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----------

Warnings and Precautions, Cardiovascular Events (5.3)	X/2015
Warnings and Precautions, Thrombotic Microangiopathy (5.8)	X/2015
Warnings and Precautions, Proteinuria (5.9)	6/2014
Warnings and Precautions, Dermatologic Toxicities (5.10)	6/2014
Warnings and Precautions, Hypoglycemia (5.12)	12/2014

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

SUTENT 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 (pNET) 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)

pNET:

- 37.5 mg orally once daily, with or without food, continuously without a scheduled off-treatment period. (2.2)

Dose Modification:

- Dose interruptions and/or dose adjustments of 12.5 mg recommended based on individual safety and tolerability. (2.3)

----------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. 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. (5.1)
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.2)
- 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 SUTENT, 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 SUTENT. (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 SUTENT if necrotizing fasciitis, erythema multiforme, Stevens-Johnson Syndrome or toxic epidermal necrolysis occurs. (5.10).
- 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. (5.11)
- Hypoglycemia may occur. Check blood glucose levels regularly and assess if anti-diabetic drug dose modifications are required. (5.12)
- 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 intravenous bisphosphonate therapy. (5.13)
- Wound Healing: Impaired wound healing has occurred with SUTENT. Temporary interruption of therapy with SUTENT 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, dyspnea, anorexia, and bleeding. (6)

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

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

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

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

Revised: X/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY
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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 interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability. The maximum dose administered in the Phase 3 pNET study was 50 mg daily.

Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose

reduction for SUTENT to a minimum of 37.5 mg (GIST and RCC) or 25 mg (pNET) daily should be considered if SUTENT must be co-administered with a strong CYP3A4 inhibitor *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. A dose increase for SUTENT to a maximum of 87.5 mg (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 DOSAGE FORMS AND STRENGTHS

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

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

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 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 conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor 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 other signs and symptoms of liver failure.

Safety in patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN has not been established.

5.2 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 expected to result in adverse effects on pregnancy. In animal reproductive studies in rats and rabbits, sunitinib was 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.

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 and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% 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 GIST 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 systolic function to LVEF <40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. In the double-blind treatment phase of GIST Study A, 1 patient on SUTENT and 1 patient on placebo died of diagnosed heart failure; 2 patients on SUTENT and 2 patients on placebo died of treatment-emergent cardiac arrest.

In the treatment-naïve RCC study, 103/375 (27%) and 54/360 (15%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Twenty-six patients on SUTENT (7%) and seven on IFN-α (2%) experienced declines in LVEF to >20% below baseline and to below 50%. Left ventricular dysfunction was reported in four patients (1%) and CHF in two patients (<1%) who received SUTENT.

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

5.4 QT Interval Prolongation and Torsade de Pointes

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

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

5.5 Hypertension

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

Of patients receiving SUTENT for treatment-naïve RCC, 127/375 patients (34%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 50/375 treatment-naïve RCC patients (13%) on SUTENT compared to 1/360 patients (<1%) on IFN-α.

While all-grade hypertension was similar in GIST patients on SUTENT compared to placebo, Grade 3 hypertension was reported in 9/202 GIST patients on SUTENT (4%), and none of the GIST patients on placebo. Of patients receiving SUTENT in the Phase 3 pNET study, 22/83 patients (27%) on SUTENT and 4/82 patients (5%) on placebo experienced hypertension. Grade 3 hypertension was reported in 8/83 pNET patients (10%) on SUTENT, and 1/82 patient (1%) on placebo. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) on the treatment-naive RCC study and 7/83 pNET patients (8%). Four treatment-naïve RCC patients, including one with malignant hypertension, one patient with pNET, and no GIST patients discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 8/202 GIST patients on SUTENT (4%), 1/102 GIST patients on placebo (1%), in 32/375 treatment-naïve 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.

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-naïve RCC, 140/375 patients (37%) 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 18/83 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, genital, and wound bleeding. In the double-blind treatment phase of GIST Study A, 14/202 patients (7%) receiving SUTENT and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in GIST Study A taking placebo had a fatal gastrointestinal bleeding event during Cycle 2. Most events in RCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment-naïve patient. In the pNET study, 1/83 patients (1%) receiving SUTENT had Grade 3 epistaxis, and no patients had other Grade 3 or 4 bleeding events. In pNET patients receiving placebo, 3/82 patients (4%) had Grade 3 or 4 bleeding events.

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

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

5.7 Tumor Lysis Syndrome (TLS)

Cases of TLS, some fatal, have been observed in clinical trials and have been reported in post-marketing experience, primarily 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

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