

Regimen Monograph

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A - Regimen Name

IMAT Regimen

Imatinib

Disease Site

Gastrointestinal
 Gastrointestinal Stromal Tumours
 Sarcoma
 GIST

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 metastatic Gastrointestinal Stromal Tumours (GIST) in patients with a tumour deemed to be not surgically resectable (metastatic or recurrent).

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

iMAtinib 400 to 800 * mg PO Daily
(Outpatient prescription in multiples of 100mg and 400mg tablets)
*See dose modification section for suggested dose escalations

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C - Cycle Frequency

CONTINUOUS TREATMENT

in absence of 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:

- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely
- Patients should be tested for HBV infection prior to initiating treatment. Carriers of HBV must be monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Also refer to [CCO Antiemetic Recommendations](#).

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Dose levels: 200mg, 300mg, 400mg, 600mg, 800mg

Indication	Daily Starting Dose	Escalate?	Hepatic Impairment		Renal Impairment (Clcr; mL/min)	
			Mild-mod ⁵	Severe ⁶	20-59	<20
GIST (metastatic/unresectable)	400mg or 600mg	Y ¹ → 600mg or 800mg	2	3, 4	2	Discontinue
<ol style="list-style-type: none"> 1. In absence of toxicity if insufficient response to treatment. 2. Start at 400 mg. For mild renal impairment only (Clcr = 40-59 mL/min), may consider escalation (if applicable in table) if inadequate efficacy providing lower dose well-tolerated. 3. Initially, start at 200 mg. If no toxicity may ↑ to 300mg. 4. While on treatment: Hold until bilirubin < 1.5 x ULN and AST/ALT < 2.5 x ULN and then restart by ↓ 1 dose level 5. bilirubin >1.5 - 3 x ULN or AST/ALT > ULN with bilirubin ≤ 1.5 x ULN 6. bilirubin > 3 x ULN or AST/ALT > 5 x ULN 						

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
Hypotension / Hypersensitivity reaction	Hold, treat supportively, consider steroids
Bleeding	Hold; consider discontinuing if severe
Pneumonitis	Hold, investigate, consider discontinuing if confirmed
DRESS	Consider discontinuing

Dosage with myelosuppression:

	ANC (x 10 ⁹ /L)	Platelets (x 10 ⁹ /L)	Action
Starting dose 400-600mg	< 1	< 50	<ul style="list-style-type: none"> • Hold until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$ 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. See dosage table above.

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. See dosage table above.

Dosage in the Elderly

There is no evidence of an increase in toxicity in patients older than 65 years compared to younger patients.

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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
<ul style="list-style-type: none"> • Fluid retention (including effusions; may be severe) • Musculoskeletal pain (including withdrawal syndrome) • Nausea, vomiting 	<ul style="list-style-type: none"> • Diarrhea • Rash (may be severe) • Fatigue • Headache • Abdominal pain • Infection (including opportunistic) 	<ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • 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 • 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. Avoid if possible, or monitor closely.
- 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:

- Should be administered orally 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 a dose is missed, the patient should not take the missed dose, but take the next prescribed dose.
- If unable to swallow, 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.

Contraindications:

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

Other Warnings/Precautions:

- Consultation with a liver disease expert is recommended prior to starting imatinib in chronic HBV carriers (including those with active disease), and for patients who test positive for HBV infection while on treatment

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- Imatinib results in serious fluid retention in 6% of patients, 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.
 - Bleeding, including GI, CNS and intra-tumoural, have been reported in patients with GIST; concomitant use of warfarin or antiplatelet agents should be avoided. Consider the use of LMWH rather than warfarin if anticoagulation is mandatory.
 - Exercise caution if drugs that may increase bleeding (e.g. anticoagulants, antiplatelets or prostacyclins) must be used.

Pregnancy and Lactation:

- Imatinib is contraindicated during pregnancy. Spontaneous abortions have been reported in women who have taken imatinib. Highly effective contraception (failure rate < 1%) is recommended for both sexes during treatment, and for at least 6 months (general recommendation) after imatinib cessation.
- Women of childbearing potential should have a negative serum or urine pregnancy test (with a sensitivity of at least 25 mIU/ml) within one week before starting therapy.
- Breastfeeding is not recommended. Imatinib and/or its metabolites are excreted in human milk.
- Fertility may be affected in males.

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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.

Recommended Clinical Monitoring

- Brain imaging for patients suspected of having subdural hemorrhage; as clinically indicated
- CBC; weekly for first month, biweekly for second month, and as indicated thereafter (e.g. every 2 to 3 months)
- Electrolytes and serum creatinine; baseline and regular
- INR for patients taking warfarin, especially when starting treatment and with imatinib dose adjustments; baseline and regular
- Liver function tests; baseline and monthly or as clinically indicated
- 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

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- TSH levels in patients with previous thyroidectomy or patients on replacement therapy; baseline and regular
 - Serum or urine pregnancy test in women of childbearing potential; within one week before starting treatment
 - 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 discontinues
 - Clinical assessment of fluid retention, bleeding, infection, cardiac effects, thromboembolism, rhabdomyolysis, tumour lysis syndrome and gastrointestinal effects, pneumonitis, 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

BCR-ABL Tyrosine Kinase Inhibitors [GLEEVEC (imatinib mesylate), TASIGNA (nilotinib), BOSULIF (bosutinib), SPRYCEL (dasatinib), ICLUSIG (ponatinib hydrochloride)] - Risk of Hepatitis B Reactivation. Health Canada, May 4, 2016. [Accessed May 13, 2016]. Available from: <http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/58222a-eng.php>

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Verweij J, Casali PG, Zalcberg J, Le Cesne A, Reichardt P, Blay J-Y, et al. Progression-free survival

in gastrointestinal stromal tumours with high-dose imatinib: Randomized trial. *Lancet*. 2004; 364(9440):1127-34.

Zalberg JR, Verweij J, Casali P, Le Cesne A, Reichardt P, Blay J-Y, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800mg after progression on 400mg. *Eur J Cancer*. 2005;41(12):1751-7.

April 2024 Changed imatinib to ODB general benefit

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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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