregnant women of potential risk to the fetus.

Importance of advising women to avoid nursing while receiving the drug and for 1 week after the last dose.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and herbal supplements, as well as any concomitant illnesses.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity. For further information on the handling of antineoplastic agents, see the ASHP Guidelines on Handling Hazardous Drugs at http://www.ahfsdruginformation.com.

PREPARATIONS

Entrectinib can only be obtained through designated specialty pharmacies and distributors. (See Restricted Distribution under Dosage and Administration: General.)

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Entrectinib

Oral		
Capsules	100 mg	**Rozlytrek®**, Genentech
	200 mg	**Rozlytrek®**, Genentech