DRUG NAME: Pralsetinib

SYNONYM(S): BLU-667[1], CS 3009[2]

COMMON TRADE NAME(S): GAVRETO®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Pralsetinib is an orally administered selective RET (REarranged during Transfection) tyrosine kinase inhibitor. RET gene fusions or mutations can result in constitutively active RET kinases, promoting tumour cell proliferation. Pralsetinib inhibits RET kinase autophosphorylation and prevents downstream signaling pathways. Pralsetinib has demonstrated activity against wild-type RET, oncogenic RET fusions, and RET mutations, including V804 gatekeeper mutants that are associated with drug resistance. *In vitro* pralsetinib also inhibits DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRb, and FGFR1.[2-4]

PHARMACOKINETICS:

Oral Absorption	T_{max} = 2-4 h (delayed to 8.5 h with high fat meal); AUC and C_{max} are increased following high fat meal by 122% and 104% respectively	
Distribution	highly bound to plasma proteins	
	cross blood brain barrier?	yes[1]
	volume of distribution	228-303 L
	plasma protein binding	97%
Metabolism	primarily metabolized by CYP 3A4; minor contribution by CYP 2D6 and CYP 1A2	
	active metabolite(s)	no information found
	inactive metabolite(s)[2]	M531, M453, M549b, M709
Excretion	primarily by fecal elimination	
	urine	6% (5% as unchanged drug)
	feces	73% (66% as unchanged drug)
	terminal half life	15-20 h
	clearance	6-11 L/h
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[3-5] unless specified otherwise.

USES:

Primary uses:
*Lung cancer, non-small cell

Other uses:
Thyroid cancer[4]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- pralsetinib dose adjustment may be required for ***drug interactions*** involving P-gp transporter and/or CYP 3A metabolic pathways[3,4]
- pre-existing ***hypertension*** should be adequately controlled prior to starting treatment[3]
- pralsetinib may cause ***impaired wound healing*** and ***bleeding***; withhold pralsetinib in patients undergoing surgical procedures[3]
- patients with a high tumour burden, rapidly growing tumour, renal dysfunction, or dehydration may be at increased risk of ***tumour lysis syndrome***[3]
- ***QTc prolongation*** is reported; correct electrolyte abnormalities prior to treatment and monitor ECG and electrolytes as indicated in patients with known risk factors [6]

Special populations**:** Pralsetinib is not recommended in children under 12 years of age**.** In animal studies, skeletal and tooth abnormalities were observed at exposures similar to those expected following human clinical exposure (including physeal dysplasia in the femur, increased physeal thickness in sternum, incisor degeneration, and tooth necrosis). Some effects were irreversible. Monitor for growth plate abnormalities in ***adolescent patients*** with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any reported abnormalities.[4]

Carcinogenicity: Carcinogenicity studies have not been conducted.[3]

Mutagenicity: Not mutagenic in Ames test. Pralsetinib was not clastogenic in the mammalian *in vivo* and *in vitro* chromosome tests.[3]

Fertility: In animal toxicology studies, reproductive effects were observed at exposures similar to those seen following human clinical exposure and included decreased testicular/epididymal weight, reduced luminal sperm in the epididymis, testis tubular degeneration, and corpus luteum degeneration. When male and female test subjects were treated with pralsetinib and mated to each other in a dedicated fertility study, there were no clear effects on mating performance or ability to conceive. However, 82% of female study subjects had totally resorbed litters with 92% post-implantation loss at doses approximately 0.35 times the expected human exposure at clinical doses. When treated males were mated with untreated females, there was no clear pralsetinib related effects on male reproductive performance or intrauterine survival of embryos at doses approximately 1.7 times the expected human exposure at clinical doses.[3,4]

Pregnancy: In animal studies, administration of pralsetinib during organogenesis caused teratogenicity and embryolethality at exposures below the expected human exposure at clinical doses. When pralsetinib was administered to pregnant females at dose levels approximately 1.8 times the expected human exposure at clinical doses, 100% post implantation loss was observed. Visceral and skeletal malformations (e.g., absent ureter, malpositioned kidney, vertebral anomalies, and reduced ossification) were observed at exposures approximately 0.2 times the expected human exposure at clinical doses. Pregnancy tests are recommended prior to starting treatment for female patients of childbearing potential. Non-hormonal methods of contraception are recommended during treatment with pralsetinib and for at least two weeks after the last dose for female patients of childbearing potential. Hormonal methods of contraception are not recommended because pralsetinib may reduce the efficacy of hormonal contraceptives. For male patients with female partners of childbearing potential, contraception is recommended during treatment and at least one week after the last dose of pralsetinib.[3,4]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for one week after the last dose of pralsetinib.[3,4]

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

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were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (37%, severe 11%)
	febrile neutropenia (2%)[7]
	leukopenia (26%, severe 6%)
	lymphopenia (12%, severe 6%)
	neutropenia (38%, severe 19%)
	pancytopenia (1-10%)
	thrombocytopenia (15%, severe 4%)
ear and labyrinth	vertigo (1-10%)
eye	blurred vision (1-10%)
	dry eye (1-10%)
gastrointestinal	*emetogenic potential:* low[8]
	abdominal pain (11-17%, severe 1%)
	constipation (35-45%, severe 1%)
	diarrhea (23-34%, severe 2-5%); includes colitis and enteritis
	dry mouth (17%)
	nausea (13-19%, severe 1%)
	stomatitis (6-17%, severe 1%); includes aphthous ulcer
	vomiting (11-14%)
general disorders and administration site conditions	***edema*** (26-44%)
	fatigue (36-42%, severe 2-6%)
	gait disturbance/fall (1-10%)
	pyrexia (20-29%, severe 2%)
hepatobiliary	ascites (severe ≥2%)[4]
	hepatotoxicity (severe 1-2%)
infections and infestations	***pneumonia*** (17-24%, severe 8-13%); fatalities reported
	coronavirus infection (severe ≥2%)[4]; fatalities reported
	urinary tract infection (12-16%, severe 2-4%)
	sepsis (severe 3%); fatalities reported
	tuberculosis (<1%); mostly extrapulmonary tuberculosis such as lymph node tuberculosis, peritoneal tuberculosis, and renal tuberculosis[6,9,10]
investigations	albumin decrease (36-52%, severe 2%)
	alkaline phosphatase increase (22-43%, severe 2%)
	ALT increase (28-58%, severe 2-4%)
	AST increase (41-80%, severe 2-5%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	bilirubin increase (17-24%, severe 1%)
	calcium decrease, corrected (39-70%, severe 2%)
	creatine kinase increase (19%, severe 9%)
	creatinine increase (20-45%, severe 1%)
	hemoglobin decrease (57-78%, severe 9-18%)
	leukocyte decrease (79%, severe 11%)
	lymphocyte decrease (55-73%, severe 19-32%)
	magnesium decrease (25-27%, severe 1%)
	magnesium increase (14%)
	neutrophil decrease (60-70%, severe 16-21%)
	phosphate decrease (28-50%, severe 11%)
	phosphate increase (11-40%, severe <1%)
	platelet decrease (27-33%, severe 3-5%)
	potassium decrease (27%, severe 5%)
	potassium increase (26%, severe 1%)
	sodium decrease (29-42%, severe 2-7%)
	QTc prolongation (5%, severe <1%)[6]; see paragraph following **Side Effects**
metabolism and nutrition	appetite decrease (15-18%, severe 1%)
	tumour lysis syndrome (3%)[1]
musculoskeletal and connective tissue	muscle spasms/weakness (1-10%)
	musculoskeletal pain (32-44%, severe 2%); includes neck, back, spinal pain
nervous system	ataxia/ balance disorder (1-10%)
	dizziness (14-19%, severe 1%)
	headache (10-24%, severe 1%)
	peripheral neuropathy (20%)
	seizure (severe ≥2%)[4]
	syncope (severe 2%)[11]
	taste disorder (14-17%); includes dysgeusia and ageusia
respiratory, thoracic and mediastinal	***cough*** (22-36%, severe 1%)
	dyspnea (12-22%, severe 2%)
	interstitial lung disease/pneumonitis (11-14%, severe 2-6%); see paragraph following **Side Effects**
	pleural effusion (severe 2%)[11]
skin and subcutaneous tissue	rash (14-24%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
vascular	***hemorrhage*** (14%, severe 4%); see paragraph following **Side Effects**
	hypertension (29-40%, severe 14-21%)
	pulmonary embolism (severe 2%)[11]

Adapted from standard reference[3-5] unless specified otherwise.

Severe ***interstitial lung disease/pneumonitis*** has been reported in patients treated with pralsetinib. Fatalities have been reported. Median time to onset is 16 weeks and median time to resolution is 4 weeks. Advise patients to promptly report any new or worsening respiratory symptoms such as cough, dyspnea, or fever. Grade 1 or 2 events can be managed with treatment interruption and dose modification. The majority of patients with grade 1 or 2 pneumonitis are able to continue pralsetinib following treatment interruption and dose reduction without experiencing recurrent pneumonitis. Permanently discontinue pralsetinib for recurrent pneumonitis and any grade 3 or 4 event.[6]

Hemorrhagic events may occur with pralsetinib and can be fatal. Reported symptoms include bruising, gingival bleeding, unusual vaginal bleeding, epistaxis, hematuria, melena, or hemoptysis. Other hemorrhagic events have included intracerebral/intracranial hemorrhage, conjunctival hemorrhage, and gastrointestinal bleeding. Withhold pralsetinib for a grade 3 or higher event until the event has recovered to grade 1 or less severity. Pralsetinib, if resumed, may be resumed at a reduced dose. Permanently discontinue pralsetinib for a life-threatening event or recurrent severe hemorrhage.[3]

Impaired wound healing has been associated with medications that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Temporary interruption of pralsetinib is recommended in patients undergoing surgical procedures. Withhold pralsetinib for at least 5 days prior to surgery and 14 days following surgery. Pralsetinib may be resumed once adequate wound healing has occurred.[3]

QTc prolongation has been reported in 5% of patients. The majority of patients reported non-serious events, although some patients have experienced grade 3 events. No life-threatening or fatal QT prolongation has been reported. Use pralsetinib with caution in patients with history of arrhythmia and correct electrolyte abnormalities prior to treatment. In patients with known risk factors for QT prolongation, monitor ECG and electrolytes as clinically indicated. Patients receiving concurrent therapy with moderate or strong CYP 3A inhibitors and/or P-gp inhibitors may require more frequent monitoring. Management of QT prolongation may include dose interruption and/or dose reduction.[6,11]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cyclosporine[4]	81% increase in pralsetinib AUC and 48% increase in C_{max}	inhibition of P-gp by cyclosporine	avoid concurrent use; if concurrent use cannot be avoided, see table below for suggested pralsetinib dose reduction and monitor for pralsetinib toxicity and QTc prolongation
efavirenz[4]	*predicted:* 45% decrease in pralsetinib AUC and 18% decrease in C_{max}	moderate induction of CYP 3A by efavirenz	avoid concurrent use; if concurrent use cannot be avoided, see table below for suggested pralsetinib dose increase

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AGENT	EFFECT	MECHANISM	MANAGEMENT
esomeprazole[12]	no clinically significant changes in pralsetinib AUC and C_{max}	pH-dependent solubility of pralsetinib (reduced solubility with increasing pH)	no action required
fluconazole[4]	*predicted:* 71% increase in pralsetinib AUC and 15% increase in C_{max}	moderate inhibition of CYP 3A by fluconazole	avoid concurrent use; if concurrent use cannot be avoided, see table below for suggested pralsetinib dose reduction and monitor for pralsetinib toxicity and QTc prolongation
grapefruit juice[6]	may increase plasma level of pralsetinib	may inhibit CYP 3A4 metabolism of pralsetinib in the intestinal wall	avoid grapefruit juice for duration of pralsetinib therapy
itraconazole[3]	251% increase in pralsetinib AUC and 84% increase in C_{max}	strong inhibition of CYP 3A and P-gp by itraconazole	avoid concurrent use; if concurrent use cannot be avoided, see table below for suggested pralsetinib dose reduction and monitor for pralsetinib toxicity and QTc prolongation
verapamil[4]	*predicted:* 108% increase in pralsetinib AUC and 60% increase in C_{max}	moderate inhibition of CYP 3A and P-gp by verapamil	avoid concurrent use; if concurrent use cannot be avoided, see table below for suggested pralsetinib dose reduction and monitor for pralsetinib toxicity and QTc prolongation
voriconazole[4]	*predicted:* 122% increase in pralsetinib AUC and 20% increase in C_{max}	strong inhibition of CYP 3A by voriconazole	avoid concurrent use; if concurrent use cannot be avoided, see table below for suggested pralsetinib dose reduction and monitor for pralsetinib toxicity and QTc prolongation
rifampin[3]	68% decrease in pralsetinib AUC and 30% decrease in C_{max}	strong induction of CYP 3A by rifampin	avoid concurrent use; if concurrent use cannot be avoided, see table below for suggested pralsetinib dose increase

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Pralsetinib is a substrate of ***CYP 3A*** and ***P-gp***. **Inhibitors** of these pathways may increase the plasma concentration of pralsetinib. Avoid concurrent use with moderate or strong CYP 3A and/or P-gp inhibitors. If coadministration cannot be avoided, see table below for suggested pralsetinib **dose reduction**. If the inhibitor has been discontinued, pralsetinib may be resumed at the prior dose after 3 to 5 half-lives of the inhibitor.[4]

Planned Pralsetinib Dose	**Suggested Pralsetinib Dose REDUCTION**[4]	
	Coadministered with **moderate** or **strong CYP 3A Inhibitor** OR **P-gp Inhibitor** OR ***combined*** **P-gp** and **moderate CYP 3A Inhibitor**	Coadministered with ***combined*** **P-gp** and **strong CYP3A Inhibitor**
400 mg once daily	300 mg once daily	200 mg once daily
300 mg once daily	200 mg once daily	200 mg once daily
200 mg once daily	100 mg once daily	100 mg once daily
100 mg once daily	no information found	

CYP 3A inducers may decrease the plasma concentration of pralsetinib. Avoid concurrent use with ***moderate*** or ***strong*** CYP 3A inducers. If coadministration with a moderate or strong CYP 3A inducer cannot be avoided, see table below for suggested pralsetinib dose **increase**. Increase pralsetinib dose **starting on day 7** of concurrent use with a CYP3A inducer. If the inducer has been discontinued, pralsetinib may be resumed at the prior dose after 14 days. Mild CYP 3A inducers are predicted to have no clinically significant effects on the plasma concentration of pralsetinib.[4]

Planned Pralsetinib Dose	**Suggested Pralsetinib Dose INCREASE**[4]	
	Coadministered with **Moderate CYP 3A Inducer**	Coadministered with **Strong CYP3A Inducer**
400 mg once daily	600 mg once daily	800 mg once daily
300 mg once daily	500 mg once daily	600 mg once daily
200 mg once daily	300 mg once daily	400 mg once daily
100 mg once daily	no information found	

In vitro, pralsetinib has shown potential to both inhibit and induce CYP 3A4/5, CYP 2C8, and CYP 2C9**.** Therefore, pralsetinib may alter the plasma concentration of substrates of these enzymes. Clinical significance is unknown. If possible, avoid concurrent use of pralsetinib with a sensitive substrate (i.e., with narrow therapeutic index) of these enzymes.[6]

Pralsetinib in an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, MATE2-K, and BSEP, and a substrate of Breast Cancer Resistance Protein (BCRP). Clinical significance is unknown.[3,4]

SUPPLY AND STORAGE:

Oral: Hoffmann-La Roche Ltd. supplies pralsetinib as 100 mg capsules. Store at room temperature.[3]

Additional information: Pralsetinib 100 mg is supplied in bottles of 60, 90 or 120 capsules. Once the bottle has been opened, remaining capsules should be discarded after 4 months.[13]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

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Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral[1,3,4]*:*	400 mg (range 100-800 mg) PO once daily* Administer on an empty stomach. Do not take with grapefruit or grapefruit juice.[6] *dose adjustment may be required for some drug interactions
Concurrent radiation:	no information found
Dosage in myelosuppression:	no information found
Dosage in renal failure:	CrCl ≥30 mL/min: no adjustment required[3,4] CrCl <30 mL/min: no adjustment required as renal elimination is negligible[6]
Dosage in hepatic failure:	mild impairment (total bilirubin ≤1-1.5X ULN): no adjustment required[3,4] moderate to severe impairment (total bilirubin >1.5X ULN): no information found
Dosage in dialysis:	no information found

Children*:*	children under 12 years of age: safety and efficacy have not been established
Oral[1,3,4]*:*	adolescents 12 years and older: 400 mg (range 100-400 mg) PO once daily* Administer on an empty stomach. Do not take with grapefruit or grapefruit juice. *dose adjustment may be required for some drug interactions

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