



MEDICAL NECESSITY REVIEW CRITERIA

BRAND NAME: **Sutent**
(Generic) (Sunitinib)

DESCRIPTION:

Sunitinib (SU11248) is an oral, multi-targeted tyrosine kinase inhibitor with anti-angiogenic and anti-tumor activities due to selective inhibition of several receptor tyrosine kinases (RTK).

MECHANISM OF ACTION:

Activation of gene pathways by hypoxia, such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), are common in solid tumors. These genes are implicated in tumor angiogenesis and proliferation.

In renal cell cancer, nearly 40% of patients have alteration of the von-Hippel Lindau (VHL) gene, a tumor suppressor gene. Changes in the VHL may increase the expression of VEGF, which promotes tumor vascularization and promotes proliferation. Suppression of this gene leads to upregulation of a number of hypoxia-induced genes including VEGF and PDGF. Transforming growth factor- α (TGF α) is also regulated by the VHL gene; TGF α acts as a ligand for EGF receptor and stimulates the growth of epithelial cells of the proximal renal tubule, where most renal cell cancers appear to start.

INDICATIONS:

- For the treatment of advanced renal cell cancer
- For the treatment of gastrointestinal stromal tumors (GIST) after disease progression on or intolerance to imatinib

ADVERSE REACTIONS:

Bleeding is one of the most common adverse events to sunitinib. Tumor-related hemorrhage has been observed in patients treated with sunitinib. Grade 3 and 4 neutropenia and febrile neutropenia have also been reported.

Hypertension (all grades) was reported in up to 28% of patients participating in clinical trials.

Left ventricular dysfunction resulting in congestive heart failure (CHF) has been reported in patients receiving sunitinib during clinical trials. Decreased left ventricular ejection fraction (LVEF) to below the lower limit of normal was reported in 22 sunitinib-treated patients (15%) in metastatic renal cell carcinoma trials (MRCC) and 22 sunitinib-treated patients (11%) in a gastrointestinal stromal tumors (GIST) randomized trial.

Gastrointestinal adverse events were reported during clinical trials in patients treated with sunitinib with the most common GI effects being diarrhea, and dysgeusia (taste alteration). Other GI effects include anorexia, nausea/vomiting, mucositis/stomatitis/oral ulceration, constipation, and abdominal pain.

Dermatologic adverse events seen during clinical trials include rash (unspecified), yellow skin discoloration, palmar-plantar erythrodysesthesia (hand and foot syndrome), hair discoloration (gray coloration) and alopecia.

Please review the prescribing information for addition adverse effects noted in clinical trials.

DOSING:

The recommended dose of Sutent in the treatment of GIST and advanced RCC is one 50-mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off. Sutent may be taken with or without food.

Dose Modification

Strong CYP3A4 inhibitors such as ketoconazole may **increase** Sutent plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for Sutent to a minimum of 37.5 mg daily should be considered if Sutent must be co-administered with a strong CYP3A4 inhibitor.

CYP3A4 inducers such as rifampin may **decrease** Sutent plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. A dose increase for Sutent to a maximum of 87.5 mg daily should be considered if Sutent must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity. St. John's Wort may decrease Sutent plasma concentrations unpredictably. Patients receiving Sutent should not take St. John's Wort concomitantly.

DRUG INTERACTIONS:

Concurrent administration of sunitinib with potent inhibitors of cytochrome P450 (CYP) 3A4 results in increased concentrations of sunitinib and its primary active metabolite. Whenever possible selection of an alternative concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction should be considered when sunitinib must be administered concurrently with ketoconazole, itraconazole, clarithromycin, atazanavir, amprenavir, fosamprenavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole.

Other CYP3A4 inhibitors that may cause increased concentrations of sunitinib and increase the risk of toxicity include amiodarone, aprepitant, chloramphenicol, conivaptan, cyclosporine, dalfopristin; quinupristin, danazol, delavirdine, diltiazem, efavirenz, erythromycin, fluconazole, fluvoxamine, isoniazid, INH, mifepristone, RU-486, nicardipine, tipranavir, troleandomycin, verapamil, and zafirlukast.

Food that contains grapefruit juice may also increase sunitinib plasma concentrations.

Concurrent administration of sunitinib with potent inducers of cytochrome P450 (CYP) 3A4 results in decreased concentrations of sunitinib and its primary active metabolite. Whenever possible selection of an alternative concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose increase should be considered when sunitinib must be administered concurrently with dexamethasone, phenytoin/fosphenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort.

St. John's Wort may decrease sunitinib plasma concentrations unpredictably; concurrent administration of sunitinib and St. John's Wort is not recommended. Other CYP3A4 inducers that may cause decreased concentrations and, hence, decreased efficacy of sunitinib include aminoglutethimide, other barbiturates, bosentan, efavirenz, griseofulvin, modafinil, nevirapine, and oxcarbazepine.

CRITERIA FOR APPROVAL

- Member presents with a diagnosis of advanced renal cell carcinoma or
- Member presents with a diagnosis of gastrointestinal stromal tumor (GIST) and has demonstrated disease progression despite treatment with imatinib or has demonstrated intolerance to imatinib (Gleevec).
- *Medication is prescribed by a physician with a specialty in oncology.*

LENGTH OF APPROVAL:

As requested by the provider, but not to exceed 6 months.

RENEWAL OF BENEFIT:

Continued approval will be based on documentation relating to the patient's clinical response to therapy including but not limited to the status of disease progression as demonstrated by CT or MRI studies (lack of appearance of new lesions, lack of growth of existing lesions).

REFERENCES

Clinical Pharmacology, Gold Standard Multimedia, ©2006; Sunitinib;
<http://cp.gsm.com/apps/default.asp?a=522605&b=1&c=11&sitecode=1&g=0&o=1&p=0&ppda=0&calc=0>

Sutent; prescribing information

http://www.pfizer.com/pfizer/download/uspi_sutent.pdf