Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

IMAT Regimen

Imatinib (Adjuvant)

Disease Site	Gastrointestinal Gastrointestinal Stromal Tumours Sarcoma GIST
Intent	Adjuvant
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	Adjuvant treatment of adult patients with KIT-expressing (CD117+) primary, non-metastatic GIST following complete resection, who are at intermediate to high risk of relapse.
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 mg	PO	Daily

(Outpatient prescription in multiples of 100 mg and 400 mg tablets)

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C - Cycle Frequency

CONTINUOUS TREATMENT

Treat for one year until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Febrile Neutropenia Risk: Low

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 are 200mg, 300mg, 400mg.

Indication	Daily Starting Dose	Escalate?	Hepatic Impairment		Renal Impairment (Clcr, ml/min)	
			Mild-Mod[4]	Severe[5]	20-59	<20
GIST (adjuvant)	400mg	No	1	2, 3	1	Discontinue

1. Starting dose 400 mg.
2. Initially, start at 200 mg. If no toxicity may ↑ to 300mg.
3. While on treatment: Hold until bilirubin < 1.5 x ULN and AST/ALT < 2.5 x ULN and then restart by ↓ 1 dose level
4. bilirubin >1.5 - 3 x ULN or AST/ALT > ULN with bilirubin ≤ 1.5 x ULN
5. 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

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Dosage with myelosuppression:

	ANC (x 10^9/L)	Platelets (x 10^9/L)	Action
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. See dosage table.

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.

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

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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 and viral reactivation)	• Abnormal electrolytes • Cough, dyspnea (may be severe) • Dizziness • Depression (may be severe) • Insomnia • Increased LFTs (may be severe) • Myelosuppression +/- bleeding (may be severe, including CNS, GI hemorrhage) • Dyspepsia • Constipation • Flu-like symptoms (w/o infection) • Anxiety	• Arterial / 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 • Pneumonitis

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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

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
- 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.

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Pregnancy & 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 as clinically indicated
- 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
- TSH levels in patients with previous thyroidectomy or patients on replacement therapy; baseline and as clinically indicated
- 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,

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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

De Matteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009; 373(9669): 1097-104.

Imatinib drug monograph, Cancer Care Ontario.

Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307(12):1265-72.

April 2024 Changed imatinib to ODB general benefit

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M - Disclaimer

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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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