Regimen Monograph

A - Regimen Name

IMAT Regimen

Imatinib

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

- Adult patients with newly diagnosed, Philadelphia chromosome-positive (Ph+) CML in chronic phase
- Adult patients with Ph+ CML in blast crisis, accelerated phase or chronic phase after failure of interferon-alpha therapy

Supplementary Public Funding

iMAtinib
ODB - General Benefit (iMAtinib - Refer to listed Health Canada indications for generic imatinib formulations. Patients must meet generic substitution policies for access to Gleevec®) (ODB Formulary)

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B - Drug Regimen

Chronic Phase:†

iMAtinib	400 mg	PO	Daily

Accelerated Phase or Blast Crisis:†

iMAtinib	600 mg	PO	Daily

†See dosing section for dose escalation recommendations.

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:

- Also refer to CCO Antiemetic Recommendations.
- **Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

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E - Dose Modifications

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

Dose levels are 200mg, 300mg, 400mg, 600mg, and 800mg.

Indication		Daily Starting Dose	Escalate?
CML	New diagnosis	400mg	Yes[1] → 600 or 800mg
	Chronic	400mg	Yes[1]→ 600 or 800mg
	Blast crisis/accelerated	600mg	Yes[1] → 800mg
1. in absence of severe toxicity if progression (± prior response), no hematologic response after 3 months or no cytogenetic response after 12 months			

Dosage with toxicity

Toxicity	Action
Fluid retention (grade 3,4)	Hold until ≤ grade 1; resume with 1 dose level ↓.
Rash (grade 3, 4)	Hold until ≤ grade 1; resume with 1 dose level ↓ or discontinue.
Bilirubin 3 x ULN OR AST or ALT > 5 x ULN	Hold*; resume with 1 dose level ↓.
Hypotension / Hypersensitivity reaction	Hold, treat supportively, consider steroids.
Bleeding	Hold; consider discontinuing if severe.
Pneumonitis	Hold, investigate, consider discontinuing if confirmed.
DRESS	Consider discontinuing.

*Hold until bilirubin < 1.5 x ULN, and AST or ALT < 2.5 x ULN.

Dosage with Myelosuppression:

	ANC (x 10^9/L)	Platelets (x 10^9/L)	Action
Accelerated, blast crisis CML	< 0.5	< 10	• If related to disease (i.e., marrow), consider escalating dose. • If unrelated to leukemia ↓ one dose level. • If no recovery in 2 weeks, ↓ further by one dose level. • If no recovery in further 2 weeks, hold until ANC ≥ 1 x 10^9/L and platelets ≥ 20 x 10^9/L and then resume treatment without further dose reduction.
Starting dose 400 mg	< 1	< 50	• Hold until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L and then resume treatment at previous dose. • If recurs, hold until recovery and restart with one dose level ↓.

Hepatic Impairment

Imatinib is excreted via the liver and increased exposure is likely in the presence of hepatic impairment.

Starting Dose:

Hepatic Impairment	Recommended Imatinib Starting Dose
Mild (bilirubin ≤ 1.5 x ULN with AST or ALT > ULN)	400 mg daily
Moderate (bilirubin > 1.5 to 3 x ULN)	400 mg daily
Severe (bilirubin > 3 X ULN)	200 mg daily; may consider ↑ to 300 mg daily if no severe toxicity

Toxicity During Treatment: Refer to Dosage with Toxicity section.

Renal Impairment

Imatinib is not excreted via the kidney to a significant extent; however, increased exposure and adverse effects are correlated with renal impairment. Exercise caution in patients with mild to moderate renal impairment.

Starting Dose:

Creatinine Clearance (mL/min)	Recommended Imatinib Starting Dose
40-59	400 mg daily.* Use with caution.
20-29	400 mg daily.*† Use with caution.
<20 or on hemodialysis	Not recommended for use

* May adjust dose based on toxicity, or for lack of efficacy if lower dose was tolerated.
† Doses ≥ 800 mg daily have not been studied.

Dosage in the Elderly

Efficacy was similar in patients ≥ 65 years of age compared to younger patients in CML.

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F - Adverse Effects

Refer to imatinib 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
• Fluid retention (including effusions; may be severe) • Musculoskeletal pain (including withdrawal syndrome) • Nausea, vomiting	• Diarrhea • Rash (may be severe) • Fatigue • Headache • Abdominal pain • Infection (including opportunistic)	• Abnormal electrolytes • Cough, dyspnea (may be severe) • Dizziness • Depression • Insomnia • Increased LFTs (may be severe) • Myelosuppression +/- bleeding (may be severe, including CNS, GI hemorrhage) • Dyspepsia • Constipation • Flu-like symptoms (w/o infection)	• Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Arrhythmia • Pericarditis • Pulmonary hypertension • GI obstruction, perforation • Hypersensitivity • Hypothyroidism • Tumour lysis syndrome • DRESS • Rhabdomyolysis • Renal failure (acute and chronic) • Optic neuritis • Pancreatitis • Osteonecrosis • Avascular necrosis

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G - Interactions

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

- Imatinib is mainly metabolized by CYP3A4. Inhibitors and inducers of CYP3A4 may affect imatinib exposure, and should be used with caution.
- Imatinib inhibits CYP3A4 and CYP2D6 and may affect the concentration of substrates of these enzymes. Caution if used with drugs with a narrow therapeutic index.
- Imatinib inhibits CYP2C9 at high doses, and may affect the concentration of CYP2C9 substrates (e.g. warfarin). Caution and monitor closely.
- Imatinib can increase the risk of bleeding when used with antiplatelet agents or anticoagulants through an additive effect. Consider the use of LMWH rather than warfarin if anticoagulation is required.
- Imatinib inhibits o-glucuronidation of acetaminophen and can increase acetaminophen exposure, increasing risk of hepatotoxicity (fatal case reported). Caution, and monitor LFTs.

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H - Drug Administration and Special Precautions

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

Administration

- Tablets should be administered whole with meal(s) and a large glass of water to reduce gastric irritation.
- Doses < 800mg should be given once daily; total daily doses of 800mg should be given as 400mg twice daily to reduce exposure to iron.
- If unable to swallow the tablet:
  - The **400 mg** tablet may be broken into two pieces; administer each piece with water, one after the other.
  - Alternatively, tablet may be dispersed in water or apple juice (use 50 mL for 100 mg tablet, and 200 mL for a 400 mg tablet) immediately before drinking this mixture. Then, rinse the container with water or apple juice and drink this, to ensure no trace of the tablet is left.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed, the patient should skip this dose and take the next dose at the usual time.
- If vomiting occurs after taking a dose, do not take an extra dose. Take the next dose at the usual time.
- Store at room temperature.

Contraindications:

- Patients with hypersensitivity to imatinib or to any other components of this product

Warnings/Precautions:

- Severe fluid retention may occur, especially with higher doses. Patients should be weighed and monitored regularly. Patients with pre-existing cardiac disease, risk factors for cardiac failure or the elderly should be monitored carefully and be treated appropriately.
- Severe bleeding, including GI, CNS and intra-tumoural, have been reported during clinical trials and post-marketing. Use caution with the concomitant use of imatinib and other drugs that may increase bleeding (e.g. anticoagulants, antiplatelets or prostacyclins). Consider the use of LMWH rather than warfarin if anticoagulation is required.

Pregnancy/Lactation:

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Effects on fertility: Yes.
  Fertility may be affected in patients who produce sperm.

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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

- CBC; baseline, weekly for first month, biweekly for second month, and as indicated thereafter (e.g. every 2 to 3 months)
- Liver function tests; baseline and monthly or as clinically indicated
- Electrolytes, serum creatinine and creatinine clearance; baseline and monthly or as clinically indicated
- INR for patients taking warfarin, especially when starting treatment and with imatinib dose adjustments; baseline and regular
- LVEF, in patients with known underlying heart disease or in elderly patients; baseline and as clinically indicated
- Platelet counts and prothrombin time when imatinib is used concurrently with anticoagulants, prostacyclins, or other medications that increase bleeding risk; baseline and periodic
- TSH levels in patients with previous thyroidectomy or patients on replacement therapy; baseline and regular
- Brain imaging for patients suspected of having subdural hemorrhage; as clinically indicated
- Serum or urine pregnancy test in women of childbearing potential; within one week before starting treatment
- Clinical assessment of fluid retention (including weight monitoring), bleeding, infection, cardiac effects, thromboembolism, rhabdomyolysis, tumour lysis syndrome, osteonecrosis, gastrointestinal effects, pneumonitis, and rash; at each visit

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

Suggested Clinical Monitoring

- EKG and troponin in patients with hypereosinophilia and cardiac involvement

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with a Philadelphia chromosome. NEJM 2001;344 (14):1038-42.

Druker BJ, Sawyers CL, Kantarjian H, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. NEJM 2001;344(14):1031-7.

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

O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. NEJM 2003;348 (11):994-1004.

October 2024 Modified Dose modifications, Adverse effects, Warnings/precautions, Pregnancy/lactation and Monitoring sections

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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.

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