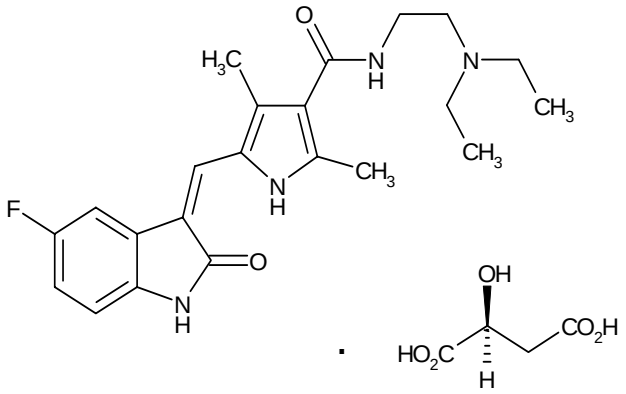
SUTENT® (SUNITINIB MALATE) CAPSULES

DESCRIPTION

SUTENT®, an oral multi-kinase inhibitor targeting several receptor tyrosine kinases (RTK), is the malate salt of sunitinib. Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S)-, compound with *N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-*3H*-indol-3-ylidine)methyl]-2,4-dimethyl-*1H*-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$ and the molecular weight is 532.6 Daltons. The chemical structure of sunitinib malate is:



Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2.

SUTENT (sunitinib malate) capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

The orange gelatin capsule shells contain titanium dioxide, and red iron oxide. The caramel gelatin capsule shells also contain yellow iron oxide and black iron oxide. The printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Sunitinib malate is a small molecule that inhibits multiple RTKs, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an 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 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the

activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets *in vivo* and demonstrated inhibition of tumor growth or tumor regression and/or inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) *in vitro* and to inhibit PDGFRβ- and VEGFR2-dependent tumor angiogenesis *in vivo*.

Pharmacokinetics

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and in 266 patients with solid tumors.

Absorption, Distribution, Metabolism, and Elimination

Maximum plasma concentrations (C_{max}) of sunitinib are generally observed between 6 and 12 hours (T_{max}) following oral administration. Food has no effect on the bioavailability of sunitinib. Sunitinib may be taken with or without food.

Binding of sunitinib and its primary metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no concentration dependence in the range of 100 – 4000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was 2230 L. In the dosing range of 25 - 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionately with dose.

Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23 to 37% of the total exposure. Elimination is primarily via feces. In a human mass balance study of [^{14}C] sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/hr with an inter-patient variability of 40%.

Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite ranged from 62.9 – 101 ng/mL. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

The pharmacokinetics were similar in healthy volunteers and in the solid tumor patient populations tested, including patients with gastrointestinal stromal tumor (GIST) and metastatic renal cell carcinoma (MRCC) (see CLINICAL STUDIES).

Special Populations

Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, race, gender or ECOG score on the pharmacokinetics of SUTENT or the active metabolite.

The pharmacokinetics of sunitinib have not been evaluated in pediatric patients.

Hepatic Insufficiency

No clinical studies were conducted in patients with impaired hepatic function. Studies that were conducted excluded patients with ALT or AST > 2.5 x ULN or, if due to underlying disease, > 5.0 x ULN.

Renal Insufficiency

No clinical studies were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in patients with calculated creatinine clearances in the range of 42 –347 mL/min.

Drug-Drug Interactions

In vitro studies indicate that sunitinib does not induce or inhibit major CYP enzymes.

***In Vitro Studies of CYP Inhibition and Induction*:** The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

CYP3A4 Inhibitors: Concurrent administration of sunitinib malate with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib malate in healthy volunteers. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors (see DOSAGE AND ADMINISTRATION).

CYP3A4 Inducers: Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers (see DOSAGE AND ADMINISTRATION).

CLINICAL STUDIES

The clinical safety and efficacy of SUTENT have been studied in patients with gastrointestinal stromal tumor (GIST) after progression on or intolerance to imatinib mesylate, and in patients with metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy.

Gastrointestinal Stromal Tumor (GIST)

Study A

Study A was a two-arm, international, randomized, double-blind, placebo-controlled trial of SUTENT in patients with GIST who had disease progression during prior imatinib mesylate (imatinib) treatment or who were intolerant of imatinib. The primary objective was to compare time-to-tumor progression (TTP) in patients receiving SUTENT plus best supportive care versus patients receiving placebo plus best supportive care. Secondary objectives included progression-free survival (PFS), objective response rate (ORR), and overall survival (OS). Patients were randomized (2:1) to receive either 50 mg SUTENT or placebo orally, once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) until disease progression or withdrawal from the study for another reason. Treatment was unblinded at the time of disease progression. Patients randomized to placebo were then offered crossover to open-label SUTENT, and patients randomized to SUTENT were permitted to continue treatment per investigator judgment.

The intent-to-treat (ITT) population included 312 patients. Two-hundred seven patients were randomized to the SUTENT arm, and 105 patients were randomized to the placebo arm. Baseline age, gender, race and ECOG performance status were comparable between the placebo and SUTENT groups. Prior exposure to imatinib was similar between the two study arms. Demographics and patient characteristics are shown in Table 1.

Table 1. Baseline Demographics in Study A

	SUTENT (N=207)	Placebo (N=105)
Gender [N (%)]		
Male	132 (64)	64 (61)
Female	75 (36)	41 (39)
Self-identified Race [N (%)]		
White	183 (88)	92 (88)
Asian	10 (5)	5 (5)
Black	8 (4)	4 (4)
Not reported	6 (3)	4 (4)
Age Group [N (%)]		
< 65 years	143 (69)	76 (72)
≥ 65 years	64 (31)	29 (28)
Performance Status [N (%)]		
0	92 (44)	48 (46)
1	113 (55)	55 (52)
2	2 (1)	2 (2)
Prior Treatment [N (%)]		
Surgery (other than biopsy)	194 (94)	98 (93)
Radiotherapy	16 (8)	16 (15)
Imatinib outcome [N (%)]		
Intolerance	9 (4)	4 (4)
Progression within 6 months	36 (17)	17 (16)
Progression beyond 6 months	162 (78)	84 (80)

A planned interim efficacy and safety analysis was performed after 149 TTP events had occurred. There was a statistically significant advantage for SUTENT over placebo in the primary endpoint of TTP, as well as in the secondary endpoint of progression-free survival. Data were not mature enough to determine the overall survival benefit. Efficacy results are summarized in Table 2.

Table 2. GIST Efficacy Results (interim analysis)

Efficacy Parameter	Study A			
	SUTENT (N = 207)	Placebo (N = 105)	P-value (log-rank test)	HR (95% CI)
Time to Tumor Progression[a] [median, weeks (95% CI)]	27.3 (16.0, 32.1)	6.4 (4.4, 10.0)	<0.0001*	0.33 (0.23, 0.47)
Progression Free Survival[b] [median, weeks (95% CI)]	24.1 (11.1, 28.3)	6.0 (4.4, 9.9)	<0.0001*	0.33 (0.24, 0.47)
Objective Response Rate (PR) [%, (95% CI)]	6.8 (3.7, 11.1)	0	0.006[c]	

CI=Confidence interval, HR=Hazard ratio, PR=Partial response

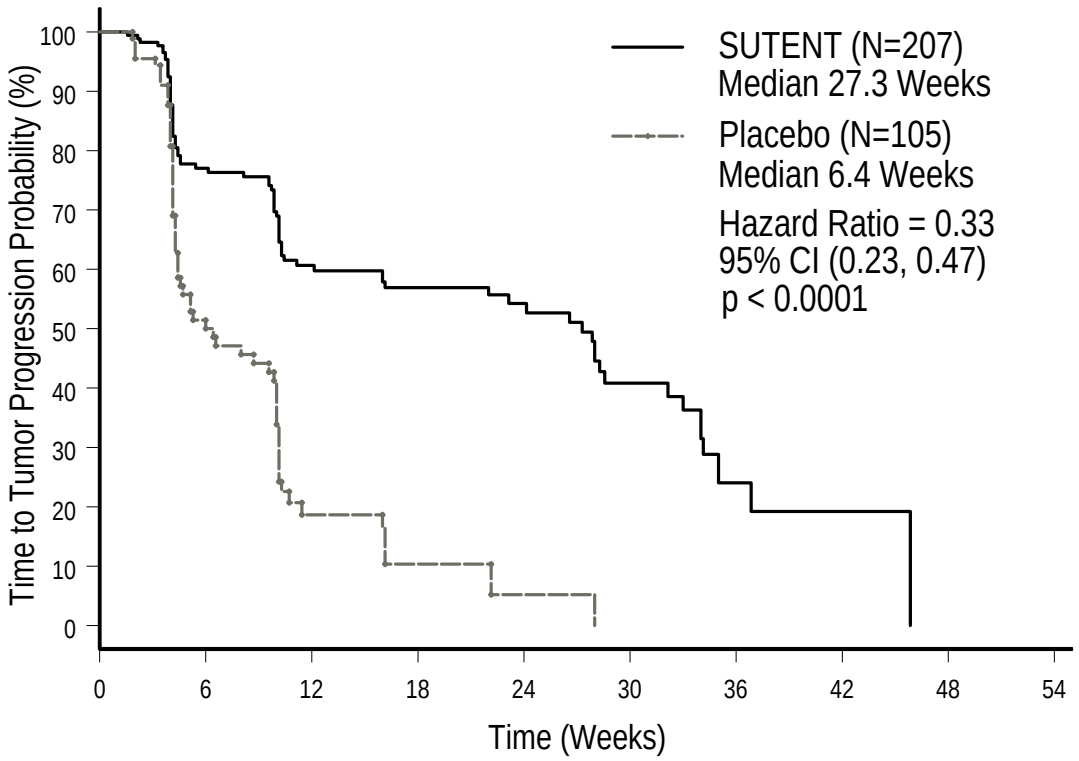
* A comparison is considered statistically significant if the p-value is < 0.0042 (O'Brien Fleming stopping boundary)

[a] Time from randomization to progression; deaths prior to documented progression were censored at time of last radiographic evaluation

[b] Time from randomization to progression or death due to any cause

[c] Pearson chi-square test

Figure 1. Kaplan-Meier Curve of TTP in Study A (Intent-to-Treat Population)



Study B

Study B was an open-label, multi-center, single-arm, dose-escalation study conducted in patients with GIST following progression on or intolerance to imatinib. Following identification of the recommended Phase 2 regimen (50 mg once daily on Schedule 4/2), 55 patients in this study received the 50 mg dose of SUTENT on treatment Schedule 4/2. Partial responses were observed in 5 of 55 patients [9.1% PR rate, 95% CI (3.0, 20.0)].

Metastatic Renal Cell Carcinoma (MRCC)

The use of single agent SUTENT in the treatment of cytokine-refractory MRCC was investigated in two single-arm, multi-center studies. All patients enrolled into these studies experienced failure of prior cytokine-based therapy. In Study 1, failure of prior cytokine therapy was based on radiographic evidence of disease progression defined by RECIST or World Health Organization (WHO) criteria during or within 9 months of completion of 1 cytokine therapy treatment (interferon-α, interleukin-2, or interferon-α plus interleukin-2; patients who were treated with interferon-α alone must have received treatment for at least 28 days). In Study 2, failure of prior cytokine therapy was defined as disease progression or unacceptable treatment-related toxicity. The primary endpoint for both studies was ORR. Duration of response (DR) was also evaluated.

One hundred six patients were enrolled into Study 1, and 63 patients were enrolled into Study 2. Patients received 50 mg SUTENT on Schedule 4/2. Therapy was continued until the patients met withdrawal criteria or had progressive disease. The baseline age, gender, race and ECOG performance statuses of the patients were comparable between Studies 1 and 2. Approximately 86-94% of patients in the two studies were white. Men comprised 65% of the pooled SUTENT population. The median age was 57 years and ranged from 24 to 87 years in the studies. All patients had an ECOG performance status <2 at the screening visit.

The baseline malignancy and prior treatment history of the patients were comparable between Studies 1 and 2. Across the two studies, 95% of the pooled population of patients had at least some component of clear-cell histology. All patients in Study 1 were required to have a histological clear-cell component. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in Study 1. All patients had received one previous cytokine regimen. Metastatic disease present at the time of study entry included lung metastases in 81% of patients. Liver metastases were more common in Study 1 (27% vs. 16% in Study 2) and bone metastases were more common in Study 2 (51% vs. 25% in Study 1); 52% of patients in the pooled population had at least 3 metastatic sites. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

Results of Studies 1 and 2

The ORR and DR data from Studies 1 and 2 are provided in Table 3.

Table 3. MRCC Efficacy Results

Efficacy Parameter	**Study 1 (N = 106)**	**Study 2 (N = 63)**
Objective Response Rate (PR) [%, (95% CI)]	25.5[1] (17.5, 34.9)	36.5[2] (24.7, 49.6)
Duration of Response [median, weeks (95% CI)]	27.1(24.4, *)	54 (34.3, 70.1)

CI=Confidence interval, PR=Partial response
[1] Assessed by blinded core radiology laboratory
[2] Assessed by investigators
* Data not mature enough to determine upper confidence limit

There were 27 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 25.5% (95% CI 17.5, 34.9). There were 23 PRs in Study 2 as assessed by the investigators for an ORR of 36.5% (95% CI 24.7-49.6). The majority (>90%) of objective disease responses were observed during the first four cycles; the latest reported response was observed in cycle 10. DR data from Study 1 is premature as only 4 of 27 patients (15%) responding to treatment had experienced disease progression. At the time of the data cutoff, Study 1 was ongoing with 44 of 106 patients (41.5%) continuing treatment, and 11 of the 63 patients (17.5%) enrolled on Study 2 continued to receive SUTENT on continuation protocols.

INDICATIONS AND USAGE

SUTENT is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

SUTENT is indicated for the treatment of advanced renal cell carcinoma. Approval for advanced renal cell carcinoma is based on partial response rates and duration of responses. There are no randomized trials of SUTENT demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in renal cell carcinoma.

CONTRAINDICATIONS

Use of SUTENT is contraindicated in patients with hypersensitivity to sunitinib malate or to any other component of SUTENT.

WARNINGS

Pregnancy Category D

Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤ 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

PRECAUTIONS

Adverse events described in the following sections for MRCC patients are derived from Study 1 and Study 2. Adverse events discussed for GIST patients are derived from Study A, the randomized, placebo-controlled trial.

Left Ventricular Dysfunction

In the two MRCC studies, twenty-five patients (15%) had decreases in left ventricular ejection fraction (LVEF) to below the lower limit of normal (LLN). In GIST Study A, 22 patients (11%) on SUTENT and 3 patients (3%) on placebo had treatment-emergent LVEF values below the LLN. Nine of twenty-two GIST patients on SUTENT with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction- 1 patient; addition of antihypertensive or diuretic medications- 4 patients). Six patients went off study without documented recovery. Additionally, three patients (1%) on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF < 40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. In GIST Study A, 1 patient (<1%) on SUTENT and 1 patient (1%) on placebo died of diagnosed heart failure; 2 patients (1%) on SUTENT and 2 patients (2%) on placebo died of treatment-emergent cardiac arrest

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

In the presence of clinical manifestations of CHF, discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Hemorrhagic Events

Bleeding events occurred in 44/169 patients (26%) receiving SUTENT for MRCC and 37/202 patients (18%) receiving SUTENT in GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in MRCC or GIST patients included rectal, gingival, upper GI, genital, and wound bleeding. Most events in MRCC patients were Grade 1 or 2; there was one Grade 3 event (bleeding foot wound). In GIST Study A, 14/202 patients (7%) receiving SUTENT and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in Study A taking placebo had a fatal gastrointestinal bleeding event during cycle 2.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life threatening hemoptysis or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC. Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5 of 202 patients (3%) with GIST receiving SUTENT on Study A. Tumor hemorrhages were observed as early as cycle 1 and as late as cycle 6. One of these five patients received no further drug following tumor hemorrhage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the Study A placebo arm were observed to undergo intratumoral hemorrhage. Tumor hemorrhage has not been observed in patients with MRCC. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

Hypertension

Hypertension (all grades) was reported in 48/169 MRCC patients (28%), 31/202 GIST patients on SUTENT (15%), and 11/102 GIST patients on placebo (11%). Grade 3 hypertension was reported in 10 MRCC patients (6%), 9 GIST patients on SUTENT (4%), and none of the GIST patients on placebo. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 6/169 MRCC patients (4%) and none of the patients in GIST Study A. No patients were discontinued from treatment with SUTENT due to systemic hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 10/169 MRCC patients (6%), 8/202 GIST patients on SUTENT (4%), and 1/102 GIST patients on placebo (1%).

Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

Adrenal Function

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of

12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Information for Patients

Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

Skin discoloration possibly due to the drug color (yellow) occurred in approximately 1/3 of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet.

Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements (see Drug Interactions).

Laboratory Tests

CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

Drug Interactions

Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconizole) may increases sunitinib concentrations. Grapefruit may also increase plasma concentrations of SUTENT (see CLINICAL PHARMACOLOGY). Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations (see CLINICAL PHARMACOLOGY). St. John's Wort may decrease SUTENT plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. SUTENT dose modification is recommended in patients using concomitant CYP3A4 inhibitors or inducers (see DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with sunitinib have not been performed.

Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (approximately 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6 mg/kg dose produced a mean AUC that was approximately 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day [(0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was approximately 5 times the AUC in patients administered the RDD], however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10-mg/kg/day dose produced a mean AUC that was approximately 25.8 times the AUC in patients administered the RDD).

Pregnancy Category D: see WARNINGS.

Nursing Mothers

Sunitinib and/or its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether SUTENT or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking SUTENT.

Pediatric Use

The safety and efficacy of SUTENT in pediatric patients have not been studied in clinical trials.

Physeal dysplasia was observed in Cynomolgus monkeys with open growth plates treated for ≥ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were > 0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5,

and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at > 5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment however findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤ 2 mg/kg/day.

Geriatric Use

Of the 450 patients with solid tumors reported from clinical studies of SUTENT, 115 (25.6%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

ADVERSE REACTIONS

Overview

Four hundred fifty (450) patients with solid tumors including 257 patients (57%) with GIST and 169 patients (38%) with cytokine-refractory MRCC have been treated in 7 completed non-randomized, open-label, single arm clinical trials and 1 randomized, double-blind, placebo-controlled clinical trial. All patients received SUTENT once daily as a 50-mg oral capsule on Schedule 4/2 (see CLINICAL STUDIES). One hundred two (102) patients received placebo in the randomized, double-blind, placebo-controlled clinical trial conducted in patients with GIST.

Adverse events occurring in GIST and MRCC studies are described below.

Adverse Events in GIST Study A

Median duration of blinded study treatment was two cycles for patients on SUTENT (mean 3.0, range 1-9) and one cycle (mean 1.8, range 1-6) for patients on placebo. Dose reductions occurred in 23 patients (11%) on SUTENT and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUTENT and 31 patients (30%) on placebo. The rates of treatment-emergent, non-fatal adverse events resulting in permanent discontinuation were 7% and 6% in the SUTENT and placebo groups, respectively.

Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 56% vs. 51% of patients on SUTENT versus placebo, respectively. Diarrhea, hypertension, bleeding, mucositis, skin abnormalities, and altered taste were more common in patients receiving SUTENT. Table 4 compares the incidence of common (>10%) treatment-emergent adverse events for patients receiving SUTENT versus those on placebo.

Table 4. Treatment-Emergent Adverse Events Reported in at Least 10% of GIST Patients Who Received SUTENT or Placebo in Study A*

	GIST			
	SUTENT (n=202)		Placebo (n=102)	
Adverse Event, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any		114 (56)		52 (51)
Constitutional				
Fatigue	84 (42)	17 (8)	48 (47)	8 (8)
Fever	36 (18)	3 (2)	17 (17)	1 (1)
Gastrointestinal				
Diarrhea	81 (40)	9 (4)	27 (27)	0 (0)
Nausea	63 (31)	3 (2)	33 (32)	5 (5)
Mucositis/stomatitis	58 (29)	2 (1)	18 (18)	2 (2)
Vomiting	49 (24)	4 (2)	24 (24)	3 (3)
Constipation	41 (20)	0 (0)	14 (14)	2 (2)
Abdominal pain[c]	67 (33)	22 (11)	39 (38)	12 (12)
Cardiac				
Hypertension	31 (15)	9 (4)	11 (11)	0 (0)
Dermatology				
Rash	28 (14)	2 (1)	9 (9)	0 (0)
Skin Discoloration	61 (30)	0 (0)	23 (23)	0 (0)
Hand-foot syndrome	28 (14)	9 (4)	10 (10)	3 (3)
Neurology				
Altered taste	42 (21)	0 (0)	12 (12)	0 (0)
Headache	26 (13)	3 (2)	23 (23)	0 (0)
Musculoskeletal				
Arthralgia	24 (12)	2 (1)	16 (16)	0 (0)
Back pain	23 (11)	2 (1)	16 (16)	4 (4)
Myalgia/limb pain	28 (14)	1 (1)	9 (9)	1 (1)
Respiratory				
Dyspnea	20 (10)	0 (0)	19 (19)	3 (3)
Cough	17 (8)	0 (0)	13 (13)	0 (0)
Metabolism/Nutrition				
Anorexia[d]	67 (33)	1 (1)	30 (29)	5 (5)
Asthenia	45 (22)	10 (5)	11 (11)	3 (3)
Hemorrhage/bleeding				
Bleeding, all sites	37 (18)	14 (7)	17 (17)	9 (9)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

[a] Grade 4 AEs in patient on SUTENT included abdominal pain (2%) and bleeding (2%).

[b] Grade 4 AEs in patients on placebo included fatigue (3%), mucositis (1%), vomiting (1%), abdominal pain (3%), back pain (1%), and bone pain (1%).

[c] Includes abdominal quadrant, gastric, hypochondrial, abdominal, flank, and cancer-related pain

[d] Includes decreased appetite

Oral pain other than mucositis/stomatitis occurred in 12 patients (6%) on SUTENT versus 3 (3%) on placebo. Hair color changes occurred in 15 patients (7%) on SUTENT versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on SUTENT versus 2 (2%) on placebo.

Table 5 provides common (≥10%) treatment-emergent laboratory abnormalities.

Table 5. Treatment-Emergent Laboratory Abnormalities (≥10%) from Study A*

	SUTENT (n=202)		Placebo (n=102)	
Adverse Event, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any		68 (34)		22 (22)
Gastrointestinal				
AST / ALT	78 (39)	3 (2)	23 (23)	1 (1)
Alkaline phosphatase	48 (24)	7 (4)	21 (21)	4 (4)
Total Bilirubin	32 (16)	2 (1)	8 (8)	0 (0)
Indirect Bilirubin	20 (10)	0 (0)	4 (4)	0 (0)
Amylase	35 (17)	10 (5)	12 (12)	3 (3)
Lipase	50 (25)	20 (10)	17 (17)	7 (7)
Cardiac				
Decreased LVEF	21 (10)	2 (1)	3 (3)	0 (0)
Renal / Metabolic				
Creatinine	25 (12)	1 (1)	7 (7)	0 (0)
Hypokalemia	24 (12)	1 (1)	4 (4)	0 (0)
Hypernatremia	20 (10)	0 (0)	4 (4)	1 (1)
Uric acid	31 (15)	16 (8)	16 (16)	8 (8)
Hematology				
Neutropenia	107 (53)	20 (10)	4 (4)	0 (0)
Lymphopenia	76 (38)	0 (0)	16 (16)	0 (0)
Anemia	52 (26)	6 (3)	22 (22)	2 (2)
Thrombocytopenia	76 (38)	10 (5)	4 (4)	0 (0)

*Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

[a] Grade 4 AEs in patients on SUTENT included alkaline phosphatase (1%), lipase (2%), creatinine (1%), hypokalemia (1%), neutropenia (2%), anemia (2%), and thrombocytopenia (1%).

[b] Grade 4 AEs in patients on placebo included amylase (1%), lipase (1%), anemia (2%), and thrombocytopenia (1%).

Grade 3 or 4 treatment-emergent laboratory abnormalities were observed in 68 (34%) versus 22 (22%) patients on SUTENT and placebo, respectively. Elevated liver function tests, pancreatic enzymes, and creatinine were more common in patients treated with SUTENT than placebo. Decreased LVEF and myelosuppression were also more common with SUTENT treatment. Treatment-emergent electrolyte disturbances of all types were more common in patients on SUTENT than on placebo, including hyperkalemia (6% vs. 4%), hypokalemia (12% vs. 4%), hypernatremia (10% vs. 4%), hyponatremia (6% vs. 1%), and hypophosphatemia (9% vs. 0%). Three SUTENT patients (1.5%) had Grade 3 hypophosphatemia. Acquired hypothyroidism was noted in 8 patients (4%) on SUTENT versus 1 (1%) on placebo.

Adverse Events in the MRCC Studies

The data described below reflect exposure to SUTENT in 169 patients with MRCC enrolled in Studies 1 and 2. The median duration of treatment was 5.5 months (range: 0.8-11.2) for Study 1 and 7.7 months (range: 0.2-16.1) for Study 2. Dose interruptions occurred in 48 patients (45%) on Study 1 and 45 patients (71%) on Study 2; one or more dose reductions occurred in 23 patients (22%) on Study 1 and 22 patients (35%) on Study 2. Table 6 summarizes treatment emergent adverse events for at least 10 % of all patients with MRCC who received at least one 50-mg dose of SUTENT. Hematology laboratory abnormalities are presented separately, in Table 7.

Table 6. Treatment-Emergent Adverse Events Reported in at Least 10% of MRCC Patients Treated with SUTENT*

	MRCC (N=169)	
Adverse Event, n (%)	**All Grades**	**Grade 3****
Any	169 (100)	123 (73)
Constitutional		
Fatigue	125 (74)	19 (11)
Fever	26 (15)	2 (1)
Gastrointestinal		
Diarrhea	93 (55)	8 (5)
Nausea	92 (54)	4 (2)
Mucositis/stomatitis	90 (53)	7 (4)
Dyspepsia	77 (46)	1 (1)
Vomiting	63 (37)	7 (4)
Constipation	57 (34)	1 (1)
Abdominal pain	34 (20)	5 (3)
Glossodynia	25 (15)	0 (0)
Flatulence	24 (14)	0 (0)
Cardiac		
Hypertension	48 (28)	10 (6)
Edema, peripheral	28 (17)	1 (1)
Dermatology		
Rash	64 (38)	1 (1)
Skin Discoloration	55 (33)	0 (0)
Dry skin	29 (17)	0 (0)
Hair color changes	29 (17)	0 (0)
Hand-foot syndrome	21 (12)	5 (3)
Alopecia	20 (12)	0 (0)
Neurology		
Altered taste	73 (43)	0 (0)
Headache	43 (25)	2 (1)
Dizziness	27 (16)	3 (2)
Musculoskeletal		
Arthralgia	48 (28)	2 (1)
Pain in limb	31 (18)	1 (1)
Back pain	29 (17)	1 (1)
Myalgia	29 (17)	1 (1)
Respiratory		
Dyspnea	47 (28)	8 (5)
Cough	29 (17)	1 (1)
Metabolism/Nutrition		
Anorexia	53 (31)	1 (1)
Dehydration	19 (11)	5 (3)
Hemorrhage/bleeding		
Bleeding, all sites	44 (26)	1 (1)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

** There were no Grade 4 adverse events among the events reported with a ≥10% incidence in the MRCC population.

Other significant adverse events occurring in MRCC patients receiving SUTENT included peripheral neuropathy (10%), appetite disturbance (9%), blistering of the skin (7%), periorbital edema (7%) and increased lacrimation (6%).

Table 7. Treatment-Emergent Grade 3 and 4 Hematology Laboratory Abnormalities* from Studies 1 and 2

Laboratory Test	Unit	MRCC (N=169)		
		Grade 3	Grade 4	Total (Grade 3 + 4)
Hematology, n (%)		54 (32)	4 (2)	58 (34)
Neutropenia	10^9/L	21 (12)	1 (1)	22 (13)
Anemia	g/L	9 (5)	3 (2)	12 (7)
Lymphopenia	10^9/L	33 (20)	2 (1)	35 (21)
Thrombocytopenia	10^9/L	5 (3)	0 (0)	5 (3)
Leukopenia	10^9/L	12 (7)	0 (0)	12 (7)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

Common treatment-emergent Grade 3 and 4 chemistry laboratory abnormalities in the MRCC studies included increased lipase (16%), increased amylase (5%), hypophosphatemia (10%), and hyperuricemia (10%).

Cardiovascular

See PRECAUTIONS section for information on left ventricular dysfunction.

Two patients with MRCC experienced Grade 3 myocardial ischemia, one had Grade 2 "cardiovascular toxicity" reported as an adverse event and one patient experienced a fatal myocardial infarction while on treatment.

Data from non-clinical (*in vitro* and *in vivo*) studies indicate that sunitinib has the potential to inhibit the cardiac action potential repolarization process (e.g., prolongation of QT interval). In GIST Study A, 23 patients (11%) on SUTENT versus 12 (12%) on placebo had observed QT prolongation greater than 20 milliseconds from baseline. No consistent, clinically significant QTc prolongation has been observed in completed clinical studies.

Venous Thromboembolic Events

Four patients (2%) on the two MRCC studies had venous thromboembolic events reported; two patients with pulmonary embolism (both Grade 4) and two patients with deep venous thrombosis (DVT) (both Grade 3). Dose interruption occurred in one of these cases. Seven patients (3%) on SUTENT and none on placebo in GIST Study A experienced venous thromboembolic events; five of the seven were Grade 3 DVTs, and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Seizures

In clinical studies of SUTENT, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension

of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Laboratory Abnormalities/Testing

Hematologic Events

Grade 3 and 4 neutropenia were reported in 21 (13%) and 1 (1%) patients with MRCC, 19 (9%) and 3 (2%) patients with GIST on SUTENT, respectively. In Study A, one patient each in the SUTENT and placebo groups had febrile neutropenia. Grade 3 and 4 thrombocytopenia was reported in 5 (3%) and 0 patients with MRCC, 7 (4%) and 1 (1%) patients with GIST on SUTENT, respectively. No GIST patients receiving placebo experienced either Grade 3 or 4 neutropenia or thrombocytopenia. The rates of dose reductions and delays for hematologic abnormalities were 4% and 2% for neutropenia, 2% and 0% for anemia, and 1% and 1% for thrombocytopenia for MRCC and GIST patients, respectively. One MRCC patient with an adverse event report of Grade 4 thrombocytopenia discontinued treatment.

Patients receiving SUTENT should be monitored regularly for myelosuppression.

Hypothyroidism

Hypothyroidism was reported as an adverse event in 7 patients (4%) across the two MRCC studies. Additionally, TSH elevations were reported in 4 patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Treatment-emergent acquired hypothyroidism was noted in 8 GIST patients (4%) on SUTENT versus 1 (1%) on placebo.

Patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Pancreatic Function

Grade 3 and 4 increases in serum lipase were observed in 23 (14%) and 4 (2%), respectively, of 169 patients receiving SUTENT for MRCC. Grade 3 and 4 increases in serum amylase were observed in 8 (5%) and 1 (1%) MRCC patients, respectively. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with either MRCC or GIST. Pancreatitis has been observed rarely (<1%) in patients receiving SUTENT for GIST or MRCC. If symptoms of pancreatitis are present, patients should have SUTENT discontinued and be provided with appropriate supportive care.

OVERDOSAGE

No overdose of SUTENT was reported in completed clinical studies. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations. Treatment of

overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage.

DOSAGE AND ADMINISTRATION

The recommended dose of SUTENT for 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

Dose increase or reduction of 12.5-mg increments is recommended based on individual safety and tolerability.

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 (see CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions).

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 (see CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions). St. John's Wort may decrease SUTENT plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly.

HOW SUPPLIED

12.5-mg capsules:

Hard gelatin capsule with orange cap and orange body, printed with white ink "Pfizer" on the cap, "STN 12.5 mg" on the body; available in:
Bottles of 30: NDC 0069-0550-30

25-mg capsules

Hard gelatin capsule with caramel cap and orange body, printed with white ink "Pfizer" on the cap, "STN 25 mg" on the body; available in:
Bottles of 30: NDC 0069-0770-30

50-mg capsules:

Hard gelatin capsule with caramel cap and caramel body, printed with white ink “Pfizer” on the cap, “STN 50 mg” on the body; available in:
Bottles of 30: NDC 0069-0980-30

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rx only

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