DRUG NAME: Sunitinib

SYNONYM(S): SU11248,[1] sunitinib malate[2]

COMMON TRADE NAME(S): SUTENT®

CLASSIFICATION: tyrosine kinase inhibitor

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Sunitinib inhibits the phosphorylation of multiple receptor tyrosine kinases (RTKs).[2] It is a potent inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT-3), colony stimulating factor receptor (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Consistent with its multi-targeted profile, Sunitinib may inhibit tumour growth, cause tumour regression, inhibit pathologic angiogenesis, and inhibit metastatic progression of cancer.

PHARMACOKINETICS:

Oral Absorption	food has no effect on bioavailability	
Distribution	cross blood brain barrier?	animal studies suggest that sunitinib is able to cross the blood brain barrier
	volume of distribution	2230 L
	plasma protein binding	95% (sunitinib), 90% (primary active metabolite)
Metabolism	hepatic metabolism by CYP3A4	
	active metabolite(s)[1]	SU12662
	inactive metabolite(s)	no information found
Excretion	predominantly via feces	
	feces	61%
	urine	16%
	terminal half life	sunitinib; 40-60 h SU12662; 80-110 h
	clearance	34-62 L/h
Gender	no clinically significant differences	
Elderly	no clinically significant differences	
Ethnicity	no clinically significant differences	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Gastrointestinal stromal tumour (GIST)

*Renal cell cancer (RCC)

*Pancreatic cancer

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:
- ***osteonecrosis of the jaw*** has been reported with sunitinib; patients receiving ***intravenous bisphosphonates*** either concurrently or sequentially with sunitinib may be at higher risk[3-7]
- pre-existing uncontrolled ***hypertension***, ***left ventricular dysfunction***, or ***arrhythmias*** or in patients taking concomitant drugs with arrhythmic potential[2]

Carcinogenicity: no information found

Mutagenicity: Sunitinib is not mutagenic in the Ames test.[8] Sunitinib is not clastogenic in mammalian *in vitro* or *in vivo* chromosome tests.[2]

Fertility: Sunitinib may impair fertility in humans. Animal studies have shown ovarian, uterine and vaginal changes.[2]

Pregnancy: FDA Pregnancy Category D.[8] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Male contraception is advised, as the drug may be present in the semen.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Sunitinib and/or its metabolites are excreted in rat milk.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[9] When placebo-controlled trials are available, adverse events are included if the incidence is ≥ 5% higher in the treatment group.[10]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow/ febrile neutropenia	anemia (12-74%, severe 3-14%)
	leukopenia (14%, severe 6%)
	lymphopenia (38-59%, severe 0-20%)
	neutropenia (14-69%, severe 8-14%)
	thrombocytopenia (14-59%, severe 3-7%)
cardiovascular (arrhythmia)	bradycardia (<1%)
	PR interval prolongation (<1%)
	QT interval prolongation (<1%)
cardiovascular (general)	***hypertension*** (14-28%, severe 4-6%); see paragraph following **Side Effects** table
	left ventricular dysfunction (11-14%, severe 1-2%); see paragraph following **Side Effects** table
	myocardial ischemia/infarction (severe 1%)[11]
constitutional symptoms	asthenia (22%, severe 5%)
	fatigue (42-60%, severe 7-11%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pyrexia (16%, severe 1%)
dermatology/skin	alopecia (5%, severe 0%)
	bullous lesions (18%)[1]
	dry skin (13%, severe 0%)
	erythema (12%, severe 0%)
	hair discolouration (7-14%, severe 0%)
	hand-foot skin reaction (12-14%, severe 4-5%)
	rash (15-26%, severe <1%); see paragraph following **Side Effects** table
	yellow discolouration of skin (26-32%, severe 0%); see paragraph following **Side Effects** table
	subungal splinter hemorrhages (25%, severe 0%)[1]
endocrine	adrenal insufficiency (<1%)
	hypothyroidism (36%, severe 0%)[12]; see paragraph following **Side Effects** table
	serum thyroid-stimulating hormone (TSH) abnormality (62%)[12]
gastrointestinal	*emetogenic potential: rare*
	anorexia (28-31%, severe 1%)
	constipation (20%, severe 0%)
	diarrhea (41-49%, severe 3-5%)
	dyspepsia (15-41%, severe 1%)
	glossodynia (15%, severe 0%)
	loss in sensation of taste (20-42%, severe 0%)
	mucositis/stomatitis (16-41%, severe 1-4%)[8]
	nausea (33-50%, severe 1%)
	osteonecrosis of the jaw[3-5]; see ***Special Precautions section***
	perforation (<1%)
	vomiting (25-31%, severe 2%)
hemorrhage	bleeding (GIST: 20%, severe 7%; RCC: 26%, severe <1%); see paragraph following **Side Effects** table
hepatobiliary/pancreas	pancreatitis (severe <1%)
infection	infections (12%, severe 2%)
lymphatics	peripheral edema (17%, severe 7%)[1,11]
metabolic/laboratory	elevated alkaline phosphatase (24-55%, severe 2-4%)
	elevated amylase (17-28%, severe 5%)
	elevated AST/ALT (39-58%, severe 2-4%)
	elevated bilirubin (total 12-16%, indirect 10%)
	elevated lipase (10-50%, severe 10-17%)
	hypoalbuminemia (28%, severe 0%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypocalcemia (43%, severe <1%), hypercalcemia (11%, severe <1%)
	hypoglycemia (20%, severe 0%), hyperglycemia (18%, severe 4%)
	hypokalemia (12%, severe 1%), hyperkalemia (14%, severe 4%)
	hyponatremia (10%, severe 4%), hypernatremia (10-13%, severe <1%)
	hypophosphatemia (22%, severe 9%)
	serum creatine kinase abnormality (39%, severe 1%)
	serum creatinine abnormality (12-60%, severe 1%)
	serum uric acid abnormality (49%, severe 15%); tumour lysis syndrome not reported
neurology	dizziness (15%)
	seizures (<1%)
ocular/visual	increased lacrimation (6%)[8]
	periorbital edema (7%)[8]
pain	pain in extremity (12-18%, severe <1%)[11]
renal/genitourinary	yellow discolouration of urine; associated with yellow discolouration of skin
vascular	DVT (severe 1-3%)[11]
	pulmonary embolism (severe 1%)

Adapted from standard reference[2] unless specified otherwise.

Hypertension may occur in both GIST and RCC patients receiving sunitinib.[2] Patients should be monitored for hypertension and treated as appropriate with standard antihypertensive therapy. Until more clinical data become available, non-dihydropyridine calcium channel blockers such as diltiazem and verapamil should be avoided, as they are known CYP3A4 inhibitors. Temporary suspension of sunitinib is recommended for patients with severe hypertension (> 200 mmHg systolic or > 110 mmHg diastolic). Treatment with sunitinib may be resumed once hypertension is controlled. Patients with hypertension that is not controlled by medications should not be treated with sunitinib.

Left ventricular dysfunction, which manifests as a decrease in left ventricular ejection fraction (LVEF), has been reported in up to 14% of patients on sunitinib.[2] Of the patients with treatment-emergent decreases in LVEF, a similar number of patients either recovered without intervention, recovered following intervention (dose reduction or addition of medication), or discontinued sunitinib without recovery. A lesser number of patients continued on sunitinib without recovery, or died. Patients who present with a recent history of cardiac events (e.g. acute coronary syndrome, arterial bypass graft, symptomatic congestive heart failure (CHF), stroke, or pulmonary embolism) should be monitored for clinical signs and symptoms of CHF, and evaluated for decreased LVEF while receiving sunitinib. In patients with LVEF < 50% and > 20% below baseline, the dose of sunitinib should be interrupted and/or reduced regardless of clinical evidence of CHF. In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended.

Hypothyroidism has been reported in patients receiving sunitinib. Abnormal TSH concentrations have been documented in 62% of patients. Persistent primary hypothyroidism developed in 36% of patients after a range of 12 to 94 weeks of sunitinib therapy.[12] Eighteen percent of patients taking sunitinib for 36 weeks developed hypothyroidism, 29% of patients taking sunitinib for one year were affected, and 90% of patients treated for more than 96 weeks developed increased TSH levels. The incidence of hypothyroidism appears to increase progressively with the duration of sunitinib therapy. A lower incidence of hypothyroidism (4-7%) has been commonly reported when sunitinib was used for shorter periods.[2,12,13] Clinical and sonographic observations suggest that sunitinib may induce a destructive thyroiditis through follicular cell apoptosis.[12]

Regular surveillance of thyroid function is warranted in patients receiving sunitinib.[12] Patients should be screened for the development of hypothyroidism with TSH measurements at 2-3 month intervals. A low serum TSH concentration and mild symptoms suggesting thyroiditis-induced thyrotoxicosis may precede the onset of hypothyroidism, which may itself progress rapidly from mild to profound. Any abnormal TSH value or symptomatology suggestive of hypothyroidism should prompt more thorough evaluation. Patients developing overt hypothyroidism should be treated with thyroid hormone replacement therapy. Treatment should be considered even in patients with subclinical hypothyroidism, as these patients are unlikely to achieve normal TSH levels without treatment. Typical levothyroxine doses should allow normalization of TSH concentrations and resolution of symptoms.

Bleeding events and ***tumour hemorrhage*** have been reported in patients receiving sunitinib. Epistaxis was the most common hemorrhagic adverse event reported (7%, severe 0%)[10]; less common bleeding events included rectal, gingival, upper GI, genital, and wound bleeding. Treatment-related tumour hemorrhage has been observed in patients receiving sunitinib (2%). In the case of pulmonary tumours/metastases, this may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. A higher incidence of pulmonary hemorrhage has been observed in lung cancer patients (8%). Assessment of hemoptysis should include serial complete blood counts and physical examination.[2]

Yellow discolouration of the skin, due to the yellow colour of the active drug and metabolite, is a common treatment-related adverse event. It occurs in approximately 30% of patients, and is reversible upon treatment discontinuation.[1] Yellow discolouration of the urine has been observed in conjunction with skin discolouration. Depigmentation of the hair and skin may also occur on treatment. Successions of depigmented and normally pigmented bands of hair may correlate with on and off periods of treatment.

Severe ***cutaneous reactions***, including cases of pyoderma gangrenosum, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been rarely reported and are sometimes fatal. Discontinue sunitinib if a progressive skin rash develops and do not restart if a diagnosis of Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.[14,15] Radiation skin reactions have been reported when sunitinib has been given concurrently with radiotherapy.[15]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[2]	may increase plasma level of sunitinib	may inhibit CYP3A4 metabolism of sunitinib in the intestinal wall	avoid grapefruit and grapefruit juice for duration of treatment with sunitinib
ketoconazole[2]	increases plasma levels of sunitinib and its active metabolite	inhibits hepatic CYP3A4 metabolism of sunitinib and its metabolite	decrease dose of sunitinib if toxicity is observed; use caution with other CYP3A4 inhibitors
rifampin[2]	decreases plasma levels of sunitinib and its active metabolite	induces hepatic CYP3A4 metabolism of sunitinib and its active metabolite	monitor for clinical response; increase dose of sunitinib; consider other treatments without CYP3A4 inducing activity

Drugs that are ***CYP3A4 inhibitors*** may decrease metabolism and increase sunitinib plasma concentrations.[2] The dose of sunitinib may be decreased to 37.5 mg in the presence of strong CYP3A4 inhibitors.[8]

Drugs that are ***CYP3A4 inducers*** may increase metabolism and decrease sunitinib plasma concentrations.[2] The dose of sunitinib may be increased up to 87.5 mg in the presence of strong enzyme inducers.[8]

Sunitinib may prolong the QT interval, and the concomitant use of sunitinib with other QT-prolonging drugs is discouraged.[2]

Sunitinib may prolong the PR interval, and the concomitant use of sunitinib with other PR-prolonging drugs is discouraged.[2]

SUPPLY AND STORAGE:

Oral: Pfizer Canada supplies sunitinib as 12.5 mg, 25 mg and 50 mg hard gelatin capsules. Store at 25ºC. Capsules do not contain lactose.[2]

Additional information: An oral liquid formulation may be compounded for patients unable to swallow the capsules. Using a mortar and pestle mix the contents of sunitinib capsules with a 1:1 mixture of ORA-PLUS®:ORA-SWEET® to yield a final concentration of 10 mg/mL. Shake well before use.[16] Store the prepared suspension in an amber plastic bottle. Suspension stable for at least 60 days at room temperature or under refrigeration. Although product stability has been demonstrated, bioequivalency of the suspension compared with the capsule has not been determined.[16]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Oral:	6 weeks:	50 mg PO once daily[2] • on a schedule of 4 weeks on treatment followed by 2 weeks off • may be taken with or without food • daily doses should not exceed 50 mg nor be decreased below 25 mg, except in the case of interactions • dose modification by 12.5 mg increments is recommended based on individual safety and tolerability • for patients unable to swallow the capsules, see additional information in **Supply and Storage**
	continuously:	37.5 mg PO once daily[17,18]
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	dosage adjustment is not required for starting doses in mild to severe impairment[3,19]; modifications for subsequent doses should be based on tolerability[3]	
Dosage in hepatic failure:	dosage adjustment is not required for starting doses in mild to moderate impairment[3,20]; modifications for subsequent doses should be based on tolerability[3]	
Dosage in dialysis:	dosage adjustment is not required for starting doses in end-stage renal disease on dialysis[3,19]; modifications for subsequent doses should be based on tolerability[3]	

Children:

Oral: safety and effectiveness not established in children[2]

REFERENCES:

1. Faivre S, Delbaldo C, Vera K, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 2006;24(1):25-35.
2. Pfizer Canada Inc. SUTENT® product monograph. Kirkland, Quebec; 16 August 2006.
3. Pfizer Canada Inc. SUTENT® product monograph. Kirkland, Quebec; 9 August 2011.
4. Annamaria Crisan. Medical Information. Pfizer Canada Inc. Personal communication. Reports of Osteonecrosis; 19 August 2011.
5. Koch FP, Walter C, Hansen T, et al. Osteonecrosis of the jaw related to sunitinib. Oral Maxillofac Surg 2011;15:63-66.
6. Christodoulou C, Pervena A, Klouvas G, et al. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. Oncology 2009;76:209-211.
7. Bozas G, Allgar V, Greenwood G, et al. Osteonecrosis of the jaw in patients treated with sunitinib and zoledronic acid. J Clin Oncol 2011;15 ASCO Annual Meeting Proceedings (Post-Meeting Edition)(May 20 supplement):abstract e15116.
8. Pfizer Labs. SUTENT® product monograph. New York, New York; January 2006.
9. Christian Kollmannsberger MD. Personal communication. BCCA Genitourinary Tumour Group; 06 December 2006.
10. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368(9544):1329-38.
11. Rose BD editor. Sunitinib: Drug information. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 14.3; 2006.
12. Desai J, Yassa L, Marqusee E, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med 2006;145(9):660-4.
13. Schoeffski P, Wolter P, Himpe U, et al. Sunitinib-related thyroid dysfunction: A single-center retrospective and prospective evaluation. J Clin Oncol (Meeting Abstracts) 2006;24(18_suppl):3092.
14. Pfizer Canada Inc. Health Canada Endorsed Important Safety Information on SUTENT® (sunitinib malate) Capsules - Association of SUTENT® (sunitinib malate) with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Health Canada, 6 September 2013. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/. Accessed 10 September 2013.
15. Pfizer Canada Inc. SUTENT® product monograph. Kirkland, Quebec; 29 July 2013.
16. Navid F, Christensen R, Minkin P, et al. Stability of Sunitinib in Oral Suspension. Ann Pharmacother 2008;42(7):962-966.
17. De Mulder PH, Roigas J, Gillessen S, et al. A phase II study of sunitinib administered in a continuous daily regimen in patients with cytokine-refractory metastatic renal cell carcinoma (mRCC). J Clin Oncol (Meeting Abstracts) 2006;24(18_suppl):4529.
18. George S, Casali PG, Blay J, et al. Phase II study of sunitinib administered in a continuous daily dosing regimen in patients (pts) with advanced GIST. J Clin Oncol (Meeting Abstracts) 2006;24(18_suppl):9532.
19. Khosravan R, Toh M, Garrett M, et al. Pharmacokinetics and safety of sunitinib maleate in subjects with impaired renal function. J Clin Pharmacol 2010;50:472-481.
20. Bello CL, Garrett M, Sherman L, et al. Pharmacokinetics of sunitinib malate in subjects with hepatic impairment. Cancer Chemother Pharmacol 2010;66:699-707.