Drug Monograph

A - Drug Name

bosutinib

COMMON TRADE NAME(S): Bosulif®

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B - Mechanism of Action and Pharmacokinetics

Bosutinib is an inhibitor of the Bcr-Abl tyrosine kinase associated with Philadelphia chromosome-positive chronic myeloid leukemia (CML) and also has inhibitory actions on EPH, TEC and STE20 kinases. It inhibits 16 of the 18 imatinib-resistant Bcr-Abl kinases *in vitro*, except T315I. There is minimal inhibition on PDGF and cKIT.

Absorption	Pharmacokinetics are dose-proportional over the dose range of 200 to 600mg. The median time-to-peak (Tmax) was reached after 6 hours.	
	Bioavailability	34% (with food)
	Effects with food	AUC increased 1.7-fold with food
Distribution	Bosutinib is extensively distributed to extra-vascular tissue.	
	Cross blood brain barrier?	No
	PPB	96%
Metabolism	CYP3A4 is the major enzyme involved in metabolism of bosutinib. Flavin-containing monooxygenase enzymes (FMOs) also play a role.	
	Active metabolites	No

	Inactive metabolites	Yes
Elimination	Urine	3% (1% unchanged)
	Feces	91.3%
	Half-life	35.5 hours (terminal)

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C - Indications and Status

Health Canada Approvals:

- Chronic myelogenous leukemia

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse effects were observed in ≥ 10% of patients treated with bosutinib 400 mg in a Phase III study of newly-diagnosed CML patients. It also includes severe or life-threatening adverse effects from other sources or post-marketing.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (2%)	E
	Arterial thromboembolism (rare)	E
	Cardiotoxicity (2%)	E D
	Hypertension (5%) (2% severe)	E
	Pericardial effusion / pleural effusion (4%)	E D
	Pulmonary hypertension (1%)	E

	QT interval prolonged (1%)	E
Dermatological	Rash, pruritus (26%) (may be severe)	E
Gastrointestinal	Abdominal pain (25%)	E
	Anorexia (10%)	I
	Diarrhea (70%) (8% severe)	E
	Nausea, vomiting (35%)	E
General	Edema (6%) (3% severe)	E
	Fatigue (19%)	E
Hematological	Myelosuppression ± infection, bleeding (35%) (14% severe; includes atypical infections (HBV reactivation), CNS and GI hemorrhage)	E
Hepatobiliary	↑ Amylase / lipase (13%) (10% severe)	E
	↑ Bilirubin (6%) (may be severe)	E
	Hepatotoxicity (3%) (2% severe)	E
	↑ LFTs (31%) (19% severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (2%) (may be severe)	I
Immune	Other (hypogammaglobulinemia - rare)	D
Metabolic / Endocrine	Abnormal electrolyte(s) (2%) (↑ K, ↓ PO4; may be severe)	E
	Tumour lysis syndrome (<1%)	I
Musculoskeletal	Fracture (3%)	D
	Musculoskeletal pain (11%)	E
Neoplastic	Secondary malignancy (rare)	L
Nervous System	Headache (19%)	E
Renal	Renal failure (6%)	E
Respiratory	Cough, dyspnea (9%) (may be severe)	E
	Pneumonitis (rare)	E
Vascular	Vasculitis Leukocytoclastic vasculitis (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for bosutinib include diarrhea, myelosuppression ± infection, bleeding, nausea, vomiting, ↑ LFTs , rash, abdominal pain, fatigue, headache, ↑ amylase / lipase and musculoskeletal pain.

Diarrhea is the most frequent adverse event and should be managed early with supportive care, including antidiarrheals and/or fluid replacement, or dose modification. In phase 3 clinical trial of newly-diagnosed patients treated with bosutinib 400 mg, the median time of onset for diarrhea (all grades) was 3 days and the median duration was 3 days; in patients treated with bosutinib 500 mg, 45.8% have experienced an episode of diarrhea for > 28 consecutive days.

Edema, including pericardial effusion, pleural effusion, and pulmonary edema, have been reported. Diuretics and/or dose modification may be used to manage symptoms.

QT prolongation and **cardiac events,** including fatal outcomes, have been reported. QTcF (corrected QT by the Fridericia method) intervals > 500 msec or increases from baseline > 60 msec have been experienced by patients.

Patients at risk of **tumour lysis syndrome** should have appropriate prophylaxis and be monitored closely.

Renal function declined over time, with more significant declines in acute phase leukemia. It is unclear whether the decline is reversible.

Patients receiving bosutinib who have renal impairment are at a higher risk of developing **hypertension**. A higher frequency of hypertension was observed among patients with renal insufficiency (14% vs 6%).

Increased serum transaminases have been associated with treatment and most occurred early in treatment within the first 3 months. The median time to onset of ALT and AST elevations was 32 and 43 days, respectively, while the median duration was 20 and 15 days, respectively. One case consistent with **Hy's Law** and **drug induced liver injury** was reported in combination with letrozole.

Reactivation of hepatitis B virus (HBV) has been reported in patients who are chronic carriers of HBV and received BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

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E - Dosing

Refer to the protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Pre-existing hypokalemia and hypomagnesemia must be corrected before starting treatment.

Patients at risk of tumour lysis syndrome should be adequately hydrated prior to starting treatment and should be monitored closely.

Adults:

Newly-diagnosed chronic phase Ph+ CML:

Oral: 400 mg Daily

Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy:

Oral: 500 mg Daily

During Ph+ CML clinical trials, dose escalation by increments of 100 mg once daily to a maximum of 600 mg once daily was allowed in patients who did not reach a hematological, cytogenic, or molecular response and who did not have Grade 3 or higher toxicities at the recommended starting dosage. Dose escalations are expected to result in increased toxicity.

Dosage with Toxicity:

Dose Level	Bosutinib Dose (mg/day)	
	Newly-diagnosed Chronic Phase Ph+ CML	**Chronic, Accelerated, or Blast Phase Ph+ CML with Resistance or Intolerance to Prior Therapy**
0	400	500
-1	300	400
-2	Doses < 300 have been used; efficacy has not been established.	300
-3		Doses < 300 have been used; efficacy has not been established.

Toxicity	Action
ANC < 1 x 10^9 /L OR Platelets < 50 x 10^9	If not related to leukemia, hold until ANC ≥ 1 x 10^9 /L and platelets ≥ 50 x 10^9 /L. If recovery takes ≤ 2 weeks, restart at same dose. If recovery takes > 2 weeks, restart with ↓ 1 dose level. If cytopenia recurs, ↓ 1 dose level upon recovery.
Increased serum lipase + abdominal symptoms	Hold and investigate. Discontinue if pancreatitis is confirmed.
Liver transaminases > 5 x ULN	Hold until recovery to ≤ 2.5 x ULN; restart at 400 mg. Consider discontinuing if recovery takes > 4 weeks.
Liver transaminases ≥ 3 x ULN AND ALP < 2 x ULN AND Bilirubin > 2 x ULN	Discontinue.

Grade 3 or 4 fluid retention	Hold until ≤ grade 1; restart with ↓ 1 dose level. Consider discontinuation depending on severity.
Grade 3 or 4 diarrhea (≥ 7 bowel movements over baseline)	Hold until ≤ grade 1; manage with antidiarrheals and/or fluid replacement; then restart with ↓ 1 dose level.
Stevens-Johnson Syndrome	Discontinue if suspected or confirmed.
Other clinically significant grade 2 to 4 toxicities	Hold until ≤ grade 1; restart with ↓ 1 dose level. May consider re-escalation by 1 dose level if clinically appropriate.*
Falls in CrCl, renal failure	See Dosage with Renal Impairment section.

*for patients who have had dose reduction due to toxicity and whose toxicity has recovered to ≤ grade 1 for at least 1 month and otherwise tolerating bosutinib (Cortes et al)

Dosage with Hepatic Impairment:

Bosutinib is **contraindicated** in patients with hepatic impairment at baseline, as higher risk of QT prolongation has been observed in these patients. Clinical studies excluded patients with LFTs > 2.5 x ULN (or > 5 x ULN, if disease-related) and/or bilirubin > 1.5 x ULN. Refer to dose modifications above for hepatic toxicity during treatment.

Dosage with Renal Impairment:

Bosutinib exposure is increased in moderate to severe renal impairment; consider benefit-risk before starting treatment and reduced starting doses are recommended. Patients with serum creatinine > 1.5 x ULN were excluded from clinical trials.

Creatinine Clearance (mL/min)	**Bosutinib Dose (mg/day)**	
	Newly-diagnosed Chronic Phase Ph+ CML	**Chronic, Accelerated, or Blast Phase Ph+ CML with Resistance or Intolerance to Prior Therapy**
> 50	No change	No change
30-50	300	400
< 30	200	300

Dosage in the elderly:

No dose adjustment is necessary. The overall frequency of adverse effects leading to treatment discontinuation was higher in older subjects (> 65 years).

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

- Administer bosutinib tablets with a meal, at approximately the same time each day.
- Tablets should be swallowed whole and not be crushed, cut or dissolved in a liquid.
- If a dose is missed, patient may take it within 12 hours of missed dose. If a dose is missed by more than 12 hours, patient should skip the missed dose and take the next dose at the next scheduled time. Extra tablets should not be taken to make up for missed dose.
- Grapefruit, pomegranate, starfruit, Seville oranges, their juices or products should be avoided during bosutinib treatment.
- Store at 20°C to 25°C.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or to any ingredient in the formulation (includes PEG, povidone and polyoxamer 188) or component of the container
- Patients with a known history of long QT syndrome or with a persistent QT interval of > 480ms
- Patients with uncorrected hypokalemia or hypomagnesemia
- Patients with hepatic impairment, as a higher risk of QT prolongation was observed in these patients

Other Warnings/Precautions:

- Use with caution in patients with a history or predisposition for QTc prolongation, or who have uncontrolled or significant cardiac disease, or who are taking medications that are known to prolong the QT interval.
- Consultation with a liver disease expert is recommended prior to starting bosutinib in chronic HBV carriers (including those with active disease), and for patients who test positive for HBV infection while on treatment.
- Exercise caution in patients with recent or ongoing clinically significant GI disorders, pre-existing diarrhea or conditions that predispose to diarrhea, fluid retention or with previous history of pancreatitis.
- Patients with coagulation dysfunction/platelet disorders may be at higher risk of bleeding events.
- Use with caution in patients with hyperparathyroidism or severe osteoporosis; monitor such patients closely.
- Use with caution in patients with pre-existing renal impairment or those with risk factors for renal dysfunction (see section E for dose modifications).

Other Drug Properties:

- Carcinogenicity:
  Second primary malignancies have been reported in clinical trials.

Pregnancy and Lactation:

- Genotoxicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
- Pregnancy:
  Bosutinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 month** after the last dose.
- Excretion into breast milk: Yes
  Breastfeeding is not recommended.
- Fertility effects: Probable
  Documented in animal studies

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H - Interactions

Bosutinib is primarily metabolized by CYP3A4 and is therefore susceptible to interactions with inducers and inhibitors of this enzyme. Bosutinib is also an *in vitro* substrate for Pgp, BCRP and MRPs; interactions between bosutinib and substrates of these transporters may occur. *In vitro,* bosutinib has the potential to inhibit BCRP in the gastrointestinal tract and OCT1.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. aprepitant, ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ bosutinib exposure (up to 9-fold) and/or toxicity	↓ metabolism of bosutinib	Avoid strong or moderate inhibitors; use caution and monitor patient with mild inhibitors. Use alternative medications with no or minimal inhibition.
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ bosutinib exposure (down to 6%) and/or efficacy	↑ metabolism of bosutinib	Avoid strong or moderate inducers. Use caution with mild inducers.
Protein pump inhibitors	↓ bosutinib exposure (up to 74%) and/or efficacy	pH dependent solubility	Caution; consider using short-acting antacids and separate administration times (i.e. morning and evening).
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin,	↑ risk of QT prolongation	Additive	Avoid.

domperidone, ondansetron, etc)			
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of QT prolongation	Additive QT prolongation	Avoid.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, weekly for the first month, and then monthly and as clinically indicated
Liver function tests (including total bilirubin)	Baseline, then monthly for the first three months and then as clinically indicated.
Renal function tests	Baseline, then monthly and as clinically indicated (more frequent with renal failure)
Electrolytes, including magnesium, calcium, phosphorous, and as well as serum lipase/amylase	Baseline, frequently during treatment and as clinically indicated
ECG	Baseline and as clinically indicated
Clinical toxicity assessment for infection, bleeding, fluid retention (including weight monitoring), tumour lysis syndrome, GI, skin, pulmonary and cardiovascular effects, hypersensitivity	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Bone abnormalities (including bone density), in patients with endocrine abnormalities (e.g. hyperparathyroidism) or severe osteoporosis	Baseline and as clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- bosutinib - For the treatment of patients with chronic, accelerated or blast phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML), according to specific criteria.

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K - References

Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011;118(17):4567-76.

Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 2012;119(15):3403-12.

Product Monograph: Bosulif® (bosutinib). Pfizer Canada Inc. August 9, 2019.

November 2024 Updated Pregnancy and Lactation section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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