**INDICATIONS**

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.\(^1,2\) In vitro findings may not correlate with clinical efficacy.

**KIDNEY CANCER CLINICAL STUDY**

In a Phase 3, randomized, multi-center trial comparing SUTENT with interferon-alpha (IFN-\(\alpha\)) as first-line therapy in 750 patients with treatment-naive advanced kidney cancer:\(^1\)
- SUTENT more than doubled median progression-free survival (PFS).\(^1\)
  - 11 months vs. 5 months with IFN-\(\alpha\) (95% CI: 9.8, 11.7 and 3.8, 5.5, respectively; HR=0.42 [95% CI: 0.32, 0.54; \(P<.000001\)])
  - PFS was the primary endpoint
- Nearly 40 percent of patients on SUTENT achieved an objective response
  - 28 percent vs. 5 percent with IFN-\(\alpha\) (95% CI: 23.0, 32.3 and 3.3, 8.1, respectively [\(P<.001\)]) in the first analysis (November 2005)\(^1\)
  - 39 percent vs. 8 percent with IFN-\(\alpha\) (95% CI: 33.7, 43.8 and 5.2, 10.9, respectively [\(P<.001\)]) in the final analysis (March 2010)\(^3\)
  - 90 patients’ scans had not been read at time of analysis\(^1\)
  - Objective response rate (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-\(\alpha\) arm (95% CI: 23.0, 32.9 and 17.9, 26.9, respectively; HR=0.82 [95% CI: 0.673, 1.001; \(P=0.051\)])\(^1,4\)
  - OS was a secondary endpoint

**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; \(P<.0001\)])).\(^1\)
- 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 4.4, 9.9 respectively; HR=0.33 [95 percent CI: 0.24, 0.47; \(P<.0001\)])\(^1\)
- 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 percent CI: 61.3, 83.0 and 45.7, 96.0 respectively; HR=0.876 [95% CI: 0.679, 1.129])\(^1\)
- Ninety-nine of 118 patients initially randomized to placebo crossed over to receive SUTENT in the open-label treatment phase.\(^1\)
SUTENT is the only second-line agent approved for the treatment of GIST after disease progression on or intolerance to imatinib mesylate.\(^5\)

### 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=.000146]) \(^1\)
  - 57% reduced risk of progression or death
- A statistically significant difference in ORR (a secondary endpoint) favoring SUTENT over placebo was observed.\(^1\)
  - 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.\(^1\)
- The independent DMC recommended study termination prior to the pre-specified interim analysis, which may have led to an overestimate of the magnitude of PFS effect.

### IMPORTANT SAFETY INFORMATION

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

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.

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-naive metastatic RCC (all grades, vs IFNα) 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 IFNα) 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 IFNα) included lymphocytes (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%).

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 11%), 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 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%), hypertension (27% vs 5%), hand-foot syndrome (23% vs 2%), bleeding events (22% vs 10%), epistaxis (21% vs 5%), and dysgeusia (21% vs 5%). 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

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.

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2 Potapova O, Laird AD, Nannin MA, et al. Contribution of individual targets to the antitumor efficacy of the multitargeted receptor tyrosine
4 Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUTENT safely and effectively. See full prescribing information for SUTENT.

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

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

- Warfarin: Consider dose increase of SUTENT when administered with vitamin K antagonist anticoagulants.
- Anemia: Patients with anemia may require transfusion.
- Gastrointestinal perforation: Monitor patients for signs of perforation (e.g. abdominal pain, distension, ileus, shock).
- Thyroid nodules: Patients should be monitored for nodules and thyroid function.

DOSAGE AND ADMINISTRATION

- Recommended dose: 50 mg orally once daily, with or without food.
- Dose interruption: Dose interruptions or dose adjustments of 12.5 mg are recommended based on hepatic adverse events and continued 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.
- Capsules: Capsules 12.5 mg, 25 mg, 37.5 mg, 50 mg.

CONTRAINDICATIONS

- Hepatotoxicity, including liver failure, has been observed. 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.

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: 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.

- 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.

- 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.

- Hypertension may occur. Monitor blood pressure and treat as needed.

- Hemorrhagic events including tumor-related hemorrhage have occurred. Perform serial complete blood counts and physical examinations.

- 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.

- 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 SUTENT.

- Proteinuria: Monitor urine protein. Interrupt treatment for 24-hour urine protein ≥300 mg. Discontinue for repeat episodes of protein ≥3 grams despite dose reductions or nephrotic syndrome.

- Discontinue SUTENT if necrotizing fasciitis, erythema multiforme, Stevens-Johnson Syndrome or toxic epidermal necrolysis occurs.

- Thyroid dysfunction may occur. Patients with signs and/or symptoms suggestive of hypothyroidism or hyperthyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

- Hypoglycemia may occur. Check blood glucose levels regularly and assess if anti-diabetic drug dose modifications are required.

- Osteonecrosis of the jaw has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving intraosseous bisphosphonate therapy.

- Wound Healing: Impaired wound healing has occurred with SUTENT. 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.

ADVERSE REACTIONS

- The most common adverse reactions (≥20%) are fatigue, asthenia, fever, diarrhoea, 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.

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.

- CYP3A4 Inducers: Consider dose increase of SUTENT when administered with CYP3A4 inducers.

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

Revised: 4/2015

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* Sections or subsections omitted from the full prescribing information are not listed.
**WARNING: 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].)

**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 50 mg oral dose taken once daily. In the double-blind treatment phase of Study A, 22/209 patients (11%) on SUTENT and 3/102 patients on placebo had Grade 3 or 4 decreased LV EF. In Study A, 1 patient on SUTENT and 1 patient on placebo died of diagnosed heart failure; 2/209 patients (1%) on SUTENT and 2/102 patients on placebo died of treatment-emergent adverse events.

**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 interruption 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 was 87.5 mg daily.

**5.4 QT Interval Prolongation and Torsade de Pointes**

SUTENT has been shown to prolong the QT interval in a dose dependent manner, with QTc increases of 5-10 ms at doses of 37.5 mg daily, up to 20-25 ms at 75 mg daily.

**5.5 Hypertension**

Hypertension is a common adverse event observed in patients treated with SUTENT. Patients should be monitored for hypertension and treated as needed with standard antihypertensive agents.

**5.6 Hemorrhagic Events**

Hemorrhagic events reported through 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-naive RCC, 14/375 patients (3.7%) had bleeding events compared to 35/560 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 18/83 patients (22%) receiving SUTENT in the Phase 3 pNET study, compared to 8/82 patients (10%) receiving placebo. Epistaxis was reported in 17/83 patients (20%) receiving SUTENT for pNET and 4 patients (5%) receiving placebo. Less common bleeding events in GIST, RCC and pNET patients included rectal, gingival, upper gastrointestinal, genitourinary and wound bleeding. In the double-blind treatment phase of GIST Study A, 7/141 patients (5%) on SUTENT and 4/102 patients (4%) on placebo experienced hypertension. Grade 3 hypertension was reported in 22/83 patients (27%) on SUTENT and 4/82 patients (5%) on placebo experienced hypertension. Grade 3 hypertension was reported in 22/83 patients (27%) on SUTENT and 4/82 patients (5%) on placebo experienced hypertension. Grade 3 hypertension was reported in 22/83 patients (27%) on SUTENT and 4/82 patients (5%) on placebo experienced hypertension. Grade 3 hypertension was reported in 8/83 patients (10%) on SUTENT and 1/82 patients (1%) on placebo. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) in the treatment-naive RCC study and 7/83 patients (8%). Four treatment-naive RCC patients, including one with malignant hypertension, one patient with Grade 5 hypertension, and one patient with Grade 4 hypertension, discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 8/202 patients on SUTENT (4%), 1/102 GIST patients on placebo (1%), in 32/375 treatment-naive RCC patients (9%) on SUTENT, in 3/360 patients (1%) on IFN-α, and in 8/80 pNET patients (10%) on SUTENT and 2/76 pNET patients (3%) on placebo.

**6 CONTRAINDICATIONS**

**6.1 Hepatotoxicity**

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. In patients who have undergone liver transplant, concomitant treatment with SUTENT is not recommended.

**6.2 Pregnancy**

SUTENT can cause fetal harm when administered to a pregnant woman. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be result in adverse effects in utero. In a study of rats and rabbits, subcutaneous injections of SUTENT were teratogenic, 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 a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

**6.3 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 and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <30% and evidence of treatment failure (<20% improvement from baseline).

**7 DOSAGE FORMS AND STRENGTHS**

**7.1 Tablets**

Hard gelatin capsule with orange cap and orange body, printed with black ink “Pfizer” on the cap and “STN 50 mg” on the body.

25 mg capsules

Hard gelatin capsule with orange cap and orange body, printed with black ink “Pfizer” 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 “Pfizer” on the cap and “STN 37.5 mg” on the body.

50 mg capsules

Hard gelatin capsule with yellow cap and yellow body, printed with white ink “Pfizer” on the cap and “STN 50 mg” on the body.

**7.2 Hard Gelatin Capsules**

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 orange cap and orange body, printed with black ink “Pfizer” 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 “Pfizer” on the cap and “STN 37.5 mg” on the body.

50 mg capsules

Hard gelatin capsule with orange cap and orange body, printed with white ink “Pfizer” on the cap and “STN 50 mg” on the body.
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 SUFTENT. 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 uraemic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of SUFTENT as monotherapy and in combination with bevacizumab. Discontinue SUFTENT in patients developing TMA. Recovery 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 or worsening of proteinuria, and periodic urinalyses during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt SUFTENT and dose reduce for 24-hour urine protein ≥ 3 grams. Discontinue SUFTENT for patients with nephrotic syndrome or repeat episodes of urine protein ≥ 3 grams despite dose reductions. The safety of continued SUFTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

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 these were fatal. Signs or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

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 SUFTENT treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, on SUFTENT treatment. 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
SUFTENT has been associated with symptomatic hypoglycemia, which may result in loss of consciousness or require hospitalization. Hypoglycemia has occurred in clinical trials in 2% of the patients treated with SUFTENT for RCC and GIST and in approximately 10% of the patients treated with SUFTENT for pNET. For patients being treated with SUFTENT for pNET, pre-existing abnormalities in glucose homeostasis were not present in all patients who experienced hypoglycemia with SUFTENT. Check blood glucose levels regularly during and after discontinuation of treatment with SUFTENT. Assess if anti-diabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

5.13 Osteonecrosis of the Jaw (ONJ)
ONJ has been observed in clinical trials and has been reported in post-marketing experience in patients treated with suitinib. 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 SUFTENT therapy. Temporary interruption of SUFTENT 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 resume SUFTENT therapy following a surgical intervention should be based upon clinical judgment of recovery from surgery.

5.15 Adrenal Function
Physicians prescribing SUFTENT 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/or fibrosis. In clinical studies, SUFTENT was observed in 336 patients after exposure to one or more cycles of SUFTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUFTENT. Among patients with normal baseline ACTH, 12% demonstrated an abnormal response. These results were consistent with an observed adrenal suppression. None of these patients were reported to have clinical evidence of adrenal insufficiency.

5.16 Laboratory Tests
CBCs with platelet count and serum chemistries including phosphatase should be performed at the beginning of each treatment cycle for patients receiving treatment with SUFTENT.

6 ADVERSE REACTIONS
The data described below reflect exposure to SUFTENT 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, dyspepsia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dysgeusia, 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, dyspepsia, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal dysfunction 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 SUFTENT (range 1.3-3.0), 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 SUFTENT and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUFTENT 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 SUFTENT 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 SUFTENT 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 SUFTENT and reported more commonly in patients receiving SUFTENT than in patients receiving placebo.

Table 1. Adverse Reactions Reported in Study A in at Least 10% of GIST Patients Who Received SUFTENT in the Double-Blind Treatment Phase and More Commonly in Patients Given Placebo*

<table>
<thead>
<tr>
<th>Adverse Reaction, n (%)</th>
<th>SUFTENT (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 (20)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>58 (29)</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Constipation</td>
<td>41 (20)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (15)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>28 (14)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>28 (14)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered taste</td>
<td>42 (21)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia/limb pain</td>
<td>28 (14)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Metabolism/Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>67 (33)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>45 (22)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased LV EF</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>78 (39)</td>
<td>23 (15)</td>
</tr>
<tr>
<td>Lipase</td>
<td>50 (25)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>48 (24)</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Amylase</td>
<td>35 (17)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>32 (16)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>20 (10)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>107 (53)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>76 (38)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Platelets</td>
<td>78 (38)</td>
<td>16 (10)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>21 (10)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>WALEF - Left ventricular ejection fraction</td>
<td>11 (5)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

* Includes decreased appetite

In the double-blind treatment phase of GIST Study A, oral pain other than mucositis/stomatitis occurred in 12 patients (6%) on SUFTENT versus 3 (3%) on placebo. Hair color changes occurred in 15 patients (7%) on SUFTENT versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on SUFTENT 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 SUFTENT or the Placebo in the Double-Blind Treatment Phase*
reactions for patients receiving SUTUREN versus IFN-α.

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

### Table 3. Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTUREN or IFN-α

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SUTUREN (n=375)</th>
<th>IFN-α (n=380)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (34%)</td>
<td>79 (21%)</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>41 (11%)</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
<td>91 (24%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td><strong>Dermatology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>109 (29%)</td>
<td>72 (19%)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>108 (29%)</td>
<td>72 (19%)</td>
</tr>
<tr>
<td>Skin discoloration/ yellow skin</td>
<td>94 (25%)</td>
<td>17 (5%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>246 (66%)</td>
<td>181 (48%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>85 (23%)</td>
<td>66 (18%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>50 (13%)</td>
<td>41 (11%)</td>
</tr>
<tr>
<td>GERD/reflux esophagitis</td>
<td>47 (12%)</td>
<td>32 (9%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>52 (14%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Oral pain</td>
<td>54 (14%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>40 (11%)</td>
<td>24 (6%)</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>38 (10%)</td>
<td>18 (5%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>289 (77%)</td>
<td>216 (56%)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>133 (35%)</td>
<td>93 (24%)</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered taste</td>
<td>178 (47%)</td>
<td>109 (29%)</td>
</tr>
<tr>
<td>Headache</td>
<td>86 (23%)</td>
<td>61 (16%)</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>105 (28%)</td>
<td>78 (21%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>111 (30%)</td>
<td>71 (19%)</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>61 (16%)</td>
<td>44 (12%)</td>
</tr>
</tbody>
</table>

#### Treatment-Emergent Grade 3/4 laboratory abnormalities in patients on SUTUREN included uric acid (14%), lipase (1%), phosphorous (2%), electrolyte abnormalities (2%), and sodium (1%).

6.2 Adverse Reactions in the Treatment-NAIVE RCC Study

The as-treated patient population for the treatment-naive RCC study included 735 patients, 375 randomized to SUTUREN and 360 randomized to IFN-α. The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for SUTUREN treatment and 4.1 months (range: 0.1 – 45.6) for IFN-α treatment. Treatment discontinuations were more common in patients receiving SUTUREN than in patients receiving IFN-α.

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SUTUREN (n=380)</th>
<th>IFN-α (n=380)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>211 (56%)</td>
<td>150 (40%)</td>
</tr>
<tr>
<td>ALT</td>
<td>192 (51%)</td>
<td>141 (37%)</td>
</tr>
<tr>
<td>Lipase</td>
<td>211 (56%)</td>
<td>150 (40%)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>171 (46%)</td>
<td>119 (31%)</td>
</tr>
<tr>
<td>Amylase</td>
<td>130 (35%)</td>
<td>74 (20%)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>75 (20%)</td>
<td>35 (9%)</td>
</tr>
<tr>
<td><strong>Renal/Metabolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>262 (70%)</td>
<td>183 (53%)</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>183 (49%)</td>
<td>108 (29%)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>173 (46%)</td>
<td>119 (32%)</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>156 (42%)</td>
<td>96 (26%)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>116 (31%)</td>
<td>77 (21%)</td>
</tr>
<tr>
<td>Albumin</td>
<td>106 (28%)</td>
<td>77 (21%)</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>86 (23%)</td>
<td>55 (15%)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>75 (20%)</td>
<td>55 (15%)</td>
</tr>
<tr>
<td>Calcium increased</td>
<td>163 (43%)</td>
<td>108 (29%)</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>65 (17%)</td>
<td>45 (12%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>289 (77%)</td>
<td>216 (56%)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>133 (35%)</td>
<td>93 (24%)</td>
</tr>
</tbody>
</table>

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

* Adverse Reactions, n (%)

- Grade 4 laboratory abnormalities in patients on SUTUREN included uric acid (14%), lipase (1%), phosphorous (2%), electrolyte abnormalities (2%), and sodium (1%).
- Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (14%), lipase (1%), phosphorous (2%), electrolyte abnormalities (2%), and sodium (1%).
- Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
- Adverse Reactions, n (%)

6.3 Adverse Reactions in the Phase 3 pNED Study

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

Table 5 compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTUREN and reported more commonly in patients receiving SUTUREN than in patients receiving placebo.

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*This is a fragmented representation of the document content. Full context and proper format are required for a comprehensive understanding.*
Grade 3. One patient was permanently withdrawn from SUTENT due to pulmonary embolism; dose interruption occurred in two patients with pulmonary embolism and one with DVT. In treatment-naïve RCC 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, all Grade 4. One patient (1%) receiving SUTENT for pNET had a venous thromboembolic event reported compared to 5% (6%) receiving placebo. The SUTENT patient had Grade 2 thrombosis. Two placebo patients had DVT, one was Grade 3, two placebo patients had pulmonary embolism, one was Grade 3 and one was Grade 4, and one placebo patient had Grade 3 jugular thrombosis.

6.5 Reversible Posterior Leukoencephalopathy Syndrome

There were reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). 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. Treatment with SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

6.6 Pancreatic and Hepatic Function

If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Pancreatitis was observed in 5 (1%) patients receiving SUTENT for treatment-naïve RCC compared to 1 (<1%) patient receiving IFN-α. Pancreatitis was observed in 1 (1%) patient receiving SUTENT for pNET and 1 (1%) patient receiving placebo. Hepatotoxicity was observed in patients receiving SUTENT [see Boxed Warning and Warnings and Precautions (5.1)].

6.7 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of SUTENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Blood and lymphatic system disorders: hemorrhage associated with thrombocytopenia.* Suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Gastrointestinal disorders: esophagitis. Hepatobiliary disorders: cholecystitis, particularly acalculous cholecystitis. Immune system disorders: hypersensitivity reactions, including angioedema. Infections and infestations: serious infection (with or without neutropenia).* The infections most commonly observed with sunitinib treatment include respiratory, urinary tract, skin infections, sepsis/septic shock.

6.8 Skin and Subcutaneous Tissue Disorders

Skin and subcutaneous tissue disorders: pyoderma gangrenosum, including positive dechallenges.

Vascular disorders: arterial thromboembolic events*. The most frequent events included cerebrovascular accident, transient ischemic attack and cerebral infarction. *including some fatalities

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. Co-administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) Cmax and AUC values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nelfinavir, ribavirin, nefazodone, telithromycin, voriconazole) may decrease 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 AUC 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 significantly inhibit major CYP enzymes. The in vitro evidence indicated that sunitinib is a weak inhibitor of human microsomal and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, 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 (5.2)]. 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,
Sunitinib 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 7.3 5.2

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 (PDGFRs) and PDGFbeta.

Follow-up 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 to mean steady-state concentrations of 7- to 10-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.

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 recovered in the urine and feces. No accumulation for 16% of the administered dose 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 mL/hr/kg with an average of 49 mL/hr/kg.

12.3 Pharmacokinetics

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and in 266 patients with solid tumors. Maximum plasma concentrations (Cmax) of sunitinib are generally observed between 6 and 12 hours (Tmax) following oral administration. Food has no effect on the bioavailability of sunitinib. Sunitinib is well tolerated with or without food.

Binding of sunitinib and its primary active metabolite to human plasma protein is very low, thus plasma concentrations of sunitinib can be predicted from plasma concentration-time data.

The primary active metabolite accumulates after repeated dosing at possibly clinically relevant concentrations.

The pharmacokinetics of sunitinib were shown to be linear relative to dose and duration of dosing in healthy volunteers, patients with mild hepatic impairment, and patients with severe hepatic impairment. The pharmacokinetics were not significantly affected by age, body weight, creatinine clearance, race, gender, or ECOG performance status in clinical studies in healthy volunteers and patients with solid tumors.

The pharmacokinetics of sunitinib were evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits. In rabbits, cleft lip was observed at 5 mg/kg/day. In rats, cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.3 times the AUC in patients administered the ROD). No maternal reproductive toxicity was observed in rats dosed at ≥3 mg/kg/day (approximately 2.3 times the AUC in patients administered the ROD).

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postruptural development study in monkeys. Maternal body weight gains were reduced during gestation and lactation at doses ≥1 mg/kg/day but no maternal reproductive toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the ROD). At the high dose of 3 mg/kg/day, reduced body weights were observed at birth and persisted for offspring of both sexes during the post-weaning period and in males during the post-growth period. No maternal reproductive toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the ROD).

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs). The chem ical structure of sunitinib malate is:

The chemical structure of sunitinib malate is:
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 gastrointestinal carcinomas and/or gastric mucosal hyperplasia, as well as an increased incidence of background hemangiopericytomas 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 dose 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 micromass test.

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

Although fertility was not affected in rats, sunitinib 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 administered the RDD), however significant embryotoxicity was observed at the 9.0 mg/kg dose. No reproductive effects were observed for 56 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 ≥25.8 times the AUC in patients administered the RDD).

14 CLINICAL STUDIES

14.1 Gastrinostomia Stomata 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 or after imatinib mesylate (imatinib) treatment or who were intolerant of imatinib. The objective was to compare Tim e-to-Tum or 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.

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 (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: 4%; 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. 3%), 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 is in Figure 1.

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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>SUTENT (n=375)</th>
<th>Placebo (n=185)</th>
<th>p-value (log-rank test)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Tumor Progressiona (median, weeks (95% CI))</td>
<td>27.3 (16.0, 32.1)</td>
<td>6.4 (4.4, 10.0)</td>
<td>&lt;0.0001a</td>
<td>0.33 (0.23, 0.47)</td>
</tr>
<tr>
<td>Progression-Free Survivala (median, weeks (95% CI))</td>
<td>24.1 (11.2, 28.3)</td>
<td>6.0 (4.4, 9.9)</td>
<td>&lt;0.0001a</td>
<td>0.33 (0.24, 0.47)</td>
</tr>
<tr>
<td>Objective Response Rate (%) (95% CI)</td>
<td>8.8 (3.7, 11.1)</td>
<td>0 (0, 0.006)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

a A comparison is considered statistically significant if the p-value is <0.0017 (O'Brien Remington stopping boundary)

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

c Pearson Chi-square test

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. All efficacy data presented at the interim analysis was the intent-to-treat population, 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 the recommended Phase 2 regimen (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% RR rate, 95% CI (3.0, 20.0)).

14.2 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. Seventy hundred fifty (750) patients were randomized (1:1) to receive either 50 mg SUTENT or placebo daily on Schedule 4/2 or 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 included 750 patients, 375 randomized to SUTENT and 375 randomized to IFN-α. Demographics were comparable between the SUTENT and IFN-α group 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 lungs (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 OS (see Table 8 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 Survivala (median, weeks (95% CI))</td>
<td>47.3 (42.6, 50.7)</td>
<td>22.0 (16.4, 24.0)</td>
<td>&lt;0.000001bc</td>
<td>0.415 (0.320, 0.539)</td>
</tr>
<tr>
<td>Objective Response Rate (%) (95% CI)</td>
<td>27.5 (23.0, 32.3)</td>
<td>8.1 (3.3, 15.8)</td>
<td>&lt;0.001c</td>
<td>NA</td>
</tr>
</tbody>
</table>

c=Confidence interval, NA=Not applicable

a Assessed by blinded core radiology laboratory; 90% patients' scans had been read at time of analysis
b A comparison is considered statistically significant if the p-value is ≤0.0042 (O'Brien Remington stopping boundary)
c Pearson Chi-square test

c=Confidence interval, NA=Not applicable

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= 0.821, 95 CI (0.673, 1.001)). The median OS for the IFN-α arm includes 25 patients who discontinued IFN-α treatment because of disease progression and crossed over to treat with SUTENT as well as 121 patients (32%) on the IFN-α arm who received post-study cancer treatment with SUTENT.

16 HOW SUPPLIED/STORAGE AND HANDLING
12.5 mg Capsules
Hard gelatin capsule with orange cap and orange body, printed with black ink “Pfizer” on the cap, “STN 12.5 mg” on the body; available in:
Bottles of 28: NDC 0069-0550-38
25 mg Capsules
Hard gelatin capsule with cream cap and orange body, printed with black ink “Pfizer” on the cap, “STN 25 mg” on the body; available in:
Bottles of 28: NDC 0069-0770-38
50 mg Capsules
Hard gelatin capsule with cream cap and cream body, printed with white ink “Pfizer” on the cap, “STN 50 mg” on the body; available in:
Bottles of 28: NDC 0069-0830-38
3. SUTENT is supplied in bottles of 28 capsules containing hard gelatin capsules with yellow cap and yellow body, printed with black ink “Pfizer” on the cap, “S TN 25 m g” on the body; available in:
Bottles of 28: NDC 0069-0770-38

17 PATIENT COUNSELING INFORMATION
Advising the patient to read the FDA-Approved Patient Labeling (Medication Guide).

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

17.2 Skin Effects
Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet. Severe dermatologic toxicities including Stevens-Johnson Syndrome and Toxic Epidermal Nekrolysis have been reported. Patients should be advised to immediately inform their healthcare provider if severe dermatologic reactions occur.

17.3 Other Common Events
Other commonly reported adverse reactions included fatigue, high blood pressure, bleeding, swelling, mouth pain/iritation and taste disturbance.

17.4 Osteonecrosis of the Jaw
Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients being treated with SUTENT who have previously received or are receiving bisphosphonates, invasive dental procedures should be avoided, if possible.

17.5 Hypoglycemia
Patients should be advised of the signs, symptoms, and risks associated with hypoglycemia that may occur during treatment with SUTENT. Hypoglycemia may be more severe in patients with diabetes taking anti-diabetic medications. Severe hypoglycemia including loss of consciousness or requiring hospitalization has been reported. Patients should be advised to immediately inform their healthcare provider if severe signs or symptoms of hypoglycemia occur.

17.6 Thrombotic Microangiopathy
Thrombotic microangiopathy leading to renal insufficiency and neurologic abnormalities was observed in patients who received SUTENT as monotherapy or in combination with bevacizumab. Patients should be advised that signs and symptoms of thrombotic microangiopathy may occur during treatment with SUTENT. Patients should be advised to immediately inform their healthcare provider if signs and symptoms of thrombotic microangiopathy occur.

17.7 Proteinuria
Proteinuria and nephrotic syndrome has been reported. Patients should be advised that urinalysis will be performed prior to starting as well as during treatment with SUTENT. In cases with impact to renal function, treatment with SUTENT may be interrupted or discontinued.

17.8 Concomitant Medications
Patients should be advised to inform their healthcare providers of all concomitant medications, including over-the-counter medications and dietary supplements [see Drug Interactions (7)].

This product's label may have been updated. For full prescribing information, please visit www.pfizer.com.

** Data not mature enough to determine upper confidence limit
a Assessed by blinded core radiology laboratory
b Assessed by investigators

14.3 Pancreatic Neuroendocrine Tumors
The Phase 3 study was a multi-center, international, randomized, double-blind placebo-controlled study designed to compare SUTENT conducted in patients with unresectable pNET. 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 percentage of 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 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 because of 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 21 deaths in the placebo arm. No statistical difference in OS was observed favoring SUTENT over placebo was observed. Efficacy results are summarized in Table 10 and the Kaplan-Meier curve for PFS is in Figure 3.
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 (pN ET), 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 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 pN ET, 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 phosphorus 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
- The medicine in SUTENT is yellow, and it may make your skin look yellow. Your skin and hair may get lighter in color.
- tiredness
- weakness
- fever
- gastrointestinal symptoms, including diarrhea, nausea, vomiting, mouth sores, upset stomach, abdominal pain, and constipation. Talk with your healthcare provider about ways to handle these problems.
- rash or other skin changes, including drier, thicker, or cracking skin
- loss of appetite
- pain or swelling in your arms or legs
- cough
- shortness of breath
- bleeding, such as nosebleeds or bleeding from cuts

Call your healthcare provider if you have any swelling or bleeding during treatment with SUTENT.

These are not all the possible side effects of SUTENT. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How do I store SUTENT?**

- Store SUTENT at room temperature, between 59°F to 86°F (15°C to 30°C).

**Keep SUTENT and all medicines out of the reach of children.**

**General information about SUTENT**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SUTENT for a condition for which it was not prescribed. Do not give SUTENT to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide gives the most important information about SUTENT. For more information about SUTENT, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about SUTENT that is written for health professionals.

For more information go to www.SUTENT.com or call 1-877-5-SUTENT.

**What are the ingredients 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:** titanium dioxide, red iron oxide, yellow iron oxide, black iron oxide

**White printing ink:** shellac, propylene glycol, sodium hydroxide, povidone, titanium dioxide

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Gleevec® is a registered trademark of Novartis Pharmaceuticals Corp

LAB-0361-9.0

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