SUTENT (sunitinib malate) is an oral multi-kinase inhibitor, and in the United States is approved for the treatment of advanced renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate and progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.¹

MECHANISM OF ACTION

- SUTENT works by blocking multiple molecular targets implicated in the growth, proliferation and spread of cancer. Two important SUTENT targets, vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), are expressed by many types of solid tumors and are thought to play a crucial role in angiogenesis, the formation of new blood vessels that supply oxygen and nutrients needed for tumor growth. SUTENT also inhibits other targets important to tumor growth, including KIT, FLT3 and RET.¹² In vitro findings may not correlate with clinical efficacy.¹

KIDNEY CANCER CLINICAL STUDY

In a Phase 3, randomized, multi-center trial comparing SUTENT with interferon-alpha (IFN-α) as first-line therapy in 750 patients with treatment-naïve advanced kidney cancer:¹

- Median progression-free survival (PFS) was 11 months vs. 5 months with IFN-α (95% CI: 9.8, 11.7 and 3.8, 5.5, respectively; HR=0.42 [95% CI: 0.32, 0.54; P<.000001])¹
  - PFS was the primary endpoint
- Objective response rate (ORR):¹
  - 28% vs. 5% with IFN-α (95% CI: 23.0, 32.3 and 3.3, 8.1, respectively [P<.001]) in the first analysis (November 2005)¹
    - 90 patients’ scans had not been read at time of analysis¹
  - 39% vs. 8% with IFN-α (95% CI: 33.7, 43.8 and 5.2, 10.9, respectively [P<.001]) in the final analysis (March 2010)²
    - ORR was a secondary endpoint
- Median overall survival (OS) for SUTENT was 26.4 months compared to 21.8 months for patients in the IFN-α arm (95% CI: 23.0, 32.9 and 17.9, 26.9, respectively; HR=0.82 [95% CI: 0.673, 1.001; P=0.051])¹⁴
  - OS was a secondary endpoint

IMPORTANT SAFETY INFORMATION

**SUTENT can cause serious liver problems, including death.**

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

Given the potential for serious adverse reactions (ARs) in nursing infants, a decision should be made whether to discontinue nursing or SUTENT.

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. Use SUTENT with caution in patients who are at risk for, or who have a history of, these events. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies.

SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsades de Pointes, which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered.

Please see continued Important Safety Information on pages two and three and accompanying full Prescribing Information, including BOXED WARNING.
Hypertension may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS).

Hemorrhagic events, including tumor-related hemorrhage such as pulmonary hemorrhage, have occurred. Some of these events were fatal. Perform serial complete blood counts (CBCs) and physical examinations.

Cases of tumor lysis syndrome (TLS) have been reported primarily in patients with high tumor burden. Monitor these patients closely and treat as clinically indicated.

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in patients who received SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose-reduce if 24-hour urine protein is ≥3 g; discontinue SUTENT in cases of nephrotic syndrome or repeat episodes of urine protein ≥3 g despite dose reductions.

Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, treatment must not be re-started.

Necrotizing fasciitis, including fatal cases, has been reported, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and/or symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, and treat per standard medical practice.

SUTENT has been associated with symptomatic hypoglycemia, which may result in loss of consciousness or require hospitalization. Reductions in blood glucose levels may be worse in patients with diabetes. Check blood glucose levels regularly during and after discontinuation of SUTENT. Assess whether antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Osteonecrosis of the jaw (ONJ) has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving bisphosphonates.

Cases of impaired wound healing have been reported. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures.

Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.

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.

Dose adjustments are recommended when SUTENT is administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John’s Wort.

The most common ARs occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFN-α) were diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%). The most common grade 3/4 ARs (occurring in ≥5% of patients with RCC receiving SUTENT vs IFN-α) were fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diarrhea (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%).

The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with RCC receiving SUTENT vs IFN-α) included lymphocytosis (18% vs 26%), lipase (18% vs 8%), neutrophils (17% vs 9%), uric acid (14% vs 8%), platelets (9% vs 1%), hemoglobin (8% vs 5%), sodium decreased (8% vs 4%), leukocytes (8% vs 2%), glucose increased (6% vs 6%), phosphorus (6% vs 6%), and amylase (6% vs 3%).
GIST CLINICAL STUDY

SUTENT was studied in a large, Phase 3 clinical trial involving 312 patients with GIST who had disease progression during prior imatinib mesylate treatment or who were intolerant of imatinib:1

- Time to tumor progression (TTP), the primary endpoint, was significantly prolonged. The median TTP was 27.3 weeks (6.3 months) in the SUTENT treatment group compared with 6.4 weeks (1.5 months) in the placebo group (95% CI: 16.0, 32.1 and 4.4, 10.0 respectively; HR=0.33 [95% CI: 0.23, 0.47; P<.0001])
- SUTENT significantly improved PFS (a secondary endpoint). The median PFS was 24.1 weeks (5.6 months) vs. 6.0 weeks (1.4 months) in the placebo group (95% CI: 11.1, 28.3 and 4.9, 9.9 respectively; HR=0.33 [95% CI: 0.24, 0.47; P<.0001])
- The median OS (a secondary endpoint) was 72.7 weeks (16.8 months) for the SUTENT arm and 64.9 weeks (15.0 months) for the placebo arm (95% CI: 61.3, 83.0 and 45.7, 96.0 respectively; HR=0.876 [95% CI: 0.679, 1.129])
- 99 of 118 patients initially randomized to placebo crossed over to receive SUTENT in the open-label treatment phase

ADVANCED PANCREATIC NET CLINICAL STUDY

In the Phase 3, randomized, double-blind, placebo-controlled trial in advanced pNET (N=171):

- SUTENT demonstrated clinically significant improvement in PFS, the primary endpoint. The median PFS was 10.2 months for SUTENT vs. 5.4 months with placebo (95% CI: 7.4, 16.9 and 3.4, 6.0, respectively; HR=0.427 [95% CI: 0.271, 0.673; P=.0001])
- 57% reduced risk of progression or death
- A statistically significant difference in ORR (a secondary endpoint) favoring SUTENT over placebo was observed
- 9.3% of patients achieved an objective response with SUTENT vs. 0% with placebo (95% CI: 3.2, 15.4; P=.0066)
- In addition, while OS (a secondary endpoint) was not mature at the time of the primary analysis, fewer deaths had occurred in the SUTENT arm. Nine deaths were observed in patients treated with SUTENT versus 21 deaths in patients given placebo
- The independent DMC recommended study termination prior to the prespecified interim analysis, which may have led to an overestimate of the magnitude of PFS effect

IMPORTANT SAFETY INFORMATION (CONTINUED)

The most common ARs occurring in ≥20% of patients with GIST and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (40% vs 27%), anorexia (33% vs 29%), skin discoloration (30% vs 23%), mucositis/stomatitis (29% vs 18%), asthenia (22% vs 12%), altered taste (21% vs 12%), and constipation (20% vs 14%). The most common grade 3/4 ARs (occurring in ≥4% of patients with GIST receiving SUTENT vs placebo) were asthenia (5% vs 3%), hand-foot syndrome (4% vs 3%), diarrhea (4% vs 0%), and hypertension (4% vs 0%).

The most common ARs occurring in ≥20% of patients with advanced pNET and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (59% vs 39%), stomatitis/oral syndromes (48% vs 18%), nausea (45% vs 29%), abdominal pain (39% vs 34%), vomiting (34% vs 31%), asthenia (34% vs 27%), fatigue (33% vs 27%), hair color changes (29% vs 1%), hand-foot syndrome (29% vs 5%), hypertension (27% vs 5%), and constipation (20% vs 14%). The most common grade 3/4 ARs (occurring in ≥4% of patients with GIST receiving SUTENT vs placebo) were asthenia (5% vs 3%), hand-foot syndrome (4% vs 3%), diarrhea (4% vs 0%), and hypertension (4% vs 0%).

In addition, while OS (a secondary endpoint) was not mature at the time of the primary analysis, fewer deaths had occurred in the SUTENT arm. Nine deaths were observed in patients treated with SUTENT versus 21 deaths in patients given placebo

The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with GIST receiving SUTENT vs placebo) included lipase (10% vs 7%), neutrophils (10% vs 0%), amylase (5% vs 3%), and platelets (5% vs 0%).

The most common ARs occurring in ≥20% of patients with advanced pNET and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (59% vs 39%), stomatitis/oral syndromes (48% vs 18%), nausea (45% vs 29%), abdominal pain (39% vs 34%), vomiting (34% vs 31%), asthenia (34% vs 27%), fatigue (33% vs 27%), hair color changes (29% vs 1%), hand-foot syndrome (29% vs 5%), hypertension (27% vs 5%), and constipation (20% vs 14%). The most commonly reported grade 3/4 ARs (occurring in ≥5% of patients with advanced pNET receiving SUTENT vs placebo) were hypertension (10% vs 1%), hand-foot syndrome (6% vs 0%), stomatitis/oral syndromes (6% vs 0%), abdominal pain (5% vs 10%), fatigue (5% vs 9%), asthenia (5% vs 4%), and diarrhea (5% vs 2%).

The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with advanced pNET receiving SUTENT vs placebo) included decreased neutrophils (16% vs 0%), increased glucose (12% vs 18%), increased alkaline phosphatase (10% vs 11%), decreased phosphorus (7% vs 5%), decreased lymphocytes (7% vs 4%), increased creatinine (5% vs 5%), increased lipase (5% vs 4%), increased AST (5% vs 3%), and decreased platelets (5% vs 0%).

Please see full Prescribing Information, including BOXED WARNING and Medication Guide.
PATIENT ACCESS TO SUTENT

Commercially insured patients may be eligible to use the Pfizer Co-Pay One Savings Card when SUTENT is prescribed and pay no more than $10 out-of-pocket monthly for their medication (See co-pay card for Limits, Terms and Conditions that apply).

Patients who participate in federal or state healthcare programs, such as Medicaid or Medicare, are not eligible for the Pfizer Co-Pay One Savings Card. These patients can call Pfizer RxPathways™, and a counselor will work with them to research alternate funding options and help with application processes. If alternate funding cannot be secured, patients who meet eligibility requirements can receive their Pfizer medicine for free through the patient assistance program. Call 1-866-706-2400 or visit www.PfizerRxPath.com for more information.

Access to medicines is a cornerstone of Pfizer’s commitment to health care. For more than 25 years, Pfizer has offered an array of prescription assistance programs to help eligible patients get access to their Pfizer medicines. Today, this assistance is provided through Pfizer RxPathways, which helps eligible patients get access to their Pfizer medicines by offering a range of support services, including insurance counseling, co-pay help, providing Pfizer medicines for free or at a savings, and more.

Pfizer’s patient assistance programs have helped millions of uninsured and underinsured patients gain access to the medications they need. For more information on Pfizer RxPathways, please visit www.PfizerRxPath.com.

PATIENT SUPPORT:

Pfizer offers several programs to help patients throughout their treatment journey. SUTENT In Touch is a free, personalized support program that connects patients and caregivers to relevant information, tips, and tools throughout SUTENT treatment.

It also includes a partnership with an Oncology Certified Nurse. Patients can enroll by simply calling 1-877-5-SUTENT (1-877-578-8368) or visiting www.SUTENT.com.

CONTACT & ADDITIONAL INFORMATION:

If you are interested in speaking with a Pfizer Oncology representative, please contact Sally Beatty at Sally.Beatty@pfizer.com or (212) 733-6566.

For information about SUTENT clinical trials currently enrolling in their area, patients and their physicians are encouraged to call the Pfizer Oncology clinical trial information line at 1-800-718-1021 or visit www.pfizercancertrials.com.

Please see Important Safety Information on previous pages and accompanying full Prescribing Information, including BOXED WARNING.

REFERENCES

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

SUFTEN® (sunitinib maleate) capsules, oral
Initial U.S. Approval: 2006

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning.

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. [See Warnings and Precautions (5.1)]

Recent Major Changes
Warings and Precautions, Cardiovascular Events (5.3) 4/2015
Warings and Precautions, Thrombotic Microangiopathy (5.8) 4/2015
Warings and Precautions, Proteinuria (5.9) 6/2014
Warings and Precautions, Dermatologic Toxicities (5.10) 6/2014
Warings and Precautions, Hypoglycemia (5.12) 12/2014

Indications and Usage
SUFTEN is a kinase inhibitor indicated for the treatment of:
• Gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate. (1.1)
• Advanced renal cell carcinoma (RCC). (1.2)
• Progressive, well-differentiated pancreatic neuroendocrine tumors (pN ET) in patients with unresectable locally advanced or metastatic disease. (1.3)

Dosage and Administration
GIST and RCC:
• 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off. (2.1)

Dosage Forms and Strengths
Capsules: 12.5 mg, 25 mg, 37.5 mg, 50 mg (3)

Contraindications
None (4)

Warnings and Precautions
Hepatotoxicity, including liver failure, has been observed. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUFENTIN should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUFENTIN if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure. (5.1)

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.2)

Adverse Reactions
• Cardiovascular events including myocardial ischemia, myocardial infarction, left ventricular ejection fraction declines to below the lower limit of normal and cardiac failure including death have occurred. Monitor patients for signs and symptoms of congestive heart failure. (5.3)
• 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 SUFTEN, monitoring with on-treatment electrocardiograms and electrolytes should be considered. (5.4)
• Hypertension may occur. Monitor blood pressure and treat as needed. (5.5)
• Hemorrhagic events including tumor-related hemorrhage have occurred. Perform serial complete blood counts and physical examinations. (5.6)
• Cases of Tumor Lysis Syndrome (TLS) have been reported primarily in patients with RCC and GIST with high tumor burden. Monitor these patients closely and treat as clinically indicated. (5.7)
• Thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of SUFTEN. (5.8)
• Proteinuria: Monitor urine protein. Interrupt treatment for 24-hour urine protein ≥3 grams. Discontinue for repeat episodes of protein ≥3 grams despite dose reductions or nephrotic syndrome. (5.9)
• Discontinue SUFTEN if necrotizing fasciitis, erythema multiforme, Stevens-Johnson Syndrome or toxic epidermal necrolysis occurs. (5.10)
• Thyroid dysfunction may occur. Patients with signs and symptoms suggestive of hypothyroidism or hyperthyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice. (5.11)
• Hypoglycemia may occur. Check blood glucose levels regularly and assess if antidiabetic drug dose modifications are required. (5.12)
• Osteonecrosis of the jaw has been reported. Consider preventive dentistry prior to treatment with SUFTEN. If possible, avoid invasive dental procedures, particularly in patients receiving intravenous bisphosphonate therapy. (5.13)
• Wound Healing: Impaired wound healing has occurred with SUFTEN. Temporary interruption of therapy with SUFTEN is recommended in patients undergoing major surgical procedures. (5.14)
• Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma or severe infection. (5.15)

ADVERSE REACTIONS
The most common adverse reactions (≥20%) are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dysnea, anorexia, and bleeding. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-888-FDA-1088 or www.fda.gov/medwatch.

Drug Interactions
• CYP3A4 Inhibitors: Consider dose reduction of SUFTEN when administered with strong CYP3A4 inhibitors. (7.1)
• CYP3A4 Inducers: Consider dose increase of SUFTEN when administered with CYP3A4 inducers. (7.2)

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

Revised: 4/2015
1 INDICATIONS AND USAGE
1.1 Gastrointestinal Stromal Tumor (GIST)
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 (RCC)
SUTENT is indicated for the treatment of advanced renal cell carcinoma.

1.3 Advanced Pancreatic Neuroendocrine Tumors (pNET)
SUTENT is indicated for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dose for GIST and RCC
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 Recommended Dose for pNET
The recommended dose of SUTENT for pancreatic neuroendocrine tumors (pNET) is 37.5 mg taken orally once daily continuously without a scheduled off-treatment period. SUTENT may be taken with or without food.

2.3 Dose Modification
Dose intervention and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability. The maximum dose administered to patients with advanced RCC was 125 mg daily.

2.4 Administration
SUTENT may be taken with or without food. SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia. Patients should be monitored closely for changes in liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have related hepatic adverse events.

2.5 Monitoring
Complete blood counts (CBCs) and physical examinations.

3 CONTRAINDICATIONS
3.1 Hemorrhagic Events
Hemorrhagic events reported during post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. In patients receiving SUTENT in a clinical trial for treatment-naïve RCC, 14/375 patients (3.7%) had bleeding events compared with 35/360 patients (10%) receiving IFN-α. Bleeding events occurred in 37/202 patients (18%) receiving SUTENT in the double-blind treatment phase of GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Bleeding events, excluding epistaxis, occurred in 18/33 patients (55%) receiving SUTENT and 2/38 patients (5%) receiving placebo. No Grade 4 hemorrhage was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 1/278 patients (0.4%), and in 8/80 pNET patients (10%). In the Phase 3 pNET study, cardiac failure leading to death was reported in 2/83 (2%) patients on SUTENT and no patients on placebo.

4 WARNINGS AND PRECAUTIONS
4.1 Hepatotoxicity
Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. (See Warnings and Precautions [5.1].)

5.3 Cardiovascular Events
In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted or reduced in patients without clinical evidence of CHF but with an ejection fraction <28% and >20% below baseline.

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. USE SUTENT with caution in patients who are at risk for or who have a history of, these events. For SUTENT and RCC, more patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving either placebo or interferon-α (IFN-α). In the double-blind treatment phase of 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 function at baseline. In the Phase 3 pNET study, cardiac failure leading to death was reported in 2/83 (2%) patients on SUTENT and no patients on placebo. Patients who presented within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/ peripheral artery bypass graft, symmetric CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these conditions or similar 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 cardiac signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving SUTENT.

5.5 Hypertension
Hypertension is recommended until hypertension is controlled.

6 Hemorrhagic Events
Hemorrhagic events reported during post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. In patients receiving SUTENT in a clinical trial for treatment-naïve RCC, 14/375 patients (3.7%) had bleeding events compared with 35/360 patients (10%) receiving IFN-α. Bleeding events occurred in 37/202 patients (18%) receiving SUTENT in the double-blind treatment phase of GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Bleeding events, excluding epistaxis, occurred in 18/33 patients (55%) receiving SUTENT and 2/38 patients (5%) receiving placebo. No Grade 4 hemorrhage was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 1/278 patients (0.4%), and in 8/80 pNET patients (10%). In the Phase 3 pNET study, cardiac failure leading to death was reported in 2/83 (2%) patients on SUTENT and no patients on placebo.

7.4 QT Interval Prolongation and Torsade de Pointes
SUTENT should not be used until precautionary, cardiac failure leading to death was reported in 2/83 (2%) patients on SUTENT and no patients on placebo. Patients who presented within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/ peripheral artery bypass graft, symmetric CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these conditions or similar 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 cardiac signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving SUTENT.

7.5 QT Interval Prolongation and Torsade de Pointes
SUTENT has been shown to prolong the QT interval in a dose dependent manner, with a dose increase of 25 mg (GIST and RCC) or 50 mg (pNET) daily should be considered if SUTENT must be co-administered with a CYP3A4 inhibitor (See Drug Interactions [7.1] and Clinical Pharmacology [12.3]).

CYP3A4 inducers such as rifampin may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended for patients on SUTENT to a maximum of 75 mg (GIST and RCC) or 62.5 mg (pNET) 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 DOSE FORMS AND STRENGTHS
12.5 mg capsules
Hard gelatin capsule with orange cap and orange body, printed with white ink "Pifer" 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 "Pifer" on the cap and "STN 25 mg" on the body.

37.5 mg capsules
Hard gelatin capsule with yellow cap and yellow body, printed with black ink "Pifer" on the cap and "STN 37.5 mg" on the body.

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

2.4.9 QT interval prolongation and Torsade de Pointes
SUTENT has been shown to prolong the QT interval in a dose dependent manner, with a dose increase of 25 mg (GIST and RCC) or 50 mg (pNET) daily should be considered if SUTENT must be co-administered with a CYP3A4 inhibitor (See Drug Interactions [7.1] and Clinical Pharmacology [12.3]).

CYP3A4 inducers such as rifampin may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended for patients on SUTENT to a maximum of 75 mg (GIST and RCC) or 62.5 mg (pNET) 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 DOSE FORMS AND STRENGTHS
12.5 mg capsules
Hard gelatin capsule with orange cap and orange body, printed with white ink "Pifer" 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 "Pifer" on the cap and "STN 25 mg" on the body.

37.5 mg capsules
Hard gelatin capsule with yellow cap and yellow body, printed with black ink "Pifer" on the cap and "STN 37.5 mg" on the body.

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

4 CONTRAINDICATIONS
Not applicable.

5.1 Gastrointestinal Stromal Tumor (GIST)
SUTENT is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

5.2 Advanced Renal Cell Carcinoma (RCC)
SUTENT is indicated for the treatment of advanced renal cell carcinoma.

5.3 Advanced Pancreatic Neuroendocrine Tumors (pNET)
SUTENT is indicated for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease.
Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

5.7 Tumor Lysis Syndrome (TLS)
Cases of TLS, some fatal, have been observed in clinical trials and have been reported in post-marketing experience. In patients with RCC or GIST treated with SUTENT. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

5.8 Thrombotic Microangiopathy
Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Resolution of the effects of TMA has been observed after treatment was discontinued.

5.9 Proteinuria
Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development of proteinuria or nephrotic syndrome in the absence of known collagen vascular disease. Proteinuria may be a marker of renal dysfunction and should be evaluated, especially in patients known to be at risk for renal disease.

5.10 Dermatologic Toxicities
Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal or signs or symptoms suggestive of SJS, TEN, or EM (i.e., progressive skin rash often with blisters or mucosal lesions) are present. SUTENT treatment should be discontinued. In a diagnosis of SJS or TEN is suspected, SUTENT treatment must not be re-started.

5.11 Thyroid Dysfunction
Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of SUTENT treatment. All patients should be observed closely for signs of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, on treatment. Thyroid function tests of patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

5.12 Hypoglycemia
SUTENT has been associated with symptomatic hypoglycemia, which may result in loss of consciousness and, in rare cases, require hospitalization. Hypoglycemia has occurred in clinical trials in 2% of the patients treated with SUTENT for RCC and GIST and in approximately 10% of the patients treated with SUTENT for pNET. For patients being treated with SUTENT for pNET, pre-existing abnormalities in glucose homeostasis were not present in all patients who experienced blood glucose levels lower than 70 mg/dL. In patients with no pre-existing abnormalities in blood glucose levels, hypoglycemia may occur in diabetic patients. Check blood glucose levels regularly during and after discontinuation of treatment with SUTENT. Assess if anti-diabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

5.13 Onset (ONJ)
ONJ has been observed in clinical trials and has been reported in post-marketing experience in patients treated with sunblock. Concomitant exposure to other risk factors, such as bisphosphonates or dental disease, may increase the risk of osteonecrosis of the jaw.

5.14 Wound Healing
Cases of impaired wound healing have been reported during SUTENT therapy. Temporary interruption of SUTENT therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to re-start SUTENT therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

5.15 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, atrophy, and atrophy and fibrosis. In clinical studies, Delayed mTOR inhibition was seen 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 levels who received SUTENT, the mean ACTH was decreased by 14% compared to baseline and unchanged at the end of 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 mg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

5.16 Laboratory Tests
CBCs with platelet count and serum chemistry including phosphatase 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 660 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of GIST [see Clinical Studies (14.1)], an active-controlled trial (n=375) for the treatment of RCC [see Clinical Studies (14.2)] or a placebo-controlled trial (n=83) for the treatment of pNET [see Clinical Studies (14.3)]. The GIST and RCC patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles, and the pNET patients received a starting oral dose of 37.5 mg daily without scheduled off-treatment periods.

The most common adverse reactions (≥20%) in patients with GIST, RCC or pNET were fatigue, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in Warnings and Precautions (5). Other adverse reactions occurring in GIST, RCC and pNET 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 1-12), and one cycle (mean 1.8, range 1-6) for patients on placebo at the time of the interim analysis. 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, in the double-blind treatment phase of the trial. 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 in the Double-Blind Treatment Phase and More Commonly in Patients Given Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction, n (%)</th>
<th>SUTENT (n=202)</th>
<th>Placebo (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>114 (56)</td>
<td>52 (51)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81 (40)</td>
<td>27 (26)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>58 (29)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Constipation</td>
<td>41 (20)</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (15)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Dermatology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>61 (30)</td>
<td>23 (22)</td>
</tr>
<tr>
<td>Rash</td>
<td>28 (14)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>28 (14)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered taste</td>
<td>42 (21)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia/limb pain</td>
<td>28 (14)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Metabolism/Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>67 (33)</td>
<td>30 (29)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>45 (22)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Laboratory Abnorm alities Reported in Study A in at Least 10% of GIST Patients Who Received SUTENT or Placebo in the Double-Bind Treatment Phase*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Parameter, n (%)</th>
<th>SUTENT (n=202)</th>
<th>Placebo (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>68 (34)</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST / ALT</td>
<td>78 (39)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Lipase</td>
<td>50 (25)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>48 (24)</td>
<td>21 (21)</td>
</tr>
<tr>
<td>Amylase</td>
<td>35 (17)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>32 (16)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>20 (10)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased LVEF</td>
<td>22 (11)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Renal/Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>25 (12)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>25 (12)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Sodium increased</td>
<td>20 (10)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>107 (53)</td>
<td>4 (4)</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 (10)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>22 (11)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

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

In the double-blind treatment phase of GIST Study A, 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 in the Double-Bind Treatment Phase*
Table 3. Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α

<table>
<thead>
<tr>
<th>Adverse Reaction, n (%)</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any</td>
<td>372 (99)</td>
<td>290 (77)</td>
</tr>
<tr>
<td><strong>Constitutional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>233 (62)</td>
<td>55 (15)</td>
</tr>
<tr>
<td>Anemia</td>
<td>96 (26)</td>
<td>42 (11)</td>
</tr>
<tr>
<td>Fever</td>
<td>84 (22)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>60 (16)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Chills</td>
<td>53 (14)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>50 (13)</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>246 (66)</td>
<td>37 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>216 (58)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>178 (47)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>148 (39)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>128 (34)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Abdominal painc</td>
<td>113 (30)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>85 (23)</td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (34)</td>
<td>50 (13)</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>91 (24)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>61 (16)</td>
<td>10 (3)</td>
</tr>
<tr>
<td><strong>Dermatological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>109 (29)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>108 (29)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Skin discoloration/ yellow skin</td>
<td>94 (25)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>85 (23)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>73 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>51 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Erythema</td>
<td>46 (12)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>44 (12)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered taste d</td>
<td>178 (47)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Headache</td>
<td>86 (23)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>43 (11)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>105 (28)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>111 (30)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Pain in extremity/ limp discomfort</td>
<td>150 (40)</td>
<td>19 (5)</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>61 (16)</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Parameter, n (%)</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>211 (56)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>ALT</td>
<td>192 (51)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Lipase</td>
<td>211 (56)</td>
<td>69 (18)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>171 (46)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Amylase</td>
<td>130 (35)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>75 (20)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>49 (13)</td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>Renal/Metabolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>262 (70)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>185 (49)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>172 (46)</td>
<td>54 (14)</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>156 (42)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>116 (33)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Albumin</td>
<td>106 (28)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>86 (23)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>75 (20)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Sugarurine decreased</td>
<td>65 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>61 (16)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Calcium increased</td>
<td>50 (13)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>49 (13)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>48 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>289 (77)</td>
<td>65 (17)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>286 (79)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Platelets</td>
<td>255 (68)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>256 (68)</td>
<td>66 (18)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>283 (78)</td>
<td>29 (8)</td>
</tr>
</tbody>
</table>

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

| 6.3 Adverse Reactions in the Phase 3 pNET Study |

The median number of days on treatment was 139 days (range 13–532 days) for patients on SUTENT and 113 days (range 1–614 days) for patients on placebo. Nineteen patients (23%) on SUTENT and 4 patients (5%) on placebo were on study for >1 year. Dose interruptions occurred in 25 patients (30%) on SUTENT and 10 patients (12%) on placebo. Dose reductions occurred in 26 patients (31%) on SUTENT and 9 patients (11%) on placebo. Discontinuation rates due to adverse reactions were 22% for SUTENT and 17% for placebo.

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 54% versus 50% of patients on SUTENT versus placebo, respectively. Table 5 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 6. Laboratory Abnormalities Reported in the Phase 3 pNET Study in at Least 10% of Patients Who Received SUTENT

<table>
<thead>
<tr>
<th>Laboratory Parameter, n (%)</th>
<th>SUTENT (n=83)</th>
<th>pN ET</th>
<th>Placebo (n=82)</th>
<th>pN ET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>82 (59)</td>
<td>4 (5)</td>
<td>50 (56)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>82 (50)</td>
<td>2 (4)</td>
<td>48 (55)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>82 (52)</td>
<td>6 (8)</td>
<td>50 (56)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Total bilirubin increased</td>
<td>82 (60)</td>
<td>1 (1)</td>
<td>40 (46)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>74 (54)</td>
<td>3 (4)</td>
<td>54 (63)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>75 (53)</td>
<td>4 (5)</td>
<td>50 (56)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Renal/Metabolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>82 (58)</td>
<td>10 (12)</td>
<td>50 (56)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>81 (33)</td>
<td>4 (5)</td>
<td>50 (56)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Phosphorus decreased</td>
<td>81 (29)</td>
<td>6 (7)</td>
<td>50 (56)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>82 (28)</td>
<td>4 (5)</td>
<td>50 (56)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>82 (24)</td>
<td>2 (2)</td>
<td>50 (56)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>82 (22)</td>
<td>4 (5)</td>
<td>50 (56)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>82 (18)</td>
<td>2 (2)</td>
<td>50 (56)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>82 (17)</td>
<td>3 (4)</td>
<td>50 (56)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>52 (19)</td>
<td>0 (0)</td>
<td>50 (56)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>52 (19)</td>
<td>0 (0)</td>
<td>50 (56)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>82 (58)</td>
<td>13 (16)</td>
<td>50 (56)</td>
<td>16 (19)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>53 (65)</td>
<td>0 (0)</td>
<td>50 (56)</td>
<td>44 (55)</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>49 (60)</td>
<td>4 (5)</td>
<td>50 (56)</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>46 (56)</td>
<td>6 (7)</td>
<td>50 (56)</td>
<td>28 (35)</td>
</tr>
</tbody>
</table>

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

1. Grade 4 abnormalities in patients on SUTENT included creatinine (4%), lipase (4%), glucose decreased (2%), alkaline phosphatase (4%), AST (1%), ALT (1%), platelets (1%), potassium increased (1%), and total bilirubin (1%).
2. Grade 4 laboratory abnormalities in patients on placebo included creatinine (3%), alkaline phosphatase (1%) and lipase (1%).

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 induction 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-∞, respectively, after a single dose of SUTENT in healthy volunteers.

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-∞, respectively, after a single dose of SUTENT in healthy volunteers.

8. In Vitro Studies of CYP Inhibition and Induction

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

9. Pregnancy

Pregnancy Category C [see Warnings and Precautions (5.2)]. SUTENT can cause fetal harm when administered to a pregnant woman. As angio genesis 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. In animal reproductive studies in rats and rabbits, sunitinib was teratogenic, embryotoxic, and postnatal growth retardation.
embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of SUTENT in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking 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]). Sunitinib is not embryotoxic. 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 verteebrae in rats. In rabbits, cleft lip was observed at 2.7 mg/kg/day and cleft palate was shown at 0.75 mg/kg/day (approximately 2.8 times the AUC in patients administered the RDD). Nondisjunction was observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postnatal development study in rats and in rabbits. Sunitinib in the maternal body was excrated in the milk, and milk concentrations up to 19-fold higher than in plasma. It is not known whether this drug or its primary active metabolite are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SUTENT, 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.

8.4 Pediatric Use

The safety and efficacy of SUTENT in pediatric patients have not been established. Phystial dysplasia was observed in cynomolgus monkeys with open growth plates treated for >3 months (3 month dosing 2.6, 12 mg/kg/day; 8 days of dosing 0.5, 1.5, 6.0 mg/kg). Sunitinib at doses that were 0.4-17 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15 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, cardiomyopathies were found in rats. The incidence and severity of physical dysplasia were dose-related and were reversible upon cessation of treatment; however, findings in the teeth were not. 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

825 GIST and RCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. In the Phase 3 prnET study, 22 (27%) patients who received SUTENT 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 to the starting dose is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary active metabolite are 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. Hepatic impairment studies in cancer patients have excluded patients with ALT or AST >2.5 x U/L or, if due to liver metastases, >3.0 x U/L.

8.7 Renal Impairment

No adjustment to the starting dose is required when administering SUTENT to patients with mild, moderate, and severe renal impairment. Subsequent dose modifications should be based on safety and tolerability (see Dose and Administration [2.3]). In patients with end-stage renal disease (ESRD) on hemodialysis, no adjustment to the starting dose is required. However, compared to subjects with normal renal function, the sunitinib exposure is 47% lower in subjects with ESRD on hemodialysis. Therefore, the subsequent doses may be increased gradually up to 2 fold based on safety and tolerability.

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. Cases of accidental ingestion or gastrectomy were administered the recommended daily doses (RDD). Sunitinib is not indicated for gastrectomy. 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 palate was shown at 0.75 mg/kg/day (approximately 2.8 times the AUC in patients administered the RDD). Nondisjunction was observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

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 (~90 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 (FL3), 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 observed in xenograft and tumor regression models. Sunitinib's primary active metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRα, VEGFR2, KIT) in tumor xenografts expressing RTK targets in vivo and demonstrated inhibition of tumor growth, xenograft regression, and 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 PDGFR- and VEGFR2-dependent tumor angiogenesis in vivo.

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 (~90 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 (FL3), 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 observed in xenograft and tumor regression models. Sunitinib's primary active metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.
12.4 Cardiac Electrophysiology

See Warnings and Precautions (4).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of sunitinib has been evaluated in two species; rash2 transgenic mice and Sprague-Dawley rats. There were similar positive findings in both species. In rash2 transgenic mice gastroduodenal carcinomas and/or gastric mucosal hyperplasia, as well as an increased incidence of background hemangiosarcomas were observed at doses of ≥25 mg/kg/day following daily dose administration of sunitinib in studies of 1 or 6 months duration. No proliferative changes were observed in rash2 transgenic mice at 8 mg/kg/day. Similarly, in a 2-year rat carcinogenicity study, administration of sunitinib in 28-day cycles followed by 7-day dose-free periods resulted in findings of duodenal carcinomas at doses as low as 1 mg/kg/day (approximately 0.9 times the AUC in patients given the RDD of 50 mg/day). At the high dose of 3 mg/kg/day (approximately 7.8 times the AUC in patients at the RDD of 50 mg/day) the incidence of duodenal tumors was increased and was accompanied by findings of gastric mucosal hyperplasia and by an increased incidence of pheochromocytoma and hyperplasia of the adrenal. 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.

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 (≥5 times the AUC in patients administering the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (≥0.4 times the AUC in patients administering the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were observed at 6 mg/kg/day in the 9-month mouse study (0.3, 1.5, and 6 mg/kg/day administered daily for 28 days followed by a 1-day respite; the 6 mg/kg/day dose produced a mean AUC that was ≥0.8 times the AUC in patients administering 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 ≥5 times the AUC in patients administering the RDD); however significant embryotoxicity was observed at 5.0 mg/kg dose. No reproductive effects were observed at doses up to 10 mg/kg/day for 58 days. No evidence of toxicity was noted in females 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 ≥2.5 times the AUC in patients administering the RDD).

14 CLINICAL STUDIES

14.1 Gastrointestinal Stromal Tumor

GIST Study A

Study A was a two-arm, international, randomized, double-blind, placebo-controlled trial of SUTENT in patients with GIST who had disease progression during prior imatinib mesylate (imatinib) treatment or who were intolerant of imatinib. The objective was to compare the efficacy and safety of SUTENT 50 mg once daily on Schedule 4/2 or to receive 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.

At the time of a pre-specified interim analysis, 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 (68% vs 72% <65 years for SUTENT vs. placebo, respectively), gender (Male: 64% vs 61%, race (White: 88% both arms, Asian: 9% both arms, Black: 5% 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.

The 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, meeting the primary endpoint. Efficacy results are summarized in Table 7 and the Kaplan-Meier curve for TTP in Figure 2. The final ITT population enrolled in the double-blind treatment phase of the study included 243 patients randomized to the SUTENT arm and 118 patients randomized to the placebo arm. The primary endpoint was met at the interim analysis, the study was unblinded, and patients on the placebo arm were offered open-label SUTENT treatment. Ninety-nine of the patients initially randomized to placebo crossed over to receive SUTENT in the open-label treatment phase. At the protocol specified final analysis of OS, the median OS was 72.7 weeks for the SUTENT arm and 64.9 weeks for the placebo arm [HR= 0.878, 95% CI (0.679, 1.129)].

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 an intermediate Phase 2 regimen (15 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

Renal Cell Carcinoma

Treatment-Naïve RCC

A multicenter, international randomized study comparing single-agent SUTENT with IFN-α was conducted in patients with treatment-naïve RCC. 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 IU MIU three times a week. Patients were treated until disease progression or withdrawal from the study.

The ITT population 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%), 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).

There was a statistically significant advantage for SUTENT over IFN-α in the endpoint of PFS (see Table 7 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 8).

Table 8. Treatment-Naïve RCC 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</td>
<td>24.3 (42.6, 50.7)</td>
<td>22.0 (16.4, 24.0)</td>
<td>&lt;0.0001c</td>
<td>0.415 [0.320, 0.539]</td>
</tr>
<tr>
<td>Survival (median, weeks) (95% CI)</td>
<td>57 (23.0, 32.3)</td>
<td>3.8 (3.3, 8.1)</td>
<td>&lt;0.001c</td>
<td>NA</td>
</tr>
<tr>
<td>Objective Response Rate [% (95% CI)]</td>
<td>27.5</td>
<td>5.3</td>
<td>0.0001c</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 7. GIST Efficacy Results from Study A (Double-Blind Treatment Phase)

<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 [median, weeks (95% CI)]</td>
<td>27.3 (16.0, 32.1)</td>
<td>6.4 (4.4, 10.0)</td>
<td>&lt;0.001c</td>
<td>0.33 (0.23, 0.47)</td>
</tr>
<tr>
<td>Progression-Free Survival [median, weeks (95% CI)]</td>
<td>24.1 (11.1, 28.3)</td>
<td>6.0 (4.4, 9.9)</td>
<td>&lt;0.0001c</td>
<td>0.33 (0.24, 0.47)</td>
</tr>
<tr>
<td>Objective Response Rate [% (95% CI)]</td>
<td>8.8</td>
<td>0</td>
<td>0.006c</td>
<td></td>
</tr>
</tbody>
</table>

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

Figure 2. Kaplan-Meier Curve of PFS in Treatment-Naïve RCC Study (Intent-to-Treat Population)
At the protocol-specified final analysis of OS, the median OS was 114.6 weeks for the SUTENT arm and 94.9 weeks for the IFN-α arm [HR = 0.82, 95% CI (0.67, 1.00)]. The median OS for the IFN-α arm includes 25 patients who discontinued IFN-α treatment because of disease progression and crossed over to treatment with SUTENT as well as 121 patients (32%) on the IFN-α arm who received post-study cancer treatment with SUTENT.

**Cytokine-Refractory RCC**

The use of single agent SUTENT in the treatment of cytokine-refractory RCC 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 a 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 (72% 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 9. 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 similarity (<80%) of objective disease responses was 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 9. Cytokine-Refractory RCC Efficacy Results

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study 1 (N=106)</th>
<th>Study 2 (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate (%, 95% CI)</td>
<td>(25.0, 43.8)</td>
<td>(42.7, 57.1)</td>
</tr>
<tr>
<td>Duration of Response (DR) [median, weeks (95% CI)]</td>
<td>9 weeks</td>
<td>30 weeks</td>
</tr>
</tbody>
</table>

14.3 Pancreatic Neuroendocrine Tumors

The Phase 3 study was a multi-center, international, randomized, double-blind placebo-controlled study of SUTENT conducted in patients with unresectable pN ET. Patients were required to have documented RECIST-defined disease progression within the prior 12 months and were randomized (1:1) to receive either 37.5 mg SUTENT (n=86) or placebo (n=85) once daily without a scheduled off-treatment period. The primary objective was to compare the objective response rate (ORR) and duration of response (DR) for patients receiving SUTENT versus patients receiving placebo. Other endpoints included Overall Survival (OS), Objective Response Rate (ORR), and safety. Use of somatostatin analogs was allowed in the study. Demographics were comparable between the SUTENT and placebo groups. Additionally, 49% of SUTENT patients had non-functioning tumors vs 52% of placebo patients, and 92% patients in both arms had liver metastases. A total of 66% of SUTENT patients received prior systemic therapy compared with 72% of placebo patients and 35% of SUTENT patients had received somatostatin analogs compared with 38% of placebo patients. Patients were treated until disease progression or withdrawal from the study. Upon disease progression, or study closure, patients were offered access to SUTENT in a separate extension study.

As recommended by the Independent Data Monitoring Committee, the study was terminated prematurely due to the pre-specified interim analysis. This may have led to an overestimate of the magnitude of PFS effect. A clinically significant improvement for SUTENT over placebo in PFS was seen by both investigator and independent assessment. A hazard ratio favoring SUTENT was observed in all subgroups of baseline characteristics evaluated. OS data were not mature at the time of the analysis. There were 9 deaths in the SUTENT arm and 24 deaths in the placebo arm. A statistically significant difference in ORR favoring SUTENT over placebo was observed. Efficacy results are summarized in Table 10 and the Kaplan-Meier curve for PFS is in Figure 3.

### Table 10. pNET Efficacy Results from the Phase 3 Study

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>SUTENT (n=86)</th>
<th>Placebo (n=85)</th>
<th>P-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-Free Survival [median, months (95% CI)]</td>
<td>10.2 (7.4, 16.9)</td>
<td>3.4 (3.4, 6.0)</td>
<td>0.000146*</td>
<td>0.427</td>
</tr>
<tr>
<td>Objective Response Rate (%, 95% CI)</td>
<td>9.3 (4.3, 15.4)</td>
<td>0.000661*</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

CI=Confidence interval; HR=Hazard ratio; NA=Not applicable

*2-sided unstratified log-rank test

Fisher’s Exact test
SUTENT (su TENT) (sunitinib malate) capsules

Read the Medication Guide that comes with SUTENT before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about SUTENT, ask your healthcare provider or pharmacist.

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

SUTENT can cause serious liver problems, including death.

- Tell your healthcare provider right away if you develop any of the following signs and symptoms of liver problems during treatment with SUTENT:
  - itching,
  - yellow eyes or skin,
  - dark urine, and
  - pain or discomfort in the right upper stomach area.

- Your healthcare provider should do blood tests to check your liver function before you start taking SUTENT and during treatment.

What is SUTENT?

SUTENT is a prescription medicine used to treat people with:

- a rare cancer of the stomach, bowel, or esophagus called GIST (gastrointestinal stromal tumor) and when:
  - the medicine Gleevec® (imatinib mesylate) did not stop the cancer from growing, or
  - you cannot take Gleevec®.

- advanced kidney cancer (advanced renal cell carcinoma or RCC).

- a type of pancreatic cancer known as pancreatic neuroendocrine tumors (pNET), that has progressed and cannot be treated with surgery.

It is not known if SUTENT is safe and effective in children.

What should I tell my healthcare provider before taking SUTENT?

Before taking SUTENT tell your healthcare provider if you:

- have any heart problems
- have high blood pressure
- have thyroid problems
- have a history of low blood sugar or diabetes
- have kidney function problems (other than cancer)
- have liver problems
- have any bleeding problem
- have seizures
- have or have had pain in the mouth, teeth or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth
- have any other medical conditions
- are pregnant, could be pregnant or plan to become pregnant. SUTENT may harm an unborn baby. You should not become pregnant while taking SUTENT. Tell your healthcare provider right away if you become pregnant while taking SUTENT.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take SUTENT or breastfeed. You should not do both. Tell all of your healthcare providers and dentists that you are taking SUTENT. They should talk to the healthcare provider who prescribed SUTENT for you, before you have any surgery, or medical or dental procedure.

Tell your healthcare provider about all the medicines you take, including prescription medicines and non-prescription medicines, vitamins, and herbal supplements. Using SUTENT with certain other medicines can cause serious side effects.

You may have an increased risk of severe jaw bone problems (osteonecrosis) if you take SUTENT and a bisphosphonate medicine. Especially tell your healthcare provider if you are taking or have taken Actonel, Aredia, Boniva, Didronel, Fosamax, Reclast, Skelaxin or Zometa.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine. Talk with your healthcare provider before starting any new medicines.

How should I take SUTENT?

- Take SUTENT exactly the way your healthcare provider tells you.
- Take SUTENT 1 time each day with or without food.
- If you take SUTENT for GIST or RCC, you will usually take your medicine for 4 weeks (28 days) and then stop for 2 weeks (14 days). This is 1 cycle of treatment. You will repeat this cycle for as long as your healthcare provider tells you to.
- If you take SUTENT for pNET, take it one time each day until your healthcare provider tells you to stop.
- Do not open the SUTENT capsules.
- Do not drink grapefruit juice or eat grapefruit during your treatment with SUTENT. They may cause you to have too much SUTENT in your body.
- Your healthcare provider may do blood tests before each cycle of treatment.
- 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 healthcare provider about any missed dose.
- Call your healthcare provider right away, if you take too much SUTENT.

What are possible side effects of SUTENT?

SUTENT may cause serious side effects including:

- See “What is the most important information I should know about SUTENT?”

- Heart problems. Heart problems may include heart failure, heart attack and heart muscle problems (cardiomyopathy) that can lead to death. Tell your healthcare provider if you feel very tired, are short of breath, or have swollen feet and ankles.

- Abnormal heart rhythm changes. Your healthcare provider may do electrocardiograms and blood tests to watch for these problems during your treatment with SUTENT. Tell your healthcare provider if you feel dizzy, faint, or have abnormal heartbeats while taking SUTENT.

- High blood pressure. Your healthcare provider may check your blood pressure during treatment with SUTENT. Your healthcare provider may prescribe medicine for you to treat high blood pressure, if needed.

- Bleeding sometimes leading to death. Tell your healthcare provider right away if you have any of these symptoms or a serious bleeding problem during treatment with SUTENT.
  - painful, swollen stomach (abdomen)
  - vomiting blood
  - black, sticky stools
  - bloody urine
  - headache or change in your mental status

Your healthcare provider can tell you other symptoms to watch for.

- Jaw-bone problems (osteonecrosis) Severe jaw bone problems may happen when you take SUTENT. Your healthcare provider should examine your mouth before you start SUTENT. Your healthcare provider may tell you to see your dentist before you start SUTENT.

- Tumor lysis syndrome (TLS). TLS is caused by the fast breakdown of cancer cells and may lead to death. TLS may cause you to have nausea, shortness of breath, irregular heartbeat, clouding of urine and tiredness associated with abnormal laboratory test results (high potassium, uric acid and phosphorous levels and low calcium levels in the blood) that can lead to changes in kidney function and acute kidney failure. Your healthcare provider may do blood tests to check you for TLS.
Common side effects of SUTENT include:

- rash or other skin changes, including drier, thicker, or cracking skin
- loss of appetite
- fatigue, tiredness, bruising; you may develop swelling, confusion, vision loss, and seizures. Your healthcare provider may tell you to stop taking SUTENT.

Protein in your urine. Your healthcare provider will check you for this problem. If there is too much protein in your urine, your healthcare provider may tell you to stop taking SUTENT.

Serious skin and mouth reactions. SUTENT can cause serious skin reactions that can cause death. This can include rash, widespread blistering or peeling of the skin and blistering and peeling on the inside of your mouth. If you develop a rash or these skin symptoms, tell your healthcare provider immediately. Your healthcare provider may tell you to stop taking SUTENT.

Hormone problems, including thyroid and adrenal gland problems. Your healthcare provider may do tests to check your thyroid and adrenal gland function during SUTENT treatment. Tell your healthcare provider if you have any of the following signs and symptoms during treatment with SUTENT:

- tiredness that worsens and does not go away
- heat intolerance
- feeling nervous or agitated, tremors
- sweating
- nausea or vomiting
- diarrhea
- fast heart rate
- weight gain or weight loss
- feeling depressed
- irregular menstrual periods or no menstrual periods
- headache
- hair loss

Low blood sugar (hypoglycemia). Low blood sugar can happen with SUTENT, and may cause you to become unconscious, or you may need to be hospitalized. Low blood sugar with SUTENT may be worse in people who have diabetes and take anti-diabetic medicines. Your healthcare provider should check your blood sugar levels regularly during treatment with SUTENT and may need to adjust the dose of your anti-diabetic medicines. Signs and symptoms of low blood sugar may include:

- headache
- drowsiness
- weakness
- dizziness
- confusion
- irritability
- hunger
- fast heart beat
- sweating
- feeling jittery

The medicine in SUTENT is yellow, and it may make your skin look yellow. Your skin and hair may get lighter in color.