Regimen Monograph

A - Regimen Name

SUNI Regimen

SUNItinib

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	Treatment of unresectable or metastatic/ recurrent gastrointestinal stromal tumour (GIST) in patients who failed imatinib mesylate (either because of disease progression or intolerance).
Supplementary Public Funding	**SUNItinib** Exceptional Access Program (SUNItinib - Unresectable or metastatic/recurrent Gastrointestinal Stromal Tumour, with specific criteria) (EAP Website)

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B - Drug Regimen

SUNItinib	37.5 to 50* mg	PO	Days 1 to 28

(Outpatient prescription in multiples of 12.5mg, 25mg and 50mg capsules)

*Consider a lower starting dose in elderly/frail patients. See section E for dose modifications for toxicity and organ dysfunction.

Alternative schedule:

SUNItinib	37.5** mg	PO	Daily continuous

**George et al. 2009

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C - Cycle Frequency

Standard schedule: REPEAT EVERY 6 WEEKS (4 WEEKS ON, 2 WEEKS OFF)

Alternative schedule: CONTINUOUS

Continue 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.

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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.

Sunitinib may be given with or without food. Daily doses should not exceed 50mg nor be decreased below 25mg. Doses should be held prior to surgery

Suggested dose levels are 50 mg, 37.5 mg and 25 mg. Doses reduced for toxicity should not be re-escalated.

Dosage with toxicity

Toxicity	Action	Dose
Severe hypertension	Hold and treat appropriately.	May resume only if hypertension is controlled. (See Appendix 8: Management of Angiogenesis Inhibitor (AI) Induced Hypertension)
CHF, arrhythmia, ↑ QTc, AV block, pancreatitis, hepatic failure, nephrotic syndrome, RPLS, perforation, fistula, TMA, ITP, TTP, HUS, DIC, hemolysis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme*, necrotizing fasciitis	Discontinue	Not applicable
Asymptomatic falls in LVEF < LLN or ≥ 20% ↓ from baseline, thrombotic microangiopathy, grade 3 hemorrhage	Hold until ≤ Grade 1	↓ 1 dose level
Other grade 3 non-hematological toxicity, including ↑ LFTs	Hold until ≤ Grade 2	↓ 1 dose level
Grade 3 or 4 hematological (excluding lymphopenia)	Hold until ≤ Grade 2	↓ 1 dose level
Grade 4 non-hematological toxicity, including ↑ LFTs	Discontinue	Not applicable

* may consider rechallenge at a lower dose after resolution of erythema multiforme if clinically

indicated.

Hepatic Impairment

Multiple dosing pharmacokinetic studies have not been conducted; single dose studies have only been conducted in patients with mild-moderate hepatic impairment, Hepatic metabolism / excretion is significant; consider dose modification for patients with mild to moderate impairment (Child Pugh A and B).

Renal Impairment

Only single dose studies have been conducted in patients with renal impairment. No adjustment to starting dose is required in patients with mild to severe renal impairment or with end-stage renal disease. Patients with end stage renal disease on dialysis may have lower exposure than expected. Exercise extreme caution in patients especially with severe renal impairment or ESRD, since fatal renal failure has been reported with sunitinib. Subsequent dosing should be based on tolerability.

Dosage in the Elderly

Dose modification not required; consider dose reduction for frail patients.

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F - Adverse Effects

Refer to SUNItinib 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
• Increased LFTs (may be severe) • Increased	• Increased CPK (may be severe) • Dysgeusia	• Respiratory disorders • Myelosuppression +/- infection (may be severe, including	• Arterial thromboembolism • Venous thromboembolism

creatinine (may be severe) • Diarrhea • Fatigue • Increased amylase (may be severe) • Nausea, vomiting	• Abnormal electrolytes • Dyspepsia • Mucositis • Anorexia, weight loss • Skin discolouration • Rash (may be severe) • Abdominal pain • Hand-foot syndrome • Hypertension (may be severe) • Hair depigmentation • Hemorrhage • Left-ventricular dysfunction (may be severe)	viral/fungal) • Hyper or hypoglycemia • Constipation • Headache • Dizziness • Hypothyroidism • Musculoskeletal pain • Insomnia • Psychiatric disorders • Eye disorders	• Arrhythmia, prolonged QT • Artery aneurysm / dissection • GI fistula or perforation • Disseminated intravascular coagulation • Hemolysis • Idiopathic thrombocytopenic purpura • Hypersensitivity • Radiation dermatitis • Wound dehiscence • Cholecystitis • Necrotizing fasciitis • Adrenal insufficiency • Hyperthyroidism • Tumour lysis syndrome • Osteonecrosis of the jaw • Rhabdomyolysis • PRES, seizure • Nephrotic syndrome • Pleural effusion

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G - Interactions

Refer to SUNItinib drug monograph(s) for additional details

- Consider sunitinib dosage reduction with strong inhibitors of CYP3A4 (e.g. azole antifungals, macrolide antibiotics, Grapefruit juice)
- Consider sunitinib dosage adjustment with strong inducers of CYP3A4 (e.g. phenytoin, rifampin, St. John's wort)

- Avoid use with drugs that prolong the QT interval (e.g. amiodarone, methadone, domperidone)
- Avoid combining with bevacizumab given increased risk of microangiopathic hemolytic anemia, hypertension and ONJ
- Use with caution with drugs that cause hypoglycemia (e.g. sulfonylureas)

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H - Drug Administration and Special Precautions

Refer to SUNItinib drug monograph(s) for additional details

Administration

- Prescribed dose should be administered orally, once daily with or without food.
- Avoid any grapefruit, starfruit, Seville oranges or their juices/products while on this treatment. (See interactions)
- Store at room temperature (15-30°C).

Contraindications

- patients who have a hypersensitivity to this drug or any of its components
- patients with uncontrolled hypertension, abnormal ↑QT or AV block

Other Warnings/Precautions

- Extreme caution should be exercised in patients at increased risk of torsade de pointes, with bradycardia, QTc prolongation, cardiac or thromboembolic risk factors, electrolyte disturbances, and in patients taking medications which prolong QTc or the PR interval.
- Patients who had, within 12 months, cardiovascular events such as MI (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, CVA, TIA or pulmonary embolism were excluded from clinical trials. The risk versus benefit of sunitinib use should be carefully considered in these patients
- Concomitant use of warfarin or antiplatelet agents should be avoided.
- Hypoglycemia has been reported in both diabetic and non-diabetic patients while on sunitinib and may be severe.
- Patients with intra-abdominal malignancies are at an increased risk of perforation.
- Subclinical adrenal insufficiency may occur and stressed patients (surgery, trauma, etc.) should be monitored carefully.
- Hold treatment in patients undergoing major surgical procedures. The timing of restarting sunitinib should be based on clinical judgment of recovery.

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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

- Blood glucose; baseline and periodic; closer monitoring in diabetic patients may be needed
- CBC; baseline and before each cycle (or at each visit for continuous schedule)
- Dental evaluation; before starting treatment with preventative dentistry as needed;
- ECG; baseline and periodic during therapy
- Liver function tests, with lipase and amylase; baseline and at each visit
- LVEF in patients with cardiac risk factors; baseline and as clinically indicated
- Renal function tests and electrolytes (including Mg, Ca, PO4); baseline and at each visit
- Thyroid function tests; baseline then q3 months, and as clinically indicated
- Urinalysis; baseline and periodic
- Blood pressure and assessment for signs and symptoms of pancreatitis, hypo-/hyperthyroidism, hypertension, myopathy, delayed wound healing, TLS, thromboembolism, bleeding, cardiovascular, neurologic, GI or respiratory effects, adrenal insufficiency (especially with stress); regular

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

Suggested Clinical Monitoring

- Adrenal function tests in patients who experience stress (surgery, trauma, severe infection)

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J - Administrative Information

Outpatient prescription for home administration.

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K - References

Demetri GD, Garrett CR, Schöffski P, et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res. 2012 Jun 1;18(11):3170-9.

Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomized controlled trial. Lancet. 2006;368:1329-38.

George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. Eur J Cancer. 2009 Jul;45(11):1959-68.

Sunitinib drug monograph, Cancer Care Ontario.

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M - Disclaimer

Regimen Abstracts

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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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