DRUG NAME: Lorlatinib

SYNONYM(S): PF-6463922[1]

COMMON TRADE NAME(S): LORBRENA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Lorlatinib is an orally administered third generation tyrosine kinase inhibitor which targets anaplastic lymphoma kinase (ALK) and C-ros oncogene 1 (ROS1). Lorlatinib blocks phosphorylation of ALK, which inhibits ALK-mediated downstream signaling pathways and prevents proliferation of cancer cells. Lorlatinib has demonstrated activity against multiple mutated forms of the ALK enzyme, including G1202R and I1171T. *In vitro*, lorlatinib inhibits TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK.[2-4]

PHARMACOKINETICS:

Oral Absorption	T_{max} = 1-2 h; bioavailability = 81%; AUC and C_{max} are not significantly affected by food	
Distribution	moderate binding to both albumin and α1-acid glycoprotein	
	cross blood brain barrier?	yes
	volume of distribution	305 L
	plasma protein binding	66%
Metabolism	primarily metabolized by CYP 3A4 and UGT1A4; minor contribution from CYP 2C8, CYP 2C19, CYP 3A5, and UGT1A3	
	active metabolite(s)	no information found
	inactive metabolite(s)	benzoic acid metabolite (M8)[3]
Excretion	mean oral clearance is increased at steady state, possibly due to autoinduction of CYP 3A following repeated dosing[3]	
	urine	48% (<1% as unchanged drug)
	feces	41% (9% as unchanged drug)
	terminal half life	24 h
	clearance	11-18 L/h
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[2-4] unless specified otherwise.

USES:

Primary uses:

*Lung cancer, non-small cell

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- administration of ***strong CYP 3A inducers*** with lorlatinib increases the potential for serious hepatotoxicity; discontinue the CYP 3A inducer prior to initiating lorlatinib (requires a wash-out period equal to at least 3 plasma half-lives of the inducer)[2]

Caution:
- lorlatinib dose adjustment may be required for ***drug interactions*** involving the CYP 3A metabolic pathway[2]
- ***atrioventricular block*** and ***PR interval prolongation*** have been reported; correct electrolyte abnormalities prior to treatment and monitor ECG and electrolytes as indicated in patients with known risk factors[2]
- pre-existing ***hypertension*** should be adequately controlled prior to treatment[2]
- ***ability to drive or operate machinery*** may be compromised as neurologic adverse events are common[2]

Carcinogenicity: Carcinogenicity studies have not been conducted.[2]

Mutagenicity: Not mutagenic in Ames test. Lorlatinib was aneugenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: In animal studies, findings in male test subjects included reduced organ weights of the testis/epididymis/prostate, prostatic and testicular tubular atrophy, and epididymal inflammation. Effects in animals were seen at exposures 2-8 times higher than those seen following human clinical exposure and were partially or fully reversible. Consider fertility preservation for male patients prior to treatment.[2,3]

Pregnancy: In animal studies, lorlatinib caused embryofetal toxicity. Structural malformations (rotated limbs, malformed kidneys, domed head, etc.), decreased fetal body weight, and increased post-implantation loss were observed at exposures similar to, or less, than those seen following human clinical exposure.[2,3] For *female* patients of childbearing potential, pregnancy tests are recommended prior to treatment. Contraception is recommended during treatment and for at least 21 days after the last dose of lorlatinib. Lorlatinib may interact with hormonal contraceptives; therefore, non-hormonal methods of contraception are recommended.[2] For *male* patients with pregnant partners or female partners of childbearing potential, barrier methods of contraception are recommended during treatment and for at least 3 months after the last dose of lorlatinib.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for 1 week after the last dose of lorlatinib.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (48-52%, severe 2-5%)
	lymphopenia (23%, severe 3%)
	thrombocytopenia (23%)
cardiac	***atrioventricular (AV) block*** (2%, severe <1%); see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	cardiac failure, acute (1%); fatalities reported
	myocardial infarction (<1%); fatalities reported
eye	vision disorder (15-18%, severe <1%); includes diplopia, photophobia, blurred vision, and floaters
gastrointestinal	*emetogenic potential:* low[6]
	constipation (15-17%)
	diarrhea (21-23%, severe 1%)
	nausea (15-18%, severe 1%)
	vomiting (12-13%, severe 1%)
general disorders and administration site conditions	chest pain, non-cardiac (11%, severe 1%)
	edema (56%, severe 4%)
	fatigue (19-27%, severe 1%)
	pyrexia (12-17%, severe 1%)
infections and infestations	bronchitis (7%, severe 2%)
	pneumonia (7%, severe 2%); fatalities reported
	upper respiratory tract infection (11%, severe 1%)
investigations	activated partial thromboplastin time prolonged (25%)
	amylase increase (20-22%, severe 1%)
	albumin decrease (33-36%, severe 1%)
	alkaline phosphatase increase (23-24%)
	ALT increase (28-44%, severe 3%)
	AST increase (37-48%, severe 2%)
	cholesterol increase (21-95%, severe 22%); see paragraph following **Side Effects** table
	creatine kinase increase (39%, severe 2%)
	creatinine increase (81%, severe 1%)
	gamma-glutamyl transferase increase (52%, severe 6%)
	glucose increase (48-52%, severe 7%)
	lipase increase (24-28%, severe 7%)
	magnesium decrease (21%)
	potassium increase (21%, severe 1%)
	phosphate decrease (21%)
	PR prolongation (14%); see paragraph following **Side Effects** table
	triglyceride increase (21-91%, severe 19%); see paragraph following **Side Effects** table
	weight gain (24-38%, severe 4-17%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
musculoskeletal and connective tissue	arthralgia (19-24%, severe 1%)
	back pain (13-15%, severe 1%)
	myalgia (15-17%, severe 1%)
	pain in extremity (13-17%)
nervous system (see paragraph following **Side Effects** table)	***cognitive impairment*** (21-28%, severe 2%)
	dizziness (11-16%, severe <1%)
	headache (17%, severe <1%)
	peripheral neuropathy (34-48%, severe 2-3%)
	seizure (2%)
	speech disturbance (5-12%)
psychiatric (see paragraph following **Side Effects** table)	***mood disorder*** (16-23%, severe 2%)
	psychotic effects (5-7%, severe <1%); includes hallucinations
	sleep disorder (11%, severe 1%); includes insomnia, nightmare, and somnambulism
respiratory, thoracic and mediastinal	cough (16-21%)
	dyspnea (20-27%, severe 3%)
	interstitial lung disease **(ILD)/*pneumonitis*** (2%, severe <1%)
	pulmonary edema (<1%); fatalities reported
	respiratory failure (3%, severe 2%); fatalities reported
skin and subcutaneous tissue	rash (11%)
vascular	***hypertension*** (18%, severe 10%)
	peripheral artery occlusion (<1%); fatalities reported
	pulmonary embolism (<1%): fatalities reported

Adapted from standard reference[2,4,7] unless specified otherwise.

Hyperlipidemia is common with lorlatinib. Increased serum cholesterol and/or triglycerides have been reported in up to 95% of patients. The median time to onset for both hypercholesterolemia and hypertriglyceridemia is 15 days. The majority of patients require initiation of lipid-lowering therapy, with a median time to start treatment of 17 days. For grade 4 events, lorlatinib dose interruption and/or dose reduction may be required.[2]

Lorlatinib can cause a broad spectrum of ***central nervous system (CNS)*** and ***psychiatric effects***. Overall, 52% of patients experience neurologic/psychiatric events. The majority of events are grade 1 or 2 and they can generally be managed with dose interruption and/or modification. Most common CNS effects are cognitive impairment (including amnesia, attention disturbance, confusion, and delirium) and mood disorder (including suicidal ideation, self-injury, irritability, affect lability, anxiety, depression, euphoric mood, and bipolar disorder). Speech disturbance and sleep disorder are also reported. Seizures may occur in conjunction with other neurologic symptoms. The median time to onset of any CNS effect is 1.4 months. Patients should not drive or operate machinery if they are experiencing neurologic symptoms. Permanently discontinue lorlatinib for a life-threatening event or if urgent intervention is indicated.[2]

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PR interval prolongation and ***atrioventricular (AV) block*** can occur in patients taking lorlatinib. AV block has been reported in 2% of patients. Signs and symptoms of AV block may include dizziness, syncope, or slow heart rhythm. For severe symptoms associated with AV block, temporary or permanent pacemaker placement may be required. ECG monitoring is recommended prior to treatment and repeated during therapy as indicated. Drugs that prolong PR interval or disrupt electrolyte levels should be avoided during lorlatinib treatment if possible. Based on severity of AV block, lorlatinib dose interruption or dose modification may be required. Cardiology consult may be indicated.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
erythromycin[3]	no clinically significant changes in lorlatinib AUC	moderate inhibition of CYP 3A by erythromycin	no dose adjustment required
fluconazole[3]	*predicted*: 59% increase in lorlatinib AUC and 28% increase in C_{max}	moderate inhibition of CYP 3A by fluconazole and possible inhibition of CYP 2C19 by fluconazole[8]	avoid concurrent use; if unavoidable, reduce lorlatinib dose to 75 mg once daily
grapefruit juice[2]	may increase plasma concentration of lorlatinib	may inhibit CYP 3A4 metabolism of lorlatinib in the intestinal wall	avoid grapefruit juice for the duration of treatment with lorlatinib
itraconazole[2]	42% increase in lorlatinib AUC and 24% increase in C_{max}	strong inhibition of CYP 3A by itraconazole	avoid concurrent use; if unavoidable, reduce lorlatinib dose to 75 mg once daily
midazolam[3]	64% decrease in midazolam AUC and 50% decrease in C_{max}	induction of CYP 3A by lorlatinib	avoid concurrent use
modafinil[2]	23% decrease in lorlatinib AUC and 22% decrease in C_{max}	moderate induction of CYP 3A by modafinil	avoid concurrent use; if unavoidable, increase lorlatinib dose to 125 mg once daily
rabeprazole[2]	no clinically significant changes in lorlatinib AUC	pH-dependent solubility of lorlatinib	no dose adjustment required when given with acid-reducing agents (including proton-pump inhibitors, H_2-blockers or antacids)
rifampin[2,3]	***severe hepatotoxicity***; 85% decrease in lorlatinib AUC and 76% decrease in C_{max}	activation of the pregnane X receptor (PXR) by both lorlatinib and rifampin (possible mechanism for hepatotoxicity[3]) and strong induction of CYP 3A by rifampin (affecting lorlatinib AUC and C_{max})	***contraindicated;*** discontinue rifampin prior to initiating lorlatinib (requires a wash-out period equal to at least 3 plasma half-lives of rifampin)
verapamil[3]	no clinically significant changes in lorlatinib AUC	moderate inhibition of CYP 3A by verapamil	no dose adjustment required

Lorlatinib is a substrate of ***CYP 3A***. CYP 3A ***inhibitors*** may increase the plasma concentration of lorlatinib. Avoid concurrent use with ***strong*** CYP 3A inhibitors. If coadministration cannot be avoided, decrease lorlatinib dose to 75 mg PO once daily. If the CYP 3A inhibitor is discontinued, lorlatinib may be resumed at the prior dose after 3 to 5 half-lives of the inhibitor.[2]

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Concomitant use of ***CYP 3A inducers*** should be avoided. ***Moderate*** CYP 3A inducers may decrease the plasma concentration of lorlatinib. If coadministration with a ***moderate CYP 3A inducer*** cannot be avoided, increase lorlatinib dose to 125mg PO once daily. Concomitant use of a ***strong CYP 3A inducer*** with lorlatinib is contraindicated due to the potential for serious hepatotoxicity. Discontinue the strong CYP 3A inducer prior to initiating lorlatinib. A washout period of at least 3 plasmas half-lives of the inducer is recommended prior to initiating lorlatinib. Note: no clinically meaningful changes in AST/ALT have been observed when lorlatinib is coadminstered with moderate CYP 3A inducers.[2]

Lorlatinib is a moderate ***inducer of CYP 3A*** *and* ***P-gp***.[3] Concurrent use with substrates of CYP 3A or P-gp may decrease the plasma concentration of the substrate. Avoid concurrent use with a substrate for which a minimal concentration change may lead to therapeutic failure.[3]

Lorlatinib may induce CYP 2C9, CYP 2B6, and UGT. Clinical significance is unknown.[2,3] *In vitro*, lorlatinib is an inhibitor of OCT1, OAT3, MATE1, and BCRP but clinical significance is unknown.[2]

SUPPLY AND STORAGE:

Oral: Pfizer Canada Inc. supplies lorlatinib as 25 mg and 100 mg film-coated tablets. Tablets contain lactose. Store at room temperature. Protect from light.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy.

Adults:

	BC Cancer usual dose noted in ***bold, italics***
Oral[2,9]*:*	100 mg PO once daily* (range 50-125 mg once daily) *dose adjustment may be required for some drug interactions[2] Administer with food or on an empty stomach.[2] Do not take with grapefruit or grapefruit juice.[2]
Concurrent radiation:	no information found
Dosage in renal failure:	CrCl ≥30 mL/min: no adjustment required[3] CrCl 15 to <30 mL/min: reduce dose to 75 mg once daily[3]
Dosage in hepatic failure:	mild impairment (total bilirubin ≤1.5xULN): no adjustment required[3] moderate to severe impairment (total bilirubin >1.5xULN): no information found; however, hepatic impairment may increase lorlatinib plasma concentration[2]
Dosage in dialysis:	no information found

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