Repotrex

Repotrectinib INN

Everest

COMPOSITION

REPOTREX capsule: Each capsule contains Repotrectinib INN 40 mg.

PHARMACOLOGY

Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and of the tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC. Fusion proteins that include ROS1 domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. Repotrectinib exhibited anti-tumor activity in cultured cells expressing ROS1 fusions and mutations including SDC4-ROS1, SDC4-ROS1^{G2032R}, CD74-ROS1, CD74-ROS1^{G2032R}, CD74-ROS1^{D2033N}, and CD74-ROS1^{L2026M}. Repotrectinib also inhibited cell proliferation in cultured cells expressing NTRK fusions and mutations including LMNA-TRKA, LMNA-TRKA^{G595R}, EVT6-TRKB^{G639R} & ETV6-TRK^{CG623R}.

INDICATION

Repotrectinib is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC).

Repotrectinib is also indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.
- have progressed following treatment or have no satisfactory alternative therapy.

DOSAGE AND ADMINISTRATION

Patients Selection

NSCLC

Select patients for the treatment of locally advanced or metastatic NSCLC with Repotrectinib based on the presence of ROS1 rearrangements in tumor specimens. An FDA-approved test to detect ROS1 rearrangements for selecting patients for treatment with Repotrectinib is not currently available.

Solid Tumors

Select patients for the treatment of solid tumors with Repotrectinib based on the presence of NTRK1/2/3 rearrangements in tumor specimens. An FDA-approved test to detect NTRK1/2/3 rearrangements for selecting patients for treatment with Repotrectinib is not currently available.

- In patients with secretory breast cancer or mammary analogue secretory cancer, consider treatment without confirmation of NTRK rearrangements in tumor specimens.

Important Information Prior to Initiating Repotrectinib

Prior to initiating Repotrectinib, discontinue strong and moderate CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor.

Recommended Evaluation and Testing Before Initiating Repotrectinib

Prior to initiation of Repotrectinib, evaluate:

- Liver function tests including bilirubin
- Uric acid level

Recommended Dosage

The recommended dosage of Repotrectinib is 160 mg taken orally once daily with or without food for 14 days, then increase to 160 mg twice daily and continue until disease progression or unacceptable toxicity.

Dosage Modifications for Adverse Reactions

The recommended dosage reductions of Repotrectinib for the management of adverse reactions are provided in Table 1.

Table 1: Recommended Dose Reductions for Repotrectinib Adverse Reactions

Dose	Dose Reduction	
	First	Second
160 mg Once Daily	120 mg Once Daily	80 mg Once Daily
160 mg Twice Daily	120 mg Twice Daily	80 mg Twice Daily

Recommended dosage modifications of Repotrectinib for the management of adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for Repotrectinib Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Central Nervous System Effects	Intolerable Grade 2	• Withhold Repotrectinib until ≤ Grade 1 or baseline. • Resume at same or reduced dose, as clinically appropriate.
	Grade 3	• Withhold Repotrectinib until ≤ Grade 1 or baseline. • Resume at reduced dose.
	Grade 4	• Permanently discontinue Repotrectinib
Interstitial Lung Disease (ILD)/ Pneumonitis	Any Grade	• Withhold Repotrectinib if ILD/ pneumonitis is suspected. • Permanently discontinue if ILD/ pneumonitis is confirmed.
Hepatotoxicity	Grade 3	• Withhold Repotrectinib until ≤ Grade 1 or baseline. • Resume at same dose if resolution occurs within 4 weeks. • Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks.
	Grade 4	• Withhold Repotrectinib until ≤ Grade 1 or baseline. • Resume at reduced dose. • 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 Repotrectinib.
Creatine Phosphokinase (CPK) Elevation	CPK elevation greater than 5 times ULN	• Withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at same dose.
	CPK elevation greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN	• Withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at reduced dose.
Hyperuricemia	Grade 3 or Grade 4	• Withhold Repotrectinib until improvement of signs or symptoms. • Resume Repotrectinib at same or reduced dose.
Other Clinically Relevant Adverse Reactions	Intolerable Grade 2 or Grade 3 or Grade 4	• Withhold Repotrectinib until ≤ 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.

*Graded per Common Terminology Criteria for Adverse Events

Administration
Take Repotrectinib at approximately the same time each day with or without food.

Swallow Repotrectinib capsules whole. Do not open, chew, crush, or dissolve the capsule prior to swallowing. Do not take any Repotrectinib capsules that are broken, cracked, or damaged. If a dose of Repotrectinib is missed or if vomiting occurs at any time after taking a dose, skip the dose and resume Repotrectinib at its regularly scheduled time.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Central Nervous System (CNS) Effects
Can cause CNS adverse reactions including dizziness, ataxia, and cognitive impairment. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue Repotrectinib based on severity.

Interstitial Lung Disease (ILD)/Pneumonitis
Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Hepatotoxicity
Monitor liver function tests every 2 weeks during the first month of treatment, and as clinically indicated thereafter. Based on severity, withhold and then resume at same or reduced dose, or permanently discontinue.

Myalgia with Creatine Phosphokinase (CPK) Elevation
Monitor serum CPK levels during treatment in patients reporting unexplained muscle pain, tenderness, or weakness. Based on severity, withhold and resume at same or reduced dose upon improvement.

Hyperuricemia
Monitor serum uric acid levels prior to initiating and periodically during treatment. Initiate treatment with urate-lowering medications as clinically indicated. Withhold and resume at same or reduced dose, or permanently discontinue based on severity.

Skeletal Fractures
Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures.

Embryo-Fetal Toxicity
Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective non-hormonal method of contraception.

ADVERSE REACTIONS
The most common adverse reactions (≥20%) were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness, and nausea.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Repotrectinib can cause fetal harm when administered to a pregnant woman. There are no available data on Repotrectinib use in pregnant women. Advise pregnant women of the potential risk to a fetus.

Lactation
Risk Summary
Lactating woman are advice to discontinue breastfeeding during treatment with Repotrectinib and for 10 days after the last dose.

Females and Males of Reproductive Potential
Repotrectinib can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing
Verify the pregnancy status of females of childbearing potential prior to initiating Repotrectinib.

Contraception
Repotrectinib can cause embryo-fetal harm when administered to a pregnant woman.

Females
Advise females of childbearing potential to use effective non-hormonal contraception during treatment with Repotrectinib and for 2 months following the last dose. Repotrectinib can render some hormonal contraceptives ineffective.

Males
Based on genotoxicity findings, advise male patients with female partners of childbearing potential to use effective contraception during treatment with Repotrectinib and for 4 months following the last dose.

Pediatric Use
The safety and effectiveness of Repotrectinib in pediatric patients with ROS1-positive NSCLC has not been established.

Geriatric Use
There were no clinically meaningful differences in safety and efficacy between patients younger than 65 years of age and patients 65 years of age or older.

Renal Impairment
The recommended dosage of Repotrectinib has not been established in patients with severe renal impairment or kidney failure (eGFR-MDRD <30 mL/min) and patients on dialysis.

No dosage modification is recommended for patients with mild or moderate renal impairment (eGFR-MDRD 30 to 90 mL/min).

Hepatic Impairment
The recommended dosage of Repotrectinib has not been established in patients with moderate (total bilirubin >1.5 to 3 times upper limit of normal [ULN] with any AST) or severe (total bilirubin >3 times ULN with any AST) hepatic impairment.

No dosage modification is recommended for patients with mild (total bilirubin >1 to 1.5 times ULN or AST > ULN) hepatic impairment.

OVERDOSE
In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

DRUG INTERACTIONS
Strong and Moderate CYP3A Inhibitors
Avoid concomitant use with strong or moderate CYP3A inhibitors.

Contraceptives
Repotrectinib is a CYP3A4 inducer, which can decrease progestin or estrogen exposure to an extent that could reduce the effectiveness of hormonal contraceptives.

Avoid concomitant use of Repotrectinib with hormonal contraceptives. Advise females to use an effective nonhormonal contraceptive.

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

How Supplied
REPOTREX capsule: Each HDPE container contains 56 capsules (Each capsule contains Repotrectinib INN 40 mg), a silica gel desiccant and polyester coil with child resistant closure.

Manufactured by
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