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

---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)

---DOSE 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)

---ADVERSE REACTIONS---

8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.3 Nursing Mothers
  8.4 Pediatric Use
  8.5 Geriatric Use
  8.6 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.3 Pharmacokinetics
  12.4 Cardiac Electrophysiology

13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
  14.1 Gastrointestinal Stromal Tumor
  14.2 Renal Cell Carcinoma

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

---FULL PRESCRIBING INFORMATION: CONTENTS*---

1 INDICATIONS AND USAGE
  1.1 Gastrointestinal stromal tumor
  1.2 Advanced renal cell carcinoma

2 DOSAGE AND ADMINISTRATION
  2.1 Recommended Dose
  2.2 Dose Modification

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
  5.1 Pregnancy
  5.2 Left Ventricular Dysfunction
  5.3 QT Interval Prolongation and Torsade de Pointes
  5.4 Hypertension
  5.5 Hemorrhagic Events
  5.6 Hypothyroidism
  5.7 Adrenal Function
  5.8 Laboratory Tests

6 ADVERSE REACTIONS
  6.1 Adverse Reactions in GIST Study A
  6.2 Adverse Reactions in the Treatment-Naïve MRCC Study
  6.3 Venous Thromboembolic Events
  6.4 Reversible Posterior Leukoencephalopathy Syndrome
  6.5 Pancreatic and Hepatic Function

7 DRUG INTERACTIONS
  7.1 CYP3A4 Inhibitors
  7.2 CYP3A4 Inducers
  7.3 In Vitro Studies of CYP Inhibition and Induction

---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

---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

---WARNING---
- 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)
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 (7.2) 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 embolotheliality 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 encountered 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 Points
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 Points. Torsade de Points 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, 11/375 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-naïve 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) was observed 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. Erosions was the most common hemorrhagic adverse event reported. Less common bleeding events in GIST or MRCC patients included rectal, gingival, upper gastrointestinal, genial, 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 hemothysis or pulmonary hemorrhage. Tumor-related 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 (5%) 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 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 consistent normal 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.

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>
<thead>
<tr>
<th>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*</th>
<th>GIST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SUTENT (n=202)</td>
</tr>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>Any</td>
<td>114 (56)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>61 (30)</td>
</tr>
<tr>
<td>Nausea</td>
<td>28 (14)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 (14)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>42 (21)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>67 (33)</td>
</tr>
<tr>
<td><strong>Dermatology</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>45 (22)</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>61 (30)</td>
</tr>
<tr>
<td><strong>Metabolism/Nutrition</strong></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>42 (21)</td>
</tr>
<tr>
<td><strong>Adverse Reaction, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>All Grades</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3/4</strong></td>
<td></td>
</tr>
</tbody>
</table>
| + Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 + 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 1 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\(^a\)

<table>
<thead>
<tr>
<th>Laboratory Parameter, n (%)</th>
<th>SUTENT (n=202)</th>
<th>Placebo (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>All Grades (^b)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST / ALT</td>
<td>78 (39)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Lipase</td>
<td>50 (25)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>48 (24)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Amylase</td>
<td>35 (17)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>32 (16)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>20 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased LVEF</td>
<td>22 (11)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Renal/Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>25 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>24 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sodium increased</td>
<td>20 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>107 (53)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>76 (38)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Platelets</td>
<td>76 (38)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>52 (26)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

LVEF = Left ventricular ejection fraction
\(^a\) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
\(^b\) 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%).

6.2 Adverse Reactions in the Treatment-Naive 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-\(\alpha\). 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-\(\alpha\) treatment. Dose reductions occurred in 121 patients (32%) on SUTENT and 77 patients (21%) on IFN-\(\alpha\). Dose interruptions occurred in 142 patients (38%) on SUTENT and 115 patients (32%) on IFN-\(\alpha\). The rates of treatment-emergent, non-fatal adverse reactions resulting in permanent discontinuation were 9% and 12% in the SUTENT and IFN-\(\alpha\) 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-\(\alpha\), respectively.

Table 3 compares the incidence of common (\(\geq 10\%\)) treatment-emergent adverse reactions for patients receiving SUTENT versus IFN-\(\alpha\).
Table 4. Laboratory Abnormalities Reported in at Least 10% of Treatment-Naïve MRCC Patients Who Received SUTENT or IFN-α

<table>
<thead>
<tr>
<th>Laboratory Parameter, n (%)</th>
<th>Treatment-Naive MRCC</th>
<th>IFN-α (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades*</td>
<td>Grade 3/4³</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>195 (52)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>ALT</td>
<td>171 (46)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Lipase</td>
<td>196 (52)</td>
<td>60 (16)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>156 (42)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Amylase</td>
<td>118 (31)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>72 (19)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>46 (12)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Renal/Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>246 (66)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>155 (41)</td>
<td>43 (12)</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>152 (41)</td>
<td>11 (&lt;1)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>134 (36)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>132 (35)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>73 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Albumin</td>
<td>68 (18)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>58 (15)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>51 (14)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>42 (11)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Sodium increased</td>
<td>40 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>271 (72)</td>
<td>44 (12)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>266 (71)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Platelets</td>
<td>244 (65)</td>
<td>30 (8)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>223 (59)</td>
<td>44 (12)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>292 (78)</td>
<td>19 (5)</td>
</tr>
</tbody>
</table>

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

³ 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-naive 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-naive 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-naive 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) Cmax and AUC0–∞ 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, azithromycin, 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) Cmax and AUC0–∞ 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 enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, 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.

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 overdose 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/m²) 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-[[5-fluoro-1,2-dihydro-2-oxo-5-[(indol-3-yl) methyl]-2,4-dimethyl-3H-pyrrrole-3-carboxamide (1:1). The molecular formula is C₉₁H₁₁₂F₂N₁₀O₁₂, 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 VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the VEGFR2 and VEGFR3) as well as the src-related tyrosine kinases. 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 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.

12.2 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 (Cmax) of sunitinib are generally observed between 6 and 12 hours (Tmax) 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 Cmax 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 [14C]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.

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 (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the RDD). 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.

Overall 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 noted 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%), chemotherapy (88% both arms, Asian: 5% both arms, Black: 4% both arms, remainder not reported), 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)

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>SUTENT (n=207)</th>
<th>Placebo (n=105)</th>
<th>P-value (log-rank test)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Tumor Progression*</td>
<td>27.3 (16.0, 32.1)</td>
<td>6.4 (4.4, 10.0)</td>
<td>&lt;0.0001*</td>
<td>0.33 (0.23, 0.47)</td>
</tr>
<tr>
<td>Progression-free Survival†</td>
<td>24.4 (11.1, 28.3)</td>
<td>6.0 (4.4, 9.9)</td>
<td>&lt;0.0001*</td>
<td>0.33 (0.24, 0.47)</td>
</tr>
<tr>
<td>Objective Response Rate (PR) ‡</td>
<td>6.8 (3.7, 11.1)</td>
<td>0</td>
<td>0.0066†</td>
<td></td>
</tr>
</tbody>
</table>

Cl=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)
† Time from randomization to progression; deaths prior to documented progression were censored at time of last radiographic evaluation
‡ 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: 44% vs 46%, ECOG 1: 55% vs 52%, 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 225 PFS events had occurred. There was 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)

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=375)</th>
<th>P-value (log-rank test)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-Free Survival*</td>
<td>47.3 (42.6, 50.7)</td>
<td>22.0 (16.4, 24.0)</td>
<td>&lt;0.000001*</td>
<td>0.415 (0.320, 0.539)</td>
</tr>
<tr>
<td>Objective Response Rate (%)†</td>
<td>27.5 (23.0, 32.3)</td>
<td>5.3 (3.3, 8.1)</td>
<td>&lt;0.001†</td>
<td>NA</td>
</tr>
</tbody>
</table>

Cl=Confidence interval, NA=Not applicable
* A comparison is considered statistically significant if the p-value is < 0.0042 (O’Brien Fleming stopping boundary)
† A comparison is considered statistically significant if the p-value is < 0.0042 (O’Brien Fleming stopping boundary)
Pearson Chi-square test
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 status 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.
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.

How should I take 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)
  • seizures (epilepsy)
  • infections (antibiotics)
  • fungal infections (antifungal)
  • depression
  • 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

PATIENT INFORMATION

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
©2006 Pfizer Inc All rights reserved. Printed in the USA. Sep 2006