Regimen Monograph

A - Regimen Name

BOSU Regimen

Bosutinib

Disease Site	Hematologic - Leukemia - Chronic Myeloid (CML)
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	For the treatment of patients with chronic, accelerated, or blast phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) with: • disease progression to prior TKI therapy, OR • documented mutational drug resistance to prior TKI therapy, OR • unacceptable intolerance or toxicity to prior TKI therapy (Refer to EAP for full funding criteria)
Supplementary Public Funding	**bosutinib** Exceptional Access Program (bosutinib - For the treatment of patients with chronic, accelerated or blast phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML), according to specific criteria.) (EAP Website)

back to top

B - Drug Regimen

bosutinib	500 mg	PO	Daily

back to top

C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity.

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:

- Patients at risk of tumour lysis syndrome should be adequately hydrated prior to starting treatment and should be monitored closely.
- Patients should be tested for HBV infection prior to initiating treatment.

Also refer to CCO Antiemetic Recommendations.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

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

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)
0	500
-1	400
-2	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)

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 modification above for hepatic toxicity during treatment.

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)
> 50	No change
30-50	400
< 30	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).

back to top

F - Adverse Effects

Refer to bosutinib drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea (may be severe)	• Nausea, vomiting • Myelosuppression ± infection (including atypical), bleeding (may be severe, including CNS, GI hemorrhage) • ↑ LFTs (may be severe) • Rash (may be severe) • Abdominal pain	• Fatigue • Headache • ↑ Amylase / lipase (may be severe) • Musculoskeletal pain • Anorexia	• Arrhythmia, QT interval prolonged • Arterial thromboembolism • Cardiotoxicity • Hypertension, Pulmonary hypertension • Edema (including pericardial and pleural effusion) • Tumor lysis syndrome • Hypersensitivity • Pneumonitis • Vasculitis • Fracture • Renal failure • Secondary malignancy

back to top

G - Interactions

Refer to bosutinib drug monograph(s) for additional details,

- Avoid strong or moderate CYP3A4 inhibitors due to increased risk of toxicity.
- Avoid strong or moderate CYP3A4 inducers due to risk of reduced efficacy.
- Avoid drugs that may prolong the QT interval and/or disrupt electrolyte levels given additive risk of QT prolongation.
- Consider using short-acting antacids as proton-pump inhibitors may reduce bosutinib exposure; separate antacid administration times with bosutinib (i.e. morning and evening).

back to top

H - Drug Administration and Special Precautions

Refer to bosutinib drug monograph(s) for additional details.

Administration:

- 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.

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

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).

Pregnancy/Lactation:

- Bosutinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **1 month** after the last dose.
- Breastfeeding is not recommended.
- Fertility effects: Probable

back to top

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.

Recommended Clinical Monitoring

- 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
- HBV infection status; Prior to starting treatment; consult infectious disease if positive
- For carriers of HBV: signs and symptoms of active HBV infection; At each visit during treatment and for several months after treatment is discontinued
- 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

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

back to top

J - Administrative Information

Outpatient prescription for home administration

back to top

K - References

Bosutinib drug monograph, Ontario Health (Cancer Care Ontario).

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.

March 2021 Updated dose modifications, adverse effects, interactions and administration sections

back to top

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for

the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top