Lazerib

Lazertinib Mesylate Hydrate INN

Everest

COMPOSITION

LAZERIB tablet: Each film coated tablet contains Lazertinib Mesylate Hydrate INN equivalent to Lazertinib 80 mg.

PHARMACOLOGY

Lazertinib is a kinase inhibitor of epidermal growth factor receptor (EGFR) that inhibits EGFR exon 19 deletions and exon 21 L858R substitution mutations at lower concentrations than wild- type EGFR. In human NSCLC cells and mouse xenograft models of EGFR exon 19 deletions or EGFR L858R substitution mutations, lazertinib demonstrated anti-tumor activity. Treatment with lazertinib in combination with Amivantamab increased in vivo anti-tumor activity compared to either agent alone in a mouse xenograft model of human NSCLC with an EGFR L858R mutation.

INDICATION

Lazertinib, in combination with Amivantamab, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test.

DOSAGE AND ADMINISTRATION

Patients Selection

Select patients for the first-line treatment of NSCLC with Lazertinib, in combination with Amivantamab, based on the presence of EGFR exon 19 deletions or exon 21 L858R substitution mutations in tumor or plasma specimens. If these mutations are not detected in a plasma specimen, test tumor tissue.

Recommended Dosage & and Administration

The recommended dosage of Lazertinib is 240 mg orally once daily administered in combination with Amivantamab with or without food. Swallow Lazertinib tablets whole. Do not crush, split, or chew. Continue treatment until disease progression or unacceptable toxicity.

Administer Lazertinib any time prior to Amivantamab when given on the same day. Refer to the Amivantamab prescribing information for recommended Amivantamab dosing information.

Missed Dose

If a patient misses a dose of Lazertinib within 12 hours, instruct patients to take the missed dose. If more than 12 hours has passed since the dose was to be given, instruct the patient to take the next dose at its scheduled time.

Vomiting

If vomiting occurs any time after taking Lazertinib, instruct the patient to take the next dose at its next regularly scheduled time.

Concomitant Medications

When initiating treatment with Lazertinib in combination with Amivantamab, administer anticoagulant prophylaxis to prevent venous thromboembolic events (VTE) for the first four months of treatment. If there are no signs or symptoms of VTE during the first four months of treatment, consider discontinuation of anticoagulant prophylaxis at the discretion of the healthcare provider.

When initiating treatment with Lazertinib in combination with Amivantamab, administer alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream and encourage patients to limit sun exposure during and for 2 months after treatment, to wear protective clothing and use broad-spectrum UVA/UVB sunscreen to reduce the risk of dermatologic adverse reactions. Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions.

Dosage Modifications for Adverse Reactions

The recommended Lazertinib dose reductions for adverse reactions are presented in Table 1.

Table 1: Recommended Dose Reductions for Adverse Reactions for Lazertinib

Dose at which the adverse reaction occurred	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
240 mg once daily (three 80 mg tablets)	160 mg once daily (two 80 mg tablets)	80 mg once daily (one 80 mg tablet)	Discontinue Lazertinib

The recommended management and dosage modifications of Lazertinib for specific adverse reactions are presented in Table 2. Refer to the Amivantamab prescribing information for information about dosage modifications for Amivantamab.

Table 2: Recommended Management and Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Venous Thromboembolic Events (VTE)	Grade 2 or 3	•Withhold Lazertinib and Amivantamab. •Administer anticoagulant treatment as clinically indicated. •Once anticoagulant treatment has been initiated, resume Lazertinib and Amivantamab at the same dose level, at the discretion of the healthcare provider.
	Grade 4 or recurrent Grade 2 or 3 despite therapeutic level anticoagulation	•Withhold Lazertinib and permanently discontinue Amivantamab. •Administer anticoagulant treatment as clinically indicated. •Once anticoagulant treatment has been initiated, treatment can continue with Lazertinib at the same dose level at the discretion of the healthcare provider.
Interstitial Lung Disease (ILD)/Pneumonitis	Any Grade	•Withhold Lazertinib and Amivantamab if ILD/pneumonitis is suspected. •Permanently discontinue Lazertinib and Amivantamab if ILD/pneumonitis is confirmed.
Dermatologic Adverse Reactions (including dermatitis acneiform, pruritus, dry skin)	Grade 1	•Initiate supportive care management.
	Grade 2	•Initiate supportive care management. •If there is no improvement after 2 weeks, reduce Amivantamab dose and continue Lazertinib at the same dose. •Reassess every 2 weeks, if no improvement, reduce Lazertinib dose until ≤ Grade 1 (Table 1), then may resume previous dose of Lazertinib at the discretion of the healthcare provider.
	Grade 3	•Withhold Lazertinib and Amivantamab. •Initiate supportive care management. •Upon recovery to ≤ Grade 2, resume Lazertinib at the same dose or consider dose reduction, resume Amivantamab at a reduced dose. •If there is no improvement within 2 weeks, permanently discontinue both Lazertinib and Amivantamab.
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions)	•Initiate supportive care management. •Permanently discontinue Amivantamab. •Withhold Lazertinib until recovery ≤ Grade 2 or baseline. •Upon recovery to ≤ Grade 2, resume Lazertinib at a reduced dose at the discretion of the healthcare provider.
Other Adverse Reactions	Grade 3-4	•Withhold Lazertinib and Amivantamab until the adverse reaction resolves to ≤ Grade 1 or baseline. •Resume both drugs at a reduced dose or Lazertinib alone. •Consider permanently discontinuing both Lazertinib and Amivantamab if recovery does not occur within 4 weeks.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Venous Thromboembolic Events

Lazertinib in combination with Amivantamab can cause serious and fatal venous thromboembolic events (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE). The majority of these events occurred during the first four months of therapy.

Administer prophylactic anticoagulation for the first four months of treatment. The use of Vitamin K antagonists is not recommended. Monitor for signs and symptoms of VTE and treat as medically appropriate.

Withhold Lazertinib and Amivantamab based on severity. Once anticoagulant treatment has been initiated, resume Lazertinib and Amivantamab at the same dose level at the discretion of the healthcare provider. In the event of VTE

recurrence despite therapeutic anticoagulation, permanently discontinue Amivantamab. Continue treatment with Lazertinib at the same dose level at the discretion of the healthcare provider. Refer to the Amivantamab prescribing information for recommended Amivantamab dosage modification.

Interstitial Lung Disease (ILD)/Pneumonitis
Lazertinib in combination with Amivantamab can cause interstitial lung disease (ILD)/pneumonitis.
Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold Lazertinib and Amivantamab in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions
Lazertinib in combination with Amivantamab may cause severe dermatologic adverse reactions, including rash, dermatitis acneiform, pruritus, and dry skin. When initiating treatment with Lazertinib in combination with Amivantamab, administer alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream to reduce the risk of dermatologic adverse reactions. Instruct patients to limit sun exposure during and for 2 months after treatment with Lazertinib in combination with Amivantamab. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen.

Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions. If skin reactions develop, administer topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, administer oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, reduce the dose or permanently discontinue Lazertinib and Amivantamab based on severity.

Ocular Toxicity
Lazertinib, in combination with Amivantamab, can cause ocular toxicity, including keratitis.
Promptly refer patients presenting with new or worsening eye symptoms to an ophthalmologist. Withhold, reduce the dose or permanently discontinue Amivantamab and continue Lazertinib based on severity.

Embryo-Fetal Toxicity
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Lazertinib and for 3 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Lazertinib and for 3 weeks after the last dose.

ADVERSE REACTIONS
The most common adverse reactions are:
- Venous Thromboembolic Events
- Interstitial Lung Disease/Pneumonitis
- Dermatologic Adverse Reactions
- Ocular Toxicity

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Lazertinib can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Lactation
Risk Summary
There are no data on the presence of Lazertinib or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Lazertinib and for 3 weeks after the last dose. Refer to the Amivantamab prescribing information for lactation information during treatment with Amivantamab.

Females and Males of Reproductive Potential
Based on animal data and its mechanism of action, Lazertinib can cause fetal harm when administered to a pregnant woman.
Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating Lazertinib.

Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment with Lazertinib and for 3 weeks after the last dose. Refer to the Amivantamab prescribing information for recommended duration of contraception during treatment with Amivantamab.

Males
Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Lazertinib and for 3 weeks after the last dose.

Infertility
Based on findings in animals, Lazertinib may impair fertility in females and males of reproductive potential. The effects on female fertility were reversible. The effects on male testes in animal studies were not reversible within a 2-week recovery period.

Pediatric Use
The safety and effectiveness of Lazertinib in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

Renal Impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment (eGFR 30 – 89 mL/min).

Hepatic Impairment
No dose adjustment is recommended in patients with mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin ≤ 1.5×ULN and any AST) or moderate (total bilirubin ≤ 1.5 to 3×ULN and any AST) hepatic impairment.

DRUG INTERACTIONS
Effect of Other Drugs on Lazertinib
CYP3A4 Inducers
Avoid concomitant use of Lazertinib with strong and moderate CYP3A4 inducers. Consider an alternate concomitant medication with no potential to induce CYP3A4.

Lazertinib is a CYP3A4 substrate. Concomitant use with a strong or moderate CYP3A4 inducer decreased Lazertinib concentrations, which may reduce the efficacy of Lazertinib.

Effect of Lazertinib on Other Drugs
Certain CYP3A4 Substrates
Monitor for adverse reactions associated with a CYP3A4 substrate where minimal concentration changes may lead to serious adverse reactions, as recommended in the approved product labeling for the CYP3A4 substrate.

Lazertinib is a weak CYP3A4 inhibitor. Concomitant use of Lazertinib increased concentrations of CYP3A4 substrates, which may increase the risk of adverse reactions related to these substrates.
Certain BCRP Substrates

Monitor for adverse reactions associated with a BCRP substrate where minimal concentration changes may lead to serious adverse reactions, as recommended in the approved product labeling for the BCRP substrate.

Lazertinib is a BCRP inhibitor. Concomitant use of Lazertinib increased concentrations of BCRP substrates, which may increase the risk of adverse reactions related to these substrates.

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

How Supplied
LAZERIB tablet: Each HDPE container contains 90 tablets (each film coated tablet contains Lazertinib Mesylate Hydrate INN equivalent to Lazertinib 80 mg), a silica gel desiccant and polyester coil with child resistant closure.

Manufactured by
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