

## 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

\*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:

- 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: 200mg, 300mg, 400mg, 600mg, 800mg

Indication	Daily Starting Dose	Escalate?
GIST (metastatic/unresectable)	400mg or 600mg	Yes <sup>1</sup> → 600mg or 800mg
1. In absence of toxicity if insufficient response to treatment.		

### **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 <sup>9</sup> /L)	Platelets (x 10 <sup>9</sup> /L)	Action
Starting dose 400-600mg	< 1	< 50	<ul style="list-style-type: none"> <li>Hold until ANC ≥ 1.5 x 10<sup>9</sup>/L and platelets ≥ 75 x 10<sup>9</sup>/L and then resume treatment at previous dose.</li> <li>If recurs, hold until recovery and restart with one dose level ↓.</li> </ul>

### **Hepatic Impairment**

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

#### **Starting Dose:**

<b>Hepatic Impairment</b>	<b>Recommended Imatinib Starting Dose</b>
Mild (bilirubin $\leq 1.5 \times$ ULN with AST or ALT $> \text{ULN}$ )	400 mg daily
Moderate (bilirubin $> 1.5$ to $3 \times$ ULN)	400 mg daily
Severe (bilirubin $> 3 \times$ ULN)	200 mg daily; may consider $\uparrow$ 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:**

<b>Creatinine Clearance (mL/min)</b>	<b>Recommended Imatinib Starting Dose</b>
40-59	400 mg daily.* Use with caution.
20-29	400 mg daily.* <sup>†</sup> 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.

<sup>†</sup> Doses  $\geq 800$  mg daily have not been studied.

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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"> <li>Fluid retention (including effusions; may be severe)</li> <li>Musculoskeletal pain (including withdrawal syndrome)</li> <li>Nausea, vomiting</li> </ul>	<ul style="list-style-type: none"> <li>Diarrhea</li> <li>Rash (may be severe)</li> <li>Fatigue</li> <li>Headache</li> <li>Abdominal pain</li> <li>Infection (including opportunistic)</li> </ul>	<ul style="list-style-type: none"> <li>Abnormal electrolytes</li> <li>Cough, dyspnea (may be severe)</li> <li>Dizziness</li> <li>Depression</li> <li>Insomnia</li> <li>Increased LFTs (may be severe)</li> <li>Myelosuppression +/- bleeding (may be severe, including CNS, GI hemorrhage)</li> <li>Dyspepsia</li> <li>Constipation</li> <li>Flu-like symptoms (w/o infection)</li> </ul>	<ul style="list-style-type: none"> <li>Arterial thromboembolism</li> <li>Venous thromboembolism</li> <li>Cardiotoxicity</li> <li>Arrhythmia</li> <li>Pericarditis</li> <li>Pulmonary hypertension</li> <li>GI obstruction, perforation</li> <li>Hypersensitivity</li> <li>Hypothyroidism</li> <li>Tumour lysis syndrome</li> <li>DRESS</li> <li>Rhabdomyolysis</li> <li>Renal failure (acute and chronic)</li> <li>Optic neuritis</li> <li>Pancreatitis</li> <li>Osteonecrosis</li> <li>Avascular necrosis</li> </ul>

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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.

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**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

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

Rankin C, von Mehren M, Blanke C, Benjamin R, Fletcher CDM, Bramwell V, et al. Dose effect of imatinib (IM) in patients (pts) with metastatic GIST – Phase III Sarcoma Group Study S0033. J Clin Oncol. 2004;22(14 Suppl):9005.

Verweij J, Casali PG, Zalberg 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.

**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.*

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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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