Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

SUNItinib

COMMON TRADE NAME(S): Sutent®

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B - Mechanism of Action and Pharmacokinetics

Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor with effects on cell proliferation and angiogenesis. It is a potent inhibitor of platelet-derived endothelial growth factor receptors (PDGFR-α and β), vascular endothelial growth factor receptors (VEGFR-1, 2 and 3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (CSF-1R) and the glial-cell line derived neutrotrophic factor receptor (RET).

Absorption	Pharmacokinetics are dose-proportional. Peak concentration observed 6-12 hours post-dose. Daily dosing leads to a 3-4 fold accumulation (7-10 fold for the primary metabolite). Steady state is reached in 10-14 days. Age, body weight, gender, race, creatinine clearance, or ECOG score does not appear to affect the pharmacokinetic profile.	
	Bioavailability	Unaffected by food
Distribution	Cross blood brain barrier?	No information found (unlikely)
	PPB	95% (primary metabolite 90%)
Metabolism	Sunitinib and its primary metabolite are mainly metabolized by CYP3A4.	
	Active metabolites	N-desethyl metabolite (SU12662)
	Inactive metabolites	Yes

Elimination	Urine	16%
	Feces	61%
	Half-life	40-60 hours (sunitinib) 80-110 hours (primary metabolite)

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C - Indications and Status

Health Canada Approvals:

- Treatment of patients with gastrointestinal stromal tumour (GIST) after failure of imatinib treatment due to resistance or intolerance
- Treatment of metastatic renal cell carcinoma (MRCC) of clear cell histology.
- Treatment of patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumours, whose disease is progressive.

(Indications are based on time to progression/progression-free survival, without demonstration of a significant overall survival benefit.)

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following adverse effects were reported mainly from the phase 3 study in metastatic renal cell carcinoma. Rare, but serious side effects are included from pooled data or post-marketing.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (including ↑ PR)	E
	Arterial thromboembolism (2%)	E
	Artery aneurysm (rare)	E D L
	Artery dissection (rare)	E D L

	Hypertension (30%) (may be severe)	D L
	Left ventricular dysfunction (27%) (may be severe)	E
	QT interval prolonged (or prolonged PR interval, Torsade de Pointes - rare)	E
	Venous thromboembolism (3%)	E D
Dermatological	Alopecia (5%)	E
	Dry skin (21%)	E
	Hair colour changes (depigmentation- 29%)	E
	Hand-foot syndrome (30%)	E
	Radiation dermatitis (rare)	E
	Rash (31%) (may be severe)	E
	Skin discolouration (32%) (yellow / hypopigmentation)	E
Gastrointestinal	Abdominal pain (30%)	E
	Anorexia, weight loss (34%)	E
	Constipation (21%)	E
	Diarrhea (61%)	E
	Dyspepsia (41%)	E
	Flatulence (12%)	E
	Gastrointestinal fistula or perforation (rare)	E
	Mucositis (41%)	E
	Nausea, vomiting (52%)	E
General	Fatigue (60%)	E
	Wound dehiscence (↓ healing)	E
Hematological	Disseminated intravascular coagulation (rare)	E
	Hemolysis (thrombotic microangiopathy, TMA, also TTP, HUS; rare)	E
	Hemorrhage (GI, tumour, GU, pulmonary, CNS, epistaxis - 28%)	E
	Immune thrombocytopenic purpura (rare)	E
	Myelosuppression (19%) (grade 3/4: 11%)	E
Hepatobiliary	↑ Amylase (56%) (or ↑ lipase; may be severe → pancreatitis)	E D
	Cholecystitis (rare; may be severe)	E
	↑ LFTs (72%) (may be severe)	E
Hypersensitivity	Hypersensitivity (rare)	I
Infection	Infection (with or without neutropenia, include viral/fungal; may be severe; includes necrotizing fasciitis)	E

Metabolic / Endocrine	Abnormal electrolyte(s) (43%) (Ca, Na, K, Mg)	E
	Adrenal insufficiency (2%)	E
	Hyperglycemia (23%)	E
	Hyperthyroidism (rare)	E D
	Hypoglycemia (17%)	E
	Hypothyroidism (15%)	E D
	Tumor lysis syndrome (rare)	E
Musculoskeletal	Musculoskeletal pain (12%)	E
	Osteonecrosis of jaw (rare)	E
	↑CPK (49%)	E
	Rhabdomyolysis (rare)	E
Nervous System	Dizziness (15%)	E
	Dysgeusia (47%)	E
	Headache (19%)	E
	Insomnia (12%)	E
	Other (10%) (Psychiatric disorders)	E
	RPLS / PRES (rare)	E
	Seizure (rare)	E
Ophthalmic	Eye disorders (10%)	E
Renal	Creatinine increased (70%) (up to 5% severe)	E
	Proteinuria (or nephrotic syndrome; rare)	E
	Renal failure (acute, rare)	E
Respiratory	Other (24%) (Respiratory disorders)	E
	Pleural effusion (rare; may be fatal)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for SUNItinib include ↑ LFTs, creatinine increased, diarrhea, fatigue, ↑ amylase, nausea, vomiting, ↑ CPK, dysgeusia, abnormal electrolyte(s) and dyspepsia.

Hypertension is commonly observed; it should be closely monitored and managed with

antihypertensives. (For suggested treatment algorithm, see Appendix 8: Management of Angiogenesis Inhibitor (AI) Induced Hypertension.) Posterior reversible leukoencephalopathy syndrome (PRES) has been described rarely; patients may present with hypertension, headache, altered mental functioning and visual loss.

Falls in left ventricular ejection fraction have been reported, and may be severe or associated with **cardiac failure** or rarely, death. It is unknown if patients with cardiac risk factors (infarction, CVA, etc.) are at greater risk as they were not included in clinical trials; careful monitoring is recommended in such patients. There is an increased risk of arterial thromboembolism, including myocardial ischemia and infarction in patients with risk factors such as hypertension, diabetes and prior arterial thromboembolism.

Severe cases of **artery dissection** (with or without hypertension) and **artery aneurysm** (including rupture) have been reported in patients using VEGFR TKIs.

Hypoglycemia has been reported in both diabetic and non-diabetic patients while on sunitinib and may be severe. Dosage of anti-diabetic drugs may need adjustment to minimize the risk of hypoglycemia.

Subclinical adrenal insufficiency has been seen in clinical trials. Patients should be monitored for adrenal insufficiency when they experience stress such as surgery, trauma, or severe infection. Treatment-emergent **hypothyroidism** has been observed, preceded by hyperthyroidism or thyroiditis in rare cases. All patients should be monitored for signs and symptoms of thyroid dysfunction during sunitinib treatment.

Epistaxis, gastrointestinal, genital, wound, intratumour, brain, or urinary tract **bleeds** have been reported. Fatal **pulmonary hemorrhage** occurred in 2 patients with squamous non-small cell lung cancer. Concomitant use of warfarin or antiplatelet agents should be avoided.

Thrombotic microangiopathy (TMA), also described as thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) has been reported (single agent and combination therapy). TMA is usually reversible after permanent treatment discontinuation.

Osteonecrosis of the jaw has been reported in patients treated with sunitinib. Previous or concomitant treatment with IV bisphosphonates was observed in most of these cases. Avoid invasive dentistry on treatment, especially in patients with prior bisphosphonate exposure.

Based on 9 MRCC sunitinib clinical trials, prolonged treatment (≥ 2 years) was not associated with new or increased severity of adverse effects; toxicity was not cumulative except for hypothyroidism.

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E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist depending on disease, response and concomitant therapy.

Adults:

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.

RCC and GIST:

Oral: Q6W; 50mg daily x 4 weeks (4 weeks on, 2 weeks off)

Pancreatic NET:

Oral: 37.5mg daily, continuous

Dosage with Toxicity:

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

(Continued on next page)

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.

Dosage with Hepatic Impairment:

Multiple dosing PK 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).

Dosage with 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.

Children:

Safety and effectiveness in children have not been established. Reversible, dose-related physeal dysplasia has been reported in animal models.

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F - Administration Guidelines

- 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).

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G - Special Precautions

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 due to risk of hemorrhage.
- Hypoglycemia has been reported in both diabetic and non-diabetic patients while on sunitinib and may be severe. Dosage of anti-diabetic drugs may need adjustment to minimize the risk of hypoglycemia.
- 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.

Other Drug Properties:

- Carcinogenicity: Probable

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
  Sunitinib is **CONTRAINDICATED** in pregnancy; females of childbearing potential and male patients should use effective contraception during treatment and for at least 6 months after treatment cessation (general recommendation).
- Excretion into breast milk: Yes
  Discontinue breastfeeding during treatment with sunitinib.
- Fertility effects: Yes

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H - Interactions

Sunitinib does not induce or inhibit major CYP isoenzymes, but is metabolized by CYP3A4 and is susceptible to interactions with inhibitors or inducers of this enzyme.
Radiation skin reactions have been reported when sunitinib was given with concurrent radiotherapy.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, voriconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit or pomegranate)	↑ sunitinib concentration (up to 51%)	↓ metabolism	Avoid concomitant usage; consider sunitinib dose reduction (min of 25mg) if potent inhibitor cannot be discontinued
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ sunitinib concentrations (up to 46%)	↑ metabolism	Avoid concomitant usage; consider sunitinib dose adjustment (max of 50mg) if potent inducer cannot be discontinued
Drugs that prolong QT/QTc interval (e.g. amiodarone, haloperidol, amitriptyline, methadone, fluconazole, erythromycin, ciprofloxacin, ondansetron, formoterol, quinidine, domperidone, tacrolimus)	Additive effect	QT interval prolongation	Avoid concomitant usage
Drugs that prolong the PR interval (e.g. beta blockers, calcium channel blockers, digoxin, HIV protease inhibitors)	Additive effect	↑ PR interval	Caution

Bevacizumab	Microangiopathic hemolytic anemia	Unknown	Avoid combination
Bevacizumab	↑ hypertension	Additive	Avoid combination
Bevacizumab, other antiangiogenic drugs	↑ ONJ risk	Additive	Caution
Drugs that may cause hypoglycemia	↑ risk of hypoglycemia	Additive	Caution; may need dose adjustment of drug causing hypoglycemia

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
ECG	baseline and periodic during therapy
LVEF in patients with cardiac risk factors	baseline and regular
Dental evaluation	before starting treatment with preventative dentistry as needed
Urinalysis	baseline and periodic
Thyroid function tests	baseline then q3 months, and as clinically indicated
CBC	baseline and at each cycle
Renal function tests and electrolytes (including Mg, Ca, PO4)	baseline and at each cycle
Liver function tests, with lipase and amylase	baseline and at each cycle
Blood glucose	baseline and periodic; closer monitoring in diabetic patients may be needed
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	regular

insufficiency (especially with stress)	

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Adrenal function tests in patients who experience stress (surgery, trauma, severe infection)	

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- SUNItinib - Unresectable or metastatic/recurrent Gastrointestinal Stromal Tumour, with specific criteria
- SUNItinib - Metastatic renal cell carcinoma, with specific criteria
- SUNItinib - For patients who have progressive, unresectable, well or moderately differentiated, locally advanced or metastatic pancreatic neuroendocrine tumours (pNET), according to specific criteria

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K - References

Adams VR, Leggas M. Sunitinib Malate for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. Clinical Therapeutics 2007; 29(7): 1338-53.

Health Canada Endorsed Important Safety Information on Avastin® (bevacizumab). July 11, 2008.

Houk BE, Bello CL, Kang DW, et al. A population pharmacokinetic meta-analysis of sunitinib malate (SU11248) and its primary metabolite (SU12262) in healthy volunteers and oncology patients. Clinical Cancer Research 2009; 15(7): 2497-506.

McEvoy GK, editor. AHFS Drug Information 2013. Bethesda: American Society of Health-System Pharmacists, p. 1196-9.

Prescribing Information: Sunitinib (Sutent®). Pfizer (US), November 2012.

Product Monograph: Sunitinib (Sutent®). Pfizer Canada Inc., July 2019.

Product Monograph Update: Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs). Health Canada InfoWatch, June 2020.

October 2020 Modified adverse effects section (artery dissection/aneurysm, pleural effusion)

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L - Disclaimer

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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