Lorbrexen 100

Lorlatinib 100 mg tablets

Everest

COMPOSITION

LORBREXEN 100 Tablet: Each film-coated tablet contains Lorlatinib INN 100 mg.

INDICATIONS

Lorlatinib as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after:

- Alectinib or Ceritinib as the first ALK inhibitor therapy; or
- Crizotinib and at least one other ALK inhibitor.

DOSAGE & ADMINISTRATION

The recommended dose is 100 mg Lorlatinib taken orally once daily.

Duration of treatment

Treatment with Lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity.

Delayed or missed doses

If a dose of Lorlatinib is missed, then it should be taken as soon as the patient remembers unless it is less than 4 hours before the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose modifications

Dosing interruption or dose reduction may be required based on individual safety and tolerability. Lorlatinib dose reduction levels are summarized below:

- First dose reduction: 75 mg taken orally once daily.
- Second dose reduction: 50 mg taken orally once daily.

Lorlatinib should be permanently discontinued if the patient is unable to tolerate the 50 mg dose taken orally once daily.

Special Populations

Elderly (≥ 65 years)

Due to the limited data on this population, no dose recommendation can be made for patients aged 65 years and older.

Renal impairment

No dose adjustment is needed for patients with normal renal function and mild or moderate (CLcr: ≥ 30mL/min) renal impairment based on a population pharmacokinetic analysis. Information for Lorlatinib use in patients with severe (CLcr: < 30 mL/min) renal impairment is very limited. Therefore, Lorlatinib is not recommended in patients with severe renal impairment.

Hepatic impairment

No dose adjustments is recommended for patients with mild hepatic impairment. No information is available for Lorlatinib in patients with moderate or severe hepatic impairment. Therefore, Lorlatinib is not recommended in patients with moderate to severe hepatic impairment.

Paediatric population

The safety and efficacy of Lorlatinib in paediatric patients below 18 years have not been established. No data are available.

CONTRAINDICATIONS

- Hypersensitivity to Lorlatinib
- Concomitant use of strong CYP3A4/5 inducers

WARNINGS AND PRECAUTIONS

Hyperlipidaemia

The use of Lorlatinib has been associated with increases in serum cholesterol and triglycerides. Median time of occurrence of severe increase in serum cholesterol and triglycerides is 201 days (range: 42 to 518 days) and 127 days (range: 15 to 358 days), respectively. Serum cholesterol and triglycerides should be monitored before initiation of Lorlatinib; 2, 4 and 8 weeks after initiating Lorlatinib; and regularly thereafter. Initiate or increase the dose of lipid-lowering medicinal products, if indicated.

Central nervous system effects

Central nervous system (CNS) effects have been observed in patients receiving Lorlatinib, including changes in cognitive function, mood or speech. Dose modification or discontinuation may be required for those patients who develop CNS effects.

Atrioventricular block

Lorlatinib was studied in a population of patients that excluded those with second-degree or third-degree AV block (unless paced) or any AV block with PR interval > 220 msec. PR interval prolongation and AV block have been reported in patients receiving Lorlatinib. Monitor electrocardiogram (ECG) prior to initiating Lorlatinib and monthly thereafter, particularly in patients with predisposing conditions to the occurrence of clinically significant cardiac events. Dose modification may be required for those patients who develop AV block.

Left ventricular ejection fraction decrease

Left ventricular ejection fraction (LVEF) decrease has been reported in patients receiving Lorlatinib who had baseline and at least one follow-up LVEF assessment. Based on the available clinical study data, it is not possible to determine a causal relationship between effects on changes in cardiac contractility and Lorlatinib. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including LVEF assessment at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring, including LVEF assessment, should be considered.

Lipase and amylase increase

Elevations of lipase and/or amylase have occurred in patients receiving Lorlatinib. Median time of occurrence of increase in serum lipase and amylase is 70 days (range: 7 to 696 days) and 41 days (range: 7 to 489 days), respectively. Risk of pancreatitis should be considered in patients receiving Lorlatinib due to concomitant hypertriglyceridemia and/or a potential intrinsic mechanism. Patients should be monitored for lipase and amylase elevations prior to the start of Lorlatinib treatment and regularly thereafter as clinically indicated.

Interstitial lung disease/Pneumonitis

Severe or life-threatening pulmonary adverse reactions consistent with ILD/pneumonitis have occurred with Lorlatinib. Any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g. dyspnoea, cough and fever) should be promptly evaluated for ILD/pneumonitis. Lorlatinib should be withheld and/or permanently discontinued based on severity.

Drug-drug interactions

In a study conducted in healthy volunteers, the concomitant use of Lorlatinib and rifampin, a strong CYP3A4/5 inducer, was associated with increases of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with no increase of total bilirubin and alkaline phosphatase. Concomitant use of a strong CYP3A4/5 inducer is contraindicated.

Concomitant use with moderate CYP3A4/5 inducers should be avoided, if possible, as they may also reduce Lorlatinib plasma concentrations.

Concurrent administration of Lorlatinib with CYP3A4/5 substrates with narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus and tacrolimus, should be avoided since the concentration of these medicinal products may be reduced by Lorlatinib.

Fertility and pregnancy

During treatment with Lorlatinib and for at least 14 weeks after the final dose, male patients with female partners of childbearing potential must use effective contraception, including a condom, and male patients with pregnant partners must use condoms. Male fertility may be compromised during treatment with Lorlatinib . Men should seek advice on effective fertility preservation before treatment. Women of childbearing potential should be advised to avoid becoming pregnant while receiving Lorlatinib. A highly effective non-hormonal method of contraception is required for female patients during treatment with Lorlatinib, because Lorlatinib can render hormonal contraceptives ineffective. If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 35 days after completing therapy . It is not known whether Lorlatinib affects female fertility.

Dietary sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 25 mg or 100 mg tablet. Patients on low sodium diets should be informed that this product is essentially "sodium-free".

Pharmacokinetic interactions

In vitro data indicate that Lorlatinib is primarily metabolized by CYP3A4 and uridine diphosphate-glucuronosyltransferase (UGT)1A4, with minor contributions from CYP2C8, CYP2C19, CYP3A5 and UGT1A3.

CYP3A4/5 inducers
Rifampin, a strong inducer of CYP3A4/5, administered at oral doses of 600 mg once daily for 12 days, reduced the mean Lorlatinib area under curve (AUC) by 85% and Cmax by 76% of a single 100 mg oral dose of Lorlatinib in healthy volunteers; increases in AST and ALT were also observed. Concomitant administration of Lorlatinib with strong CYP3A4/5 inducers (e.g. rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's wort) may decrease Lorlatinib plasma concentrations. The use of a strong CYP3A4/5 inducer with Lorlatinib is contraindicated. Concomitant use with moderate CYP3A4/5 inducers should be avoided, if possible, as they may also reduce Lorlatinib plasma concentrations.

CYP3A4/5 inhibitors
Itraconazole, a strong inhibitor of CYP3A4/5, administered at oral doses of 200 mg once daily for 5 days, increased the mean Lorlatinib AUC by 42% and Cmax by 24% of a single 100 mg oral dose of Lorlatinib in healthy volunteers. Concomitant administration of Lorlatinib with strong CYP3A4/5 inhibitors (e.g. boceprevir, cobicistat, itraconazole, ketoconazole, posaconazole, troleandomycin, voriconazole, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either elvitegravir, indinavir, lopinavir or tipranavir) may increase Lorlatinib plasma concentrations. Grapefruit products may also increase Lorlatinib plasma concentrations and should be avoided. An alternative concomitant medicinal product with less potential to inhibit CYP3A4/5 should be considered. If a strong CYP3A4/5 inhibitor must be concomitantly administered, a dose reduction of Lorlatinib is recommended.

SIDE EFFECTS
The most frequently reported adverse reactions were hypercholesterolaemia (84.4%), hypertriglyceridaemia (67.1%), oedema (54.6%), peripheral neuropathy (47.8%), cognitive effects (28.8%), fatigue (28.1%), weight increased (26.4%) and mood effects (22.7%).

Dose reductions due to adverse reactions occurred in 23.4% of patients receiving Lorlatinib. The most common adverse reactions that led to dose reductions were oedema and peripheral neuropathy. Permanent treatment discontinuation associated with adverse reactions occurred in 3.1% of patients receiving Lorlatinib. The most frequent adverse reaction that led to permanent discontinuations was cognitive effects.

DRUG INTERACTIONS
CYP3A4/5 substrates
In vitro studies indicated that Lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A4/5 and it activates the human pregnane-X-receptor (PXR), with the net effect in vivo being induction. Concurrent administration of Lorlatinib in patients resulted in decreased oral midazolam AUC when midazolam was administered alone, suggesting that Lorlatinib is an inducer of CYP3A4/5. Lorlatinib 150 mg orally once daily for 15 days decreased AUC_{inf} and C_{max} of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate) by 61% by 50%, respectively; hence, Lorlatinib is a moderate CYP3A inducer. Thus, concurrent administration of Lorlatinib with CYP3A4/5 substrates with narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus and tacrolimus, should be avoided since the concentration of these medicinal products may be reduced by Lorlatinib.

In vitro studies of other CYP inhibition and induction
Lorlatinib may have the potential to inhibit CYP2C9. In vitro studies also indicated that Lorlatinib is an inducer of CYP2B6 and activates the human constitutive androstane receptor (CAR). Concomitant administration of Lorlatinib with CYP2B6 substrates (e.g. bupropion, efavirenz) may result in reduced plasma concentrations of the CYP2B6 substrate. In vitro, Lorlatinib has a low potential to cause drug-drug interactions by induction of CYP1A2.

In vitro studies of UGT inhibition
In vitro studies indicated that Lorlatinib may have the potential to inhibit UGT1A1.

In vitro studies with drug transporters
In vitro studies indicated that Lorlatinib may have the potential to inhibit P-glycoprotein (P-gp, systemically and at the gastrointestinal [GI] tract), BCRP (GI tract), OATP1B1, OATP1B3, OCT1, MATE1 and OAT3 at clinically relevant concentrations.

PHARMACOLOGY
Lorlatinib is a kinase inhibitor with in vitro activity against ALK and ROS1 as well as TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK. Lorlatinib demonstrated in vitro activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on crizotinib and other ALK inhibitors.

In mice subcutaneously implanted with tumors harboring EML4 fusions with either ALK variant 1 or ALK mutations, including the G1202R and I1171T mutations detected in tumors at the time of disease progression on ALK inhibitors, administration of lorlatinib resulted in antitumor activity. Lorlatinib also demonstrated anti-tumor activity and prolonged survival in mice implanted intracranially with EML4-ALK-driven tumor cell lines. The overall antitumor activity of lorlatinib in in vivo models was dose-dependent and correlated with inhibition of ALK phosphorylation.

FERTILITY, PREGNANCY AND LACTATION
Women of childbearing potential/Contraception in males and females
Women of childbearing potential should be advised to avoid becoming pregnant while receiving Lorlatinib. A highly effective non-hormonal method of contraception is required for female patients during treatment with Lorlatinib, because Lorlatinib can render hormonal contraceptives ineffective. If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 35 days after completing therapy.

During treatment with Lorlatinib and for at least 14 weeks after the final dose, male patients with female partners of childbearing potential must use effective contraception, including a condom, and male patients with pregnant partners must use condoms.

Pregnancy
Studies in animals have shown embryo-foetal toxicity. There are no data from the use of Lorlatinib in pregnant women. Lorlatinib may cause foetal harm when administered to a pregnant woman.
Lorlatinib is not recommended during pregnancy or for women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether Lorlatinib and its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Lorlatinib should not be used during breast-feeding. Breast-feeding should be discontinued during treatment with Lorlatinib and for 7 days after the final dose.

Fertility
Based on non-clinical safety findings, male fertility may be compromised during treatment with Lorlatinib. It is not known whether Lorlatinib affects female fertility. Men should seek advice on effective fertility preservation before treatment.

OVERDOSE
Treatment of overdose with the medicinal product consists of general supportive measures. Given the dose-dependent effect on PR interval, ECG monitoring is recommended. There is no antidote for Lorlatinib.

PHARMACEUTICAL INFORMATION
How Supplied
LORBREXEN 100 Tablet: Each HDPE container of LORBREXEN 100 contains 30 film-coated tablets (each tablet contains 100 mg Lorlatinib) a silica gel desiccant and polyester coil with a child-resistant closure.

STORAGE
Store below 30°C. Keep out of the sight & reach of children. Protect from moisture & light.

Manufactured by
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