DRUG NAME: Bosutinib

SYNONYM(S): Bosutinib monohydrate, SKI-606[1-3]

COMMON TRADE NAME(S): BOSULIF®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Bosutinib is a second generation tyrosine kinase inhibitor. It targets BCR-ABL kinase, which is responsible for the pathogenesis of Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML). Bosutinib also has activity against Src kinases, which are involved in malignant cell transformation, tumour progression and metastasis. It has limited inhibition against platelet-derived growth factor receptor (PDGFR) and protein-tyrosine kinase Kit (c-KIT). Bosutinib is active in imatinib-sensitive and resistant BCR-ABL-dependent leukemia cells and inhibits proliferation and survival of CML and Ph+ acute lymphoblastic leukemia (ALL) cell lines.[1,4,5]

PHARMACOKINETICS:

Oral Absorption[1,4-6]	time to peak: 4-6 h; low oral bioavailability; 2-fold increase in C_{max} and AUC after food; pH-dependent solubility (i.e., reduced solubility with pH>5)	
Distribution	extensive distribution to extravascular tissue	
	cross blood brain barrier?	no information found
	volume of distribution[5]	5000-7000 L
	plasma protein binding	94-96%
Metabolism[1,4]	mainly hepatic via CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)[7]	oxydechlorinated (M2) bosutinib, N-desmethylated (M5) bosutinib, bosutinib N-oxide (M6)
Excretion	rapid; 75% of dose eliminated within 96 h	
	urine	3%
	feces	91%
	terminal half life[1,7]	23-34 h
	clearance	189-197 L/h

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Leukemia, chronic myelogenous

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of long QT-syndrome or persistent QT interval >480 ms[1]
- any degree of preexisting hepatic impairment[1]

Caution:
- ***QT interval prolongation*** is reported***;*** caution in patients with a history of or predisposition to QTc prolongation. Correct preexisting electrolyte disturbances and monitor ECG and electrolytes periodically during treatment. Patients with hepatic impairment may be at greater risk of developing QT prolongation on bosutinib.[1]
- ***Fractures*** are reported; patients with severe osteoporosis may be at increased risk.[1]
- ***Reactivation of Hepatitis B virus*** (HBV) has sometimes occurred in chronic carriers of HBV after receiving BCR-ABL tyrosine kinase inhibitors[8]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***.[9]

Carcinogenicity: Bosutinib was not carcinogenic in animal studies. However, cases of second primary malignancies (e.g., basal cell carcinoma, bladder cancer, gastric cancer and malignant melanoma) have been reported in pooled safety data from human clinical trials.[1]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* and *in vivo* mutation test. Bosutinib is not clastogenic in mammalian *in vivo* chromosome tests.[1]

Fertility: Decreased fertility was reported in male rats (resulting in a 16% reduction in number of pregnancies in mated females).[1,7]

Pregnancy: In animal studies, decreased weight gain, increased embryonic resorptions, decreased implantations, decreased viable embryos, and fetal anomalies (e.g., fused sternebrae and various visceral observations) have been reported. Bosutinib crosses the placenta in animals and is detected in fetal tissues. Patients should use contraceptives during treatment, during dose interruptions and for 4 weeks after stopping treatment.[1]

Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, bosutinib is excreted in breast milk and detected in the plasma of nursing rats.[1]

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.[10,11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (9-37%, severe 3-26%)[1,4]
	febrile neutropenia (1%, severe <1%)
	leucopenia (3-10%, severe 0-6%)
	neutropenia (14-39%, severe 8-18%)[1,4]
	thrombocytopenia (24-60%, severe 23-37%)[1,4]
cardiac	atrial fibrillation (2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	congestive heart failure (2%)
	pericardial effusion (1-3%, severe <1%); see paragraph following **Side Effects** table
	pericarditis (<1%)[4]
	tachycardia (2%)
ear and labyrinth	tinnitus (1-10%)[4,7]
gastrointestinal	*emetogenic potential:* low-moderate[12]
	abdominal pain (20-40%, severe 1-5%)[1,4]
	diarrhea (71-84%, severe 5-9%); manage early with supportive care
	gastritis (1-2%, severe <1%)
	gastrointestinal hemorrhage (<1%)[7]
	nausea (41-47%, severe 1-2%)[1,4]
	pancreatitis (<1%)[4]; see paragraph following **Side Effects** table
	vomiting (32-42%, severe 1-4%)[1,4]
general disorders and administration site conditions	asthenia (3-11%, severe 1%)[1,4]
	edema (4-14%, severe <1%)[1,4]; see paragraph following **Side Effects** table
	fatigue (10-26%, severe 1-4%)[1,4,7]
	pain (1-2%)
	pyrexia (3-36%, severe 1-3%)[1,4,7]
hepatobiliary	***hepatotoxicity*** (1-3%, severe <2%); see paragraph following **Side Effects** table
immune system	***hypersensitivity*** (1-3%, severe <1%); see paragraph following **Side Effects** table
infections and infestations	***infections*** (4-41%, severe <2%)
investigations	***ALT increase*** (5-21%, severe 4-7%); see paragraph following **Side Effects** table
	AST increase (2-18%, severe 2-4%); see paragraph following **Side Effects** table
	amylase increase (1-3%, severe 1%)
	bilirubin increase (2%, severe 1%)
	creatine phosphokinase increase ((1-2%)
	creatinine increase (2-6%)
	gamma-glutamyltransferase increase (2%, severe <1%)
	lipase increase (1-38%, severe 3-9%)[1,4]; see paragraph following **Side Effects** table
	QT interval prolongation (1%)
metabolism and nutrition	appetite decrease (6-14%, severe <1%)[1,4]
	dehydration (1-2%, severe <1%)
	hyperkalemia (1-3%, severe <1%)
	hypokalemia (18%, severe 2%)[4]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypophosphatemia (2-50%, severe 1-7%); see paragraph following **Side Effects** table
	tumour lysis syndrome (<1%)
musculoskeletal and connective tissue	arthralgia (4-14%, severe <1%)[1,4,7]
	back pain (1-12%, severe <1%)[1,4,7]
	fractures (2%); see paragraph following **Side Effects** table
	myalgia (3-4%, severe 1%)
neoplasms	second primary malignancies (e.g., basal cell carcinoma, bladder cancer, gastric cancer, malignant melanoma)
nervous system	dizziness (4-13%, severe 1%)[1,4,7]
	dysgeusia (1-2%)
	headache (6-20%, severe 1-4%)[1,4,7]
renal and urinary	renal failure/impairment (1-5%); declines over time, unclear if reversible
respiratory, thoracic and mediastinal	cough (1-21%)[1,4]
	dyspnea (2-19%, severe 1-6%)[1,4,7]
	pleural effusion (3-8%, severe 1-3%); see paragraph following **Side Effects** table
	pulmonary edema (<1%)[4]; see paragraph following **Side Effects** table
	pulmonary hypertension (<1%)[4,7]
	respiratory failure (1%, severe <1%)
skin and subcutaneous tissue	acne (1-2%)
	drug eruption (<1%)[4,7]
	pruritis (3-11%, severe 1%)[1,4]
	rash (22-35%, severe 4-9%)[1,4]
	urticaria (1-3%, severe <1%)

Adapted from standard reference[1] unless specified otherwise.

Pericardial effusion, ***pleural effusion,*** and ***pulmonary/peripheral edema*** due to fluid retention have been reported with bosutinib. Weigh patients regularly and monitor for signs and symptoms of fluid retention; management may include dose interruption, reduction, and/or discontinuation as well as standard-of-care treatment such as diuretics.[1]

Hepatic impairment and increases in ALT/AST can occur. Transaminase elevations usually occur within the first 3 months of treatment. Dose interruption/reduction and/or discontinuation of treatment may be necessary.[1,4-6]

Hypersensitivity reactions have been reported, including anaphylactic shock and leukocytoclastic vasculitis. Hypersensitivity reactions may be due to excipients such as polyethylene glycol, poloxamer 188, or povidone.[1]

Elevated lipase and acute ***pancreatitis*** are reported; use caution in patients with a history of pancreatitis. If patients develop elevated lipase with abdominal symptoms, interrupt treatment until diagnosis of pancreatitis has been ruled out.[1]

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Fractures and ***mineral abnormalities*** (e.g., ***hypophosphatemia***) have been reported. Patients with endocrine abnormalities (e.g., hyperparathyroidism) and severe osteoporosis may be at increased risk; monitor for osteoporosis or changes in bone density.[1,4]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[1]	may increase plasma level of bosutinib	may inhibit CYP 3A4 metabolism of bosutinib in the intestinal wall	avoid grapefruit and grapefruit juice for duration of treatment with bosutinib
ketoconazole[1]	bosutinib C_{max} increased 5-fold and AUC increased 8-fold	inhibition of CYP 3A4 by ketoconazole	avoid concomitant use
aprepitant[1]	bosutinib C_{max} increased 1.5-fold and AUC increased 2-fold	inhibition of CYP 3A4 by aprepitant	avoid concomitant use
rifampin[1,7]	bosutinib C_{max} decreased by 86% and AUC decreased by 94%	induction of CYP 3A4 by rifampin	avoid concomitant use
lansoprazole[1,4,7]	bosutinib C_{max} decreased by 46% and AUC decreased by 26%	pH-dependent solubility of bosutinib	use caution with proton pump inhibitors (PPIs); consider short-acting antacids or H2 antagonists and separate administration times from bosutinib by 2 or more hours

Moderate CYP 3A4 **inhibitors** may increase bosutinib exposure; avoid concomitant use. Moderate CYP 3A4 **inducers** may decrease bosutinib exposure; avoid concomitant use.[1]

Concurrent therapy with drugs that prolong QT/QTc interval or disrupt electrolyte levels should be avoided if possible; periodic monitoring of ECG and electrolytes is suggested.[1]

Bosutinib is a substrate and inhibitor of P-glycoprotein (P-gp); clinical significance is unknown.[1,6]

SUPPLY AND STORAGE:

Oral: Pfizer Canada Inc. supplies bosutinib as 100 mg and 500 mg film-coated tablets. Store at room temperature.[1]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

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Adults:

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

Oral[1,2,5,7,13]*:*	***500 mg*** (range 200-600 mg) ***PO once daily*** Administer with food. Do not take with grapefruit or grapefruit juice.
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure[1]*:*	Recommended starting dose: • moderate renal impairment (CrCl 30-50mL/min): 400 mg PO once daily • severe renal impairment (CrCl <30mL/min): 300 mg PO once daily Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu\text{mol/L}}$ * For males N=1.23; for females N=1.04
Dosage in hepatic failure[1]*:*	not recommended for patients with any degree of preexisting hepatic impairment
Dosage in dialysis:	no information found

Children: no information found

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