HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUTENT safely and effectively. See full prescribing information for SUTENT.

SUTENT® (sunitinib malate) capsules, oral
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage, Advanced Renal Cell Carcinoma (1.2)	2/2007
Warnings and Precautions, Left Ventricular Dysfunction (5.2)	2/2007
Warnings and Precautions, QT Interval Prolongation and Torsade de Pointes (5.3)	2/2007
Warnings and Precautions, Hypertension (5.4)	2/2007
Warnings and Precautions, Hemorrhagic Events (5.5)	2/2007
Warnings and Precautions, Hypothyroidism (5.6)	2/2007

----------INDICATIONS AND USAGE----------

SUTENT is a kinase inhibitor indicated for the treatment of:

- Gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. (1.1)
- Advanced renal cell carcinoma. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off. (2.1)
- Dose adjustments of 12.5 mg recommended based on individual safety and tolerability. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 12.5 mg, 25 mg, 50 mg (3)

----------CONTRAINDICATIONS----------

- None (4)

----------WARNINGS AND PRECAUTIONS----------

- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.1)
- Left ventricular ejection fraction declines to below the lower limit of normal have occurred. Monitor patients for signs and symptoms of congestive heart failure. (5.2)
- Prolonged QT intervals and Torsade de Pointes have been observed. Use with caution in patients at higher risk for developing QT interval prolongation. When using SUTENT, monitoring with on-treatment electrocardiograms and electrolytes should be considered. (5.3)
- Hypertension may occur. Monitor blood pressure and treat as needed. (5.4)
- Hemorrhagic events including tumor-related hemorrhage have occurred. Perform serial complete blood counts and physical examinations. (5.5)
- Hypothyroidism may occur. Patients with signs and symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice. (5.6)
- Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma or severe infection. (5.7)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (≥20%) are fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discoloration, altered taste, anorexia, and bleeding. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- CYP3A4 Inhibitors: Consider dose reduction of SUTENT when administered with strong CYP3A4 inhibitors. (7.1)
- CYP3A4 Inducers: Consider dose increase of SUTENT when administered with CYP3A4 inducers. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

1.1 Gastrointestinal Stromal Tumor

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

1.2 Advanced Renal Cell Carcinoma

SUTENT is indicated for the treatment of advanced renal cell carcinoma.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of SUTENT for gastrointestinal stromal tumor (GIST) and advanced renal cell carcinoma (RCC) is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUTENT may be taken with or without food.

2.2 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** sunitinib 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 Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

CYP3A4 inducers such as rifampin may **decrease** sunitinib 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 Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

12.5 mg capsules
Hard gelatin capsule with orange cap and orange body, printed with white ink "Pfizer" on the cap and "STN 12.5 mg" on the body.

25 mg capsules
Hard gelatin capsule with caramel cap and orange body, printed with white ink "Pfizer" on the cap and "STN 25 mg" on the body.

50 mg capsules
Hard gelatin capsule with caramel top and caramel body, printed with white ink "Pfizer" on the cap and "STN 50 mg" on the body.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pregnancy

Pregnancy Category D

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.

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 [combined AUC of sunitinib + primary active metabolite] 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).

5.2 Left Ventricular Dysfunction

In the presence of clinical manifestations of congestive heart failure (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.

More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving either placebo or interferon-α (IFN-α). In GIST Study A, 22/209 patients (11%) on SUTENT and 3/102 patients (3%) on placebo had treatment-emergent LVEF values below the lower limit of normal (LLN). Nine of 22 GIST patients on SUTENT with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction: one patient; addition of antihypertensive or diuretic medications: four patients). Six patients went off study without documented recovery. Additionally, three patients 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 on SUTENT and 1 patient on placebo died of diagnosed heart failure; 2 patients on SUTENT and 2 patients on placebo died of treatment-emergent cardiac arrest.

In the treatment-naïve MRCC study, 78/375 (21%) and 44/360 (12%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Thirteen patients on SUTENT (4%) and four on IFN-α (1%) experienced declines in LVEF of >20% from baseline and to below 50%. Left ventricular dysfunction was reported in three patients (1%) and CHF in one patient (<1%) who received SUTENT.

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 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.**

5.3 QT Interval Prolongation and Torsade de Pointes

SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.

SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered *[see Dosage and Administration (2.2)]*.

5.4 Hypertension

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.

Of patients receiving SUTENT for treatment-naïve MRCC, 111/375 patients (30%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 36/375 treatment-naïve MRCC patients (10%) on SUTENT compared to 1/360 patient (<1%) on IFN-α. While all-grade hypertension was similar in GIST patients on SUTENT compared to placebo, Grade 3 hypertension was reported in 9/202 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 18/375 patients (5%) on the treatment-naive MRCC study. Two treatment-naïve MRCC patients, including one with malignant hypertension, and no GIST patients discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 8/202 GIST patients on SUTENT (4%), 1/102 GIST patients on placebo (1%), and in 20/375 treatment-naïve MRCC patients (5%) on SUTENT and 2/360 patients (1%) on IFN-α.

5.5 Hemorrhagic Events

In patients receiving SUTENT for treatment-naïve MRCC, 112/375 patients (30%) had bleeding events compared with 27/360 patients (8%) receiving IFN-α. Bleeding events occurred in 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 GIST or MRCC patients included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. 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. Most events in MRCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment-naïve patient.

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 5/202 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.

5.6 Hypothyroidism

Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism should be treated as per standard medical practice prior to the start of SUTENT treatment. All patients should be observed closely for signs and symptoms of hypothyroidism on SUTENT treatment. Patients with signs or symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Treatment-emergent acquired hypothyroidism was noted in eight GIST patients (4%) on SUTENT versus one (1%) on placebo. Hypothyroidism was reported as an adverse reaction in eleven patients (3%) on SUTENT in the treatment-naïve MRCC study and in one patient (<1%) in the IFN-α arm. An additional seven patients (2%) with no prior history of hypothyroidism were started on thyroid replacement therapy while on study.

5.7 Adrenal Function

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

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.

5.8 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.

6 ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 577 patients who participated in a placebo-controlled trial (n=202) for the treatment of GIST or an active-controlled trial (n=375) for the treatment of MRCC. In these two studies, 225 patients were exposed to SUTENT for at least 6 months and 16 were exposed for greater than one year. The population was 23 - 87 years of age and 69% male and 31% female. The race distribution was 92% White, 3% Asian, 2% Black and 3% not reported. The patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.

The most common adverse reactions (≥20%) in patients with GIST or MRCC are fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discoloration, altered taste, anorexia, and bleeding. The potentially serious adverse reactions of left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, and adrenal function are discussed in *Warnings and Precautions (5)*. Other adverse reactions occurring in GIST and MRCC studies are described below.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adverse Reactions 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 reactions resulting in permanent discontinuation were 7% and 6% in the SUTENT and placebo groups, respectively.

Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 56% versus 51% of patients on SUTENT versus placebo, respectively. Table 1 compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT and reported more commonly in patients receiving SUTENT than in patients receiving placebo.

Table 1. Adverse Reactions Reported in Study A in at Least 10% of GIST Patients who Received SUTENT and More Commonly Than in Patients Given Placebo*

Adverse Reaction, n (%)	GIST			
	SUTENT (n=202)		Placebo (n=102)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any		114 (56)		52 (51)
Gastrointestinal				
Diarrhea	81 (40)	9 (4)	27 (27)	0 (0)
Mucositis/stomatitis	58 (29)	2 (1)	18 (18)	2 (2)
Constipation	41 (20)	0 (0)	14 (14)	2 (2)
Cardiac				
Hypertension	31 (15)	9 (4)	11 (11)	0 (0)
Dermatology				
Skin discoloration	61 (30)	0 (0)	23 (23)	0 (0)
Rash	28 (14)	2 (1)	9 (9)	0 (0)
Hand-foot syndrome	28 (14)	9 (4)	10 (10)	3 (3)
Neurology				
Altered taste	42 (21)	0 (0)	12 (12)	0 (0)
Musculoskeletal				
Myalgia/limb pain	28 (14)	1 (1)	9 (9)	1 (1)
Metabolism/Nutrition				
Anorexia[a]	67 (33)	1 (1)	30 (29)	5 (5)
Asthenia	45 (22)	10 (5)	11 (11)	3 (3)

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

[a] 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 2 provides common (≥10%) treatment-emergent laboratory abnormalities.

Table 2. Laboratory Abnormalities Reported in Study A in at Least 10% of GIST Patients Who Received SUTENT or Placebo*

Laboratory Parameter, n (%)	GIST			
	SUTENT (n=202)		Placebo (n=102)	
	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)
Lipase	50 (25)	20 (10)	17 (17)	7 (7)
Alkaline phosphatase	48 (24)	7 (4)	21 (21)	4 (4)
Amylase	35 (17)	10 (5)	12 (12)	3 (3)
Total bilirubin	32 (16)	2 (1)	8 (8)	0 (0)
Indirect bilirubin	20 (10)	0 (0)	4 (4)	0 (0)
Cardiac				
Decreased LVEF	22 (11)	2 (1)	3 (3)	0 (0)
Renal/Metabolic				
Creatinine	25 (12)	1 (1)	7 (7)	0 (0)
Potassium decreased	24 (12)	1 (1)	4 (4)	0 (0)
Sodium increased	20 (10)	0 (0)	4 (4)	1 (1)
Hematology				
Neutrophils	107 (53)	20 (10)	4 (4)	0 (0)
Lymphocytes	76 (38)	0 (0)	16 (16)	0 (0)
Platelets	76 (38)	10 (5)	4 (4)	0 (0)
Hemoglobin	52 (26)	6 (3)	22 (22)	2 (2)

LVEF=Left ventricular ejection fraction

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

[a] Grade 4 laboratory abnormalities in patients on SUTENT included alkaline phosphatase (1%), lipase (2%), creatinine (1%), potassium decreased (1%), neutrophils (2%), hemoglobin (2%), and platelets (1%).

[b] Grade 4 laboratory abnormalities in patients on placebo included amylase (1%), lipase (1%) and hemoglobin (2%).

6.2 Adverse Reactions in the Treatment-Naïve MRCC Study

The as-treated patient population for the interim safety analysis of the treatment-naive MRCC study included 735 patients, 375 randomized to SUTENT and 360 randomized to IFN-α. The median duration of treatment was 5.6 months (range: 0.4-15.6) for SUTENT treatment and 4.1 months (range: 0.1-13.7) on IFN-α treatment. Dose reductions occurred in 121 patients (32%) on SUTENT and 77 patients (21%) on IFN-α. Dose interruptions occurred in 142 patients (38%) on SUTENT and 115 patients (32%) on IFN-α. The rates of treatment-emergent, non-fatal adverse reactions resulting in permanent discontinuation were 9% and 12% in the SUTENT and IFN-α groups, respectively. Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 67% versus 51% of patients on SUTENT versus IFN-α, respectively.

Table 3 compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT versus IFN-α.

Table 3. Adverse Reactions Reported in at Least 10% of Patients with MRCC Who Received SUTENT or IFN-α*

Adverse Reaction, n (%)	Treatment-Naïve MRCC			
	SUTENT (n=375)		IFN-α (n=360)	
	All Grades	Grade 3/4[a]	All Grades	Grade 3/4[b]
Any	370 (99)	250 (67)	354 (98)	184(51)
Constitutional				
Fatigue	218 (58)	35 (9)	199 (55)	50 (14)
Asthenia	79 (21)	27 (7)	85 (24)	20 (6)
Fever	62 (17)	3 (1)	129 (36)	0 (0)
Weight decreased	45 (12)	0 (0)	54 (15)	2 (1)
Chills	42 (11)	3 (1)	108 (30)	0 (0)
Gastrointestinal				
Diarrhea	218 (58)	22 (6)	72 (20)	0 (0)
Nausea	183 (49)	16 (4)	136 (38)	5 (1)
Mucositis/stomatitis	162 (43)	12 (3)	14 (4)	2 (<1)
Vomiting	105 (28)	15 (4)	51 (14)	3 (1)
Dyspepsia	105 (28)	4 (1)	14 (4)	0 (0)
Abdominal pain[c]	83 (22)	10 (3)	42 (12)	5 (1)
Constipation	60 (16)	0 (0)	44 (12)	1 (<1)
Dry mouth	45 (12)	0 (0)	26 (7)	1 (<1)
GERD/reflux esophagitis	42 (11)	0 (0)	3 (1)	0(0)
Flatulence	39 (10)	0 (0)	8 (2)	0 (0)
Oral pain	38 (10)	0 (0)	2 (1)	0 (0)
Glossodynia	37 (10)	0 (0)	2 (1)	0 (0)
Cardiac				
Hypertension	111 (30)	36 (10)	13 (4)	1 (<1)
Edema, peripheral	42 (11)	2 (1)	15 (4)	2 (1)
Dermatology				
Rash	103 (27)	3 (1)	40 (11)	2 (1)
Hand-foot syndrome	78 (21)	20 (5)	3 (1)	0 (0)
Skin discoloration/ yellow skin	72 (19)	0 (0)	0 (0)	0 (0)
Dry skin	67 (18)	1 (<1)	23 (6)	0 (0)
Hair color changes	56 (16)	0 (0)	1 (<1)	0 (0)
Neurology				
Altered taste[d]	166 (44)	1 (<1)	52 (14)	0 (0)
Headache	68 (18)	3 (1)	61 (17)	0 (0)
Dizziness	28 (7)	1 (<1)	42 (12)	1 (<1)
Musculoskeletal				
Back pain	70 (19)	13 (3)	44 (13)	6 (2)
Arthralgia	69 (18)	5 (1)	60 (17)	1 (<1)
Pain in extremity/ limb discomfort	65 (17)	6 (2)	28 (8)	4 (1)
Respiratory				
Cough	64 (18)	2 (1)	45 (12)	0 (0)
Dyspnea	58 (15)	15 (4)	65 (18)	14 (4)
Metabolism/Nutrition				
Anorexia[e]	142 (38)	6 (2)	145 (40)	7 (2)
Dehydration	30 (8)	8 (2)	17 (5)	2 (1)
Hemorrhage/Bleeding				
Bleeding, all sites	112 (30)	10 (3)[f]	27 (8)	2 (1)
Psychiatric				
Insomnia	42 (11)	1 (<1)	31 (9)	0 (0)
Depression[g]	29 (8)	0 (0)	47 (12)	5 (1)

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

[a] Grade 4 ARs in patients on SUTENT included back pain (1%), arthralgia (<1%), asthenia (<1%), dehydration (<1%), fatigue (<1%), limb pain (<1%) and rash (<1%).

[b] Grade 4 ARs in patients on IFN-α included dyspnea (1%), fatigue (1%) and depression (<1%).

[c] Includes flank pain

[d] Includes ageusia, hypogeusia and dysgeusia

[e] Includes decreased appetite

[f] Includes one patient with Grade 5 gastric hemorrhage

[g] Includes depressed mood

Treatment-emergent Grade 3/4 laboratory abnormalities are presented in Table 4.

Table 4. Laboratory Abnormalities Reported in at Least 10% of Treatment-Naïve MRCC Patients Who Received SUTENT or IFN-α

Laboratory Parameter, n (%)	Treatment-Naïve MRCC			
	SUTENT (n=375)		IFN-α (n=360)	
	All Grades*	Grade 3/4*[a]	All Grades*	Grade 3/4*[b]
Gastrointestinal				
AST	195 (52)	6 (2)	124 (34)	6 (2)
ALT	171 (46)	10 (3)	140 (39)	6 (2)
Lipase	196 (52)	60 (16)	153 (43)	23 (6)
Alkaline phosphatase	156 (42)	7 (2)	126 (35)	6 (2)
Amylase	118 (31)	19 (5)	101 (28)	8 (2)
Total bilirubin	72 (19)	3 (1)	6 (2)	0 (0)
Indirect bilirubin	46 (12)	4 (1)	3 (1)	0 (0)
Renal/Metabolic				
Creatinine	246 (66)	1 (<1)	175 (49)	1 (<1)
Uric acid	155 (41)	43 (12)	112 (31)	29 (8)
Creatine kinase	152 (41)	1 (<1)	35 (10)	2 (1)
Phosphorus	134 (36)	17 (5)	115 (32)	22 (6)
Calcium decreased	132 (35)	1 (<1)	133 (37)	0 (0)
Glucose decreased	73 (19)	0 (0)	54 (15)	1 (<1)
Albumin	68 (18)	3 (1)	67 (19)	0 (0)
Glucose increased	58 (15)	10 (3)	49 (14)	20 (6)
Sodium decreased	51 (14)	18 (5)	41 (11)	9 (3)
Potassium increased	42 (11)	7 (2)	54 (15)	13 (4)
Sodium increased	40 (11)	0 (0)	35 (10)	0 (0)
Hematology				
Neutrophils	271 (72)	44 (12)	166 (46)	24 (7)
Hemoglobin	266 (71)	11 (3)	232 (64)	16 (4)
Platelets	244 (65)	30 (8)	77 (21)	0 (0)
Lymphocytes	223 (59)	44 (12)	227 (63)	79 (22)
Leukocytes	292 (78)	19 (5)	202 (56)	8 (2)

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

[a] Grade 4 laboratory abnormalities in patients on SUTENT included uric acid (12%), lipase (3%), amylase (1%), neutrophils (1%), ALT (<1%), calcium decreased (<1%), phosphorous (<1%), potassium increased (<1%), sodium decreased (<1%)and hemoglobin (<1%).

[b] Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (8%), lipase (1%), amylase (<1%), calcium increased (<1%), glucose decreased (<1%), potassium increased (<1%) and hemoglobin (<1%).

6.3 Venous Thromboembolic Events

Seven patients (3%) on SUTENT and none on placebo in GIST Study A experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT), and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Eight (2%) patients receiving SUTENT for treatment-naïve MRCC had venous thromboembolic events reported. Four (1%) of these patients had pulmonary embolism, one was Grade 3 and three were Grade 4, and four (1%) patients had DVT, including one Grade 3. One patient was permanently withdrawn from SUTENT due to pulmonary embolism; dose interruption occurred in two patients with pulmonary embolism and one with DVT. In treatment-naïve MRCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolism, one Grade 1 and four with Grade 4.

6.4 Reversible Posterior Leukoencephalopathy Syndrome

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.

6.5 Pancreatic and Hepatic Function

If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Pancreatitis was observed in 5 (1%) patients receiving SUTENT for treatment-naïve MRCC compared to 1 (<1%) patient receiving IFN-α. Hepatic failure was observed in <1% of solid tumor patients treated with SUTENT.

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT 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 SUTENT in healthy volunteers. Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*.

7.2 CYP3A4 Inducers

CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. 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. 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. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers *[see Dosage and Administration (2.2)]*.

7.3 In Vitro Studies of CYP Inhibition and Induction

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.1)]*.

8.3 Nursing Mothers

Sunitinib and 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 sunitinib 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, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.1)]*.

8.4 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.

8.5 Geriatric Use

Of 825 GIST and MRCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Hepatic Impairment

No dose adjustment is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

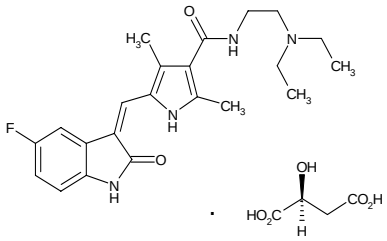
10 OVERDOSAGE

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. 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.

11 DESCRIPTION

SUTENT, an oral multi-kinase inhibitor, 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 $C_{22}H_{27}FN_4O_2 \bullet C_4H_6O_5$ 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (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.*

12.3 Pharmacokinetics

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

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. SUTENT may be taken with or without food.

Binding of sunitinib and its primary active 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 GIST and MRCC.

Pharmacokinetics in 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 primary active metabolite.

Pediatric Use: The pharmacokinetics of SUTENT have not been evaluated in pediatric patients.

Renal Insufficiency: No clinical studies of SUTENT 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.

Hepatic Insufficiency: Systemic exposures after a single dose of SUTENT were similar in subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment compared to subjects with normal hepatic function.

12.4 Cardiac Electrophysiology

See Warnings and Precautions (5.3).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Although definitive carcinogenicity studies with sunitinib have not been performed, carcinoma and hyperplasia of the Brunner's gland of the duodenum have been observed at the highest dose tested in H2ras transgenic mice administered doses of 0, 10, 25, 75, or 200 mg/kg/day for 28 days. 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).

14 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).

14.1 Gastrointestinal Stromal Tumor

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 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. Other 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 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 (207) patients were randomized to the SUTENT arm, and 105 patients were randomized to the placebo arm. Demographics were comparable between the SUTENT and placebo groups with regard to age (69% vs 72% <65 years for SUTENT vs. placebo, respectively), gender (Male: 64% vs. 61%), race (White: (88% both arms, Asian: 5% both arms, Black: 4% both arms, remainder not reported), and Performance Status (ECOG 0: 44% vs. 46%, ECOG 1: 55% vs. 52%, and ECOG 2: 1 vs. 2%). Prior treatment included surgery (94% vs. 93%) and radiotherapy (8% vs. 15%). Outcome of prior imatinib treatment was also comparable between arms with intolerance (4% vs. 4%), progression within 6 months of starting treatment (17% vs. 16%), or progression beyond 6 months (78% vs. 80%) balanced.

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 TTP and progression-free survival. OS data were not mature at the time of the interim analysis. Efficacy results are summarized in Table 5 and the Kaplan-Meier curve for TTP is in Figure 1.

Table 5. GIST Efficacy Results from Study A (interim analysis)

Efficacy Parameter	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

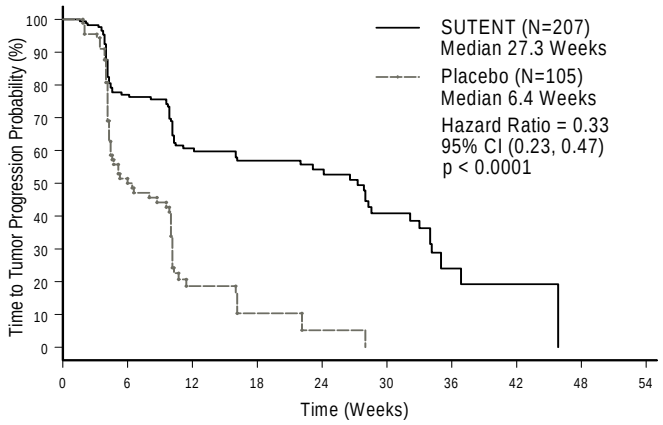
* A comparison is considered statistically significant if the p-value is < 0.0042 (O'Brien Fleming stopping boundary)

[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)].

14.2 Renal Cell Carcinoma

Treatment-Naïve MRCC

A multi-center, international randomized study comparing single-agent SUTENT with IFN-α was conducted in patients with treatment-naïve MRCC. The objective was to compare Progression-Free Survival (PFS) in patients receiving SUTENT versus patients receiving IFN-α. Other endpoints included Objective Response Rate (ORR), Overall Survival (OS) and safety. Seven hundred fifty (750) patients were randomized (1:1) to receive either 50 mg SUTENT once daily on Schedule 4/2 or to receive IFN-α administered subcutaneously at 9 MIU three times a week. Patients were treated until disease progression or withdrawal from the study.

The ITT population for this interim analysis included 750 patients, 375 randomized to SUTENT and 375 randomized to IFN-α. Demographics were comparable between the SUTENT and IFN-α groups with regard to age (59% vs. 67% <65 years for SUTENT vs. IFN-α, respectively), gender (Male: 71% vs. 72%), race (White: 94% vs. 91%, Asian: 2% vs. 3%, Black: 1% vs. 2%, remainder not reported), and Performance Status (ECOG 0: 62% vs. 61%, ECOG 1: 38% each arm, ECOG 2: 0 vs. 1%). Prior treatment included nephrectomy (91% vs. 89%) and radiotherapy (14% each arm). The most common site of metastases present at screening was the lung (78% vs. 80%, respectively), followed by the lymph nodes (58% vs. 53%, respectively) and bone (30% each arm); the majority of the patients had multiple (2 or more) metastatic sites at baseline (80% vs. 77%, respectively).

A planned interim analysis showed a statistically significant advantage for SUTENT over IFN-α in the endpoint of PFS (see Table 6 and Figure 2). In the pre-specified stratification factors of LDH (>1.5 ULN vs. ≤1.5 ULN), ECOG performance status (0 vs. 1), and prior nephrectomy (yes vs. no), the hazard ratio favored SUTENT over IFN-α. The ORR was higher in the SUTENT arm (see Table 6). OS data were not mature at the time of the interim analysis.

Table 6. Treatment-Naïve MRCC Efficacy Results (interim analysis)

Efficacy Parameter	SUTENT (n=375)	IFN-α (n=375)	P-value (log-rank test)	HR (95% CI)
Progression-Free Survival[a] [median, weeks (95% CI)]	47.3 (42.6, 50.7)	22.0 (16.4, 24.0)	<0.000001[b]	0.415 (0.320, 0.539)
Objective Response Rate[a] [%, (95% CI)]	27.5 (23.0, 32.3)	5.3 (3.3, 8.1)	<0.001[c]	NA

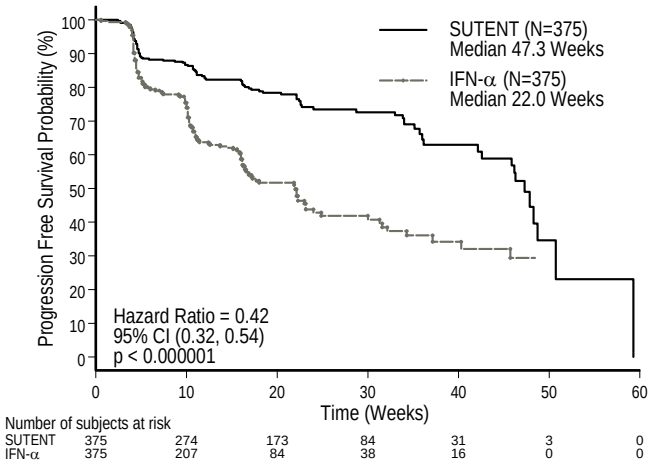
CI=Confidence interval, NA=Not applicable

[a] Assessed by blinded core radiology laboratory; 90 patients' scans had not been read at time of analysis

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

[c] Pearson Chi-square test

Figure 2. Kaplan-Meier Curve of PFS in Treatment-Naïve MRCC Study (Intent-to-Treat Population)



Cytokine-Refractory 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 (IFN-α, interleukin-2, or IFN-α plus interleukin-2; patients who were treated with IFN-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 endpoint for both studies was ORR. Duration of Response (DR) was also evaluated.

One hundred six patients (106) 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 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.

The ORR and DR data from Studies 1 and 2 are provided in Table 7. There were 36 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 34.0% (95% CI 25.0, 43.8). 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 9 of 36 patients (25%) responding to treatment had experienced disease progression or died at the time of the data cutoff.

Table 7. Cytokine-Refractory MRCC Efficacy Results

Efficacy Parameter	Study 1 (N=106)	Study 2 (N=63)
Objective Response Rate [%, (95% CI)]	34.0[a] (25.0, 43.8)	36.5[b] (24.7, 49.6)
Duration of Response (DR) [median, weeks (95% CI)]	* (42.0, **)	54[b] (34.3, 70.1)

CI=Confidence interval
* Median DR has not yet been reached
** Data not mature enough to determine upper confidence limit
[a] Assessed by blinded core radiology laboratory
[b] Assessed by investigators

16 HOW SUPPLIED/STORAGE AND HANDLING

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 28: NDC 0069-0550-38
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 28: NDC 0069-0770-38
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 28: NDC 0069-0980-38
Bottles of 30: NDC 0069-0980-30

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

17 PATIENT COUNSELING INFORMATION

See 17.5 for FDA-Approved Patient Labeling.

17.1 Gastrointestinal Disorders

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.

17.2 Skin Effects

Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third 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.

17.3 Other Common Events

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

17.4 Concomitant Medications

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 (7)]*.

17.5 FDA-Approved Patient Labeling

PATIENT INFORMATION

SUTENT (su TENT)

Read the patient information leaflet that comes with SUTENT before you start taking it. Read the leaflet each time you get a refill. There may be new information. This leaflet does not replace talking with your doctor about your condition or treatment. If you have any questions about SUTENT, ask your doctor or pharmacist.

What is the most important information I should know about SUTENT?

- **SUTENT may harm an unborn baby (cause birth defects).** Do not become pregnant. If you do become pregnant, tell your doctor right away. Stop taking SUTENT.

What is SUTENT?

SUTENT is a medicine that treats 2 kinds of cancer.

1. **GIST (gastrointestinal stromal tumor).** This is a rare cancer of the stomach, bowel, or esophagus. SUTENT is used when the medicine Gleevec® (imatinib mesylate) did not stop the cancer from growing OR when you cannot take Gleevec®.
2. **Advanced kidney cancer** (advanced renal cell carcinoma or RCC).

SUTENT may slow or stop the growth of cancer. It may help shrink tumors.

SUTENT has not been studied in children.

What should I tell my doctor before taking SUTENT?

Tell your doctor about all your medical conditions. **Be sure to tell your doctor if you:**

- are pregnant, could be pregnant, or plan to get pregnant. SUTENT may harm an unborn baby.
- are breast-feeding. Do not breast-feed while you are being treated with SUTENT.
- have any heart problems
- have high blood pressure
- have kidney function problems (other than cancer)
- have liver problems
- have any bleeding problem
- have seizures

SUTENT and other medicines

Tell your doctor about all your medicines. Include **prescription medicines,** over-the-counter drugs, vitamins, and herbal products. Some medicines can react with SUTENT and cause serious side effects.

Especially tell your doctor if you take:

- St. John's Wort. ***Do not take St. John's Wort while taking SUTENT.***
- Dexamethasone (a steroid)
- Medicine for:
  - tuberculosis (TB)
  - infections (antibiotics)
  - depression
  - seizures (epilepsy)
  - fungal infections (antifungals)
  - HIV (AIDS)

Keep a list of your medicines. Show it to your doctor or pharmacist. Talk with your doctor before starting any new medicines.

What are possible side effects of SUTENT?

Possible serious side effects include:

- **Heart Problems.** Tell your doctor if you feel very tired, are short of breath, or have swollen feet and ankles.
- **Rare life-threatening events:** hole in stomach or bowel wall (perforation) or bleeding from the tumor. Both of these side effects could cause symptoms such as painful, swollen abdomen, vomiting blood, and black, sticky stools. Your doctor can tell you other symptoms to watch for.
- **Increased blood pressure.** Your doctor may check your blood pressure. You may need treatment for high blood pressure.

Gleevec® is a registered trademark of Novartis Pharmaceuticals Corp

Rx only

Common side effects:

- Feeling tired
- Diarrhea, nausea, vomiting, mouth sores, upset stomach, abdominal pain, and constipation. Talk with your doctor about ways to handle these problems.
- The medicine in SUTENT is yellow, so it may make your skin look yellow. Your skin and hair may get lighter.
- Your skin may become dry, get thicker, or crack. You may get blisters or a rash on the palms of your hands and soles of your feet.
- Taste changes
- Loss of appetite
- Swelling
- High blood pressure
- Bleeding, such as nosebleeds or bleeding from cuts. Call your doctor if you have any swelling or bleeding.

There are other side effects. For a more complete list, ask your cancer specialist nurse or doctor.

How should I take SUTENT?

- SUTENT comes in 12.5 mg, 25 mg, and 50 mg capsules you take by mouth. Do not open the capsules.
- Take SUTENT once a day with or without food.
- Take it exactly the way your doctor tells you.
- Do not drink grapefruit juice or eat grapefruit. They may change the amount of SUTENT in your body.
- Dosing cycle:
  - Take SUTENT for 4 weeks (28 days) THEN
  - Stop for 2 weeks (14 days)
  - Repeat this cycle as long as your doctor tells you
- Your doctor may check your blood before each dosing cycle.
- If you miss a dose, take it as soon as you remember. Do not take it if it is close to your next dose. Just take the next dose at your regular time. Do not take more than 1 dose of SUTENT at a time. Tell your doctor or nurse about the missed dose.
- Call your doctor right away, if you take too much SUTENT.

How do I store SUTENT?

- Keep SUTENT and all medicines out of the reach of children.
- Store SUTENT at room temperature.

General information about SUTENT

Doctors can prescribe medicines for conditions that are not in this patient information leaflet. Use SUTENT only for what your doctor prescribed. Do not give it to other people, even if they have the same symptoms you have. It may harm them.

This leaflet gives the most important information about SUTENT. For more information about SUTENT, talk with your doctor or pharmacist. You can visit our website at www.SUTENT.com, or call 1-800-XXX-XXXX.

What is in SUTENT?

Active ingredient: sunitinib malate
Inactive ingredients: mannitol, croscarmellose sodium, povidone (K-25), magnesium stearate **Orange gelatin capsule shell:** titanium dioxide, red iron oxide **Caramel gelatin capsule shell:** yellow iron oxide, black iron oxide **Printing ink:** shellac, propylene glycol, sodium hydroxide, povidone, titanium dioxide

Distributed by: Pfizer Labs Division of Pfizer Inc, New York, NY 10017

Distributed by:

Pfizer Labs
Division of Pfizer Inc
New York, NY 10017

LAB-0317-2.1