Contact the specialty pharmacy directly to fill the prescription if one of the following applies:
- Your office knows the patient’s specialty pharmacy
- Your patient knows that the specialty pharmacy is covered in his/her plan and that the pharmacy is in the treatment network
- Your office uses a specialty pharmacy that is in the patient’s network

### SPECIALTY PHARMACY ORDERING PROCESS

**The provider’s office**
- Submits prescriptions to the specialty pharmacy via:
  - PHONE
  - FAX
  - INTERNET
- Submits any supporting documentation to the payer

**The specialty pharmacy**
- Verifies the patient’s coverage
- Helps with prior authorization, if required
- Can help patients seek co-pay assistance
- Schedules shipment of product to the patient’s home
- Bills the payer for the cost of the product
- Bills the patient for remaining co-pay/coinsurance

### Option 1
Contact the specialty pharmacy directly
(See next page for a list of specialty pharmacies.)

### Option 2
If option 1 is not applicable, contact Pfizer Patient Support

Pfizer Patient Support helps eligible patients get access to their Pfizer medicines by offering a range of prescription assistance services.
- Pfizer Patient Support helps insured patients find an appropriate specialty pharmacy
- For uninsured and underinsured patients, Pfizer Patient Support can provide eligible patients with free medicine for up to 12 months

Visit the Pfizer provider portal for the Patient Assistance Program at www.PfizerPAP.com to begin the enrollment process for new patients and to manage existing ones, or call 1-877-744-5675 Monday to Friday, 8 AM to 8 PM ET.

IBRANCE, INLYTA, XALKORI, BOSULIF, and SUTENT are NOT available through traditional retail pharmacies.

Pfizer Patient Support is a joint program of Pfizer Inc and the Pfizer Patient Assistance Foundation™. Pfizer Patient Support is a part of Pfizer’s Global Social Investments portfolio. For more information, please visit www.pfizer.com/responsibility.

Please see full Prescribing Information, including BOXED WARNING and Medication Guide, for SUTENT, on subsequent pages. Please see full Prescribing Information for all products at www.pfizerpro.com.
IBRANCE® (palbociclib), INLYTA® (axitinib), XALKORI® (crizotinib), BOSULIF® (bosutinib), and SUTENT® (sunitinib malate)—available through these specialty pharmacies

Please see full Prescribing Information, including BOXED WARNING and Medication Guide, for SUTENT, on subsequent pages.

Please see full Prescribing Information for all products at www.pfizerpro.com.
**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. ([Warnings and Precautions](#))

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**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 (pN ET) in patients with unresectable locally advanced or metastatic disease. (1.3)

**DOSAGE AND ADMINISTRATION**

GIST and RCC:

- 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 4 weeks off. (2.1)
- 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)

**DOSE 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)

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**ADVERSE REACTIONS**

- Cardiovascular events including myocardial ischemia, myocardial infarction, left ventricular ejection fraction declines to below the lower limit of normal and cardiac failure including death have occurred. Monitor patients for signs and symptoms of congestive heart failure. (5.3)
- Prolonged QT intervals and Torsade de Pointes have been observed. Use with caution in patients at higher risk for developing QT interval prolongation. When using 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 if 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. Intermittent 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 hyperthyroidism or hypothyroidism 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)

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**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.
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 (RC)

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 (RC) is 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 to patients in the pivotal trials was 75 mg daily.

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 for patients to a maximum of 57.5 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)].

2.4 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 “S TN 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 “S TN 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 “S TN 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 “S TN 50 mg” on the body.

3 CONTRAINDICATIONS

Not applicable.

4 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

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

5.2 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 in animal reproduction studies in rats and rabbits, which included teratogenicity, embryotoxicity, and fetotoxicity. 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 or reduced in patients without clinical evidence of CHF but with an ejection fraction <25% or 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 ejection fraction (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 died of treatment-related cardiovascular events. In the 21-day off-treatment phase of the SUTENT study, 2 patients on placebo died of treatment-related cardiovascular events.

In the treatment-naive 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 <50% baseline. Left ventricular failure was reported in four patients (1%) and 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 congestive heart failure 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 not clear whether patients with these 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 being treated. In patients with cardiac risk factors, a baseline evaluation of LVEF should be considered.

In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. A baseline evaluation of LVEF should be considered while these patients are being treated. In patients with cardiac risk factors, a baseline evaluation of LVEF should be considered.

In the double-blind treatment phase of GIST Study A, patients treated with 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 <50% baseline. Left ventricular failure was reported in four patients (1%) and 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 congestive heart failure 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 not clear whether patients with these 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 being treated. In patients with cardiac risk factors, a baseline evaluation of LVEF should be considered while these patients are being treated. In patients with cardiac risk factors, a baseline evaluation of LVEF should be considered.
Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intrabdominal 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 surveillance of patients with RCC or GIST treated with SUTENT. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

5.8 Thrombotic Microangiopathy
Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Resolution of the signs 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 SUTENT and dose reduce for 24-hour urine protein ≥ 3 gms. Discontinue SUTENT for patients with nephrotic syndrome or repeat episodes of urine protein ≥ 3 gms despite dose reductions. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

5.10 Dermatologic Toxocities
Severe cutaneous reactions have been included, such as cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Some cases were fatal. Signs or symptoms suggestive of a severe cutaneous reaction should be treated as per standard medical practice. A diagnosis of SJS or TEN is suspected, SUTENT treatment should not be re-started.

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with SUTENT, including of the periumbilical and peristomal regions. Discontinue SUTENT in patients who develop necrotizing fasciitis.

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

Treatment-emergent acquired hypothyroidism was noted in eight GIST patients (4%) on SUTENT versus 2% on placebo. A low dose of levothyroxine was started when hypothyroidism was identified prior to the time of the interim analysis. Dose reductions occurred in 23 patients (11%) on SUTENT and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUTENT and 31 patients (30%) on placebo. The rates of treatment-emergent, non-fatal adverse reactions resulting in permanent discontinuation were 7% and 6% in the SUTENT and placebo groups, respectively.

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

<table>
<thead>
<tr>
<th>Table 1. Adverse Reactions Reported in Study A in at Least 10% of GIST Patients Who Received SUTENT in the Double-Bind Treatment Phase and More Commonly Than in Patients Given Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reaction, n (%)</strong></td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
</tr>
<tr>
<td><strong>Metabolism/Nutrition</strong></td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
</tr>
<tr>
<td>Convulsions</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td><strong>Hypersensitivity</strong></td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Angioedema</td>
</tr>
</tbody>
</table>

6.1 Adverse Reactions in GIST Study A
Median duration of blinded study treatment was two cycles for patients on SUTENT (mean 3.0, range 1.8-6.0) and one cycle (mean 1.3, range 1.0-6.0) for patients on placebo at the time of the interim analysis. Dose reductions occurred in 23 patients (11%) on SUTENT and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUTENT and 31 patients (30%) on placebo. The rates of treatment-emergent, non-fatal adverse reactions resulting in permanent discontinuation were 7% and 6% in the SUTENT and placebo groups, respectively.

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

In the double-blind treatment phase of GIST Study A, oral pain other than mucositis/stomatitis occurred in 12 patients (6%) on SUTENT versus 3 (3%) on placebo. Hair color changes occurred in 15 patients (7%) on SUTENT versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on SUTENT versus 2 (2%) on placebo. Table 2 provides common (≥10%) treatment-emergent laboratory abnormalities.

<table>
<thead>
<tr>
<th>Table 2. Laboratory Abnormalities Reported in Study A in at Least 10% of GIST Patients Who Received SUTENT or Placebo in the Double-Bind Treatment Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter, n (%)</strong></td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>AST / ALT</td>
</tr>
<tr>
<td>Lipase</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>Amylase</td>
</tr>
<tr>
<td>Total bilirubin</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
</tr>
<tr>
<td>Decreased LVEF</td>
</tr>
<tr>
<td><strong>Renal/Metabolic</strong></td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Potassium decreased</td>
</tr>
<tr>
<td>Sodium increased</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
</tr>
<tr>
<td>Neutrophils</td>
</tr>
<tr>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td>Hemoglobin</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 SUTENT versus 3 (3%) on placebo. Hair color changes occurred in 15 patients (7%) on SUTENT versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on SUTENT versus 2 (2%) on placebo. Table 2 provides common (≥10%) treatment-emergent laboratory abnormalities.
after an interim analysis, the study was unblinded, and patients on the placebo arm were given the opportunity to receive open-label SUTENT treatment [see Clinical Studies (14.1)]. For 241 patients randomized to the SUTENT arm, including 139 who received SUTENT in both the double-blind and open-label treatment phases, the median duration of SUTENT treatment was 6 cycles (mean 8.5, range 1 – 44). For the 255 patients who ultimately received open-label SUTENT treatment, median duration of study treatment was 6 cycles (mean 7.8, range 1 – 37) from the time of the unblinding. A total of 118 patients (46%) required dosing interruptions, and a total of 72 patients (28%) required dose reductions. The incidence of treatment-emergent adverse reactions resulting in permanent discontinuation was 20%. The most common Grade 3 or 4 treatment-related adverse reactions experienced by patients receiving SUTENT in the open-label treatment phase were fatigue (10%), hypertension (8%), asthenia (5%), diarrhea (5%), hand-foot syndrome (5%), nausea (4%), abdominal pain (3%), anorexia (3%), mucositis (2%), vomiting (2%), and hypophosphatemia (2%).

### 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 SUTENT and 360 randomized to IFN-α. The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for SUTENT treatment and 4.1 months (range: 0.1 – 45.6) for IFN-α treatment. Dose interruptions occurred in 202 patients (54%) on SUTENT and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on SUTENT and 98 patients (27%) on IFN-α. Discontinuation rates due to adverse reactions were 20% for SUTENT and 24% for IFN-α. 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 77% versus 55% of patients on SUTENT versus IFN-α, respectively.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constitutional</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>84 (26)</td>
<td>2 (1)</td>
<td>72 (21)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>96 (26)</td>
<td>2 (1)</td>
<td>84 (23)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fever</td>
<td>53 (14)</td>
<td>1 (1)</td>
<td>50 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>80 (16)</td>
<td>2 (1)</td>
<td>72 (16)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Chills</td>
<td>53 (14)</td>
<td>1 (1)</td>
<td>50 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>15 (5)</td>
<td>1 (1)</td>
<td>14 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>17 (5)</td>
<td>0 (0)</td>
<td>16 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>246 (66)</td>
<td>12 (1)</td>
<td>204 (56)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>216 (58)</td>
<td>21 (6)</td>
<td>195 (52)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>178 (47)</td>
<td>19 (5)</td>
<td>159 (41)</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>148 (39)</td>
<td>5 (1)</td>
<td>143 (38)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>128 (34)</td>
<td>8 (2)</td>
<td>120 (31)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Abdominal painc</td>
<td>113 (30)</td>
<td>20 (5)</td>
<td>93 (24)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>85 (23)</td>
<td>4 (1)</td>
<td>81 (22)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>50 (13)</td>
<td>2 (1)</td>
<td>48 (13)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>GERD/reflux</td>
<td>38 (10)</td>
<td>1 (1)</td>
<td>37 (10)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (34)</td>
<td>10 (3)</td>
<td>117 (32)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>91 (24)</td>
<td>7 (2)</td>
<td>84 (21)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
<td>80 (21)</td>
<td>1 (1)</td>
<td>79 (21)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Dermatological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>109 (29)</td>
<td>5 (1)</td>
<td>104 (28)</td>
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<td>19 (5)</td>
<td>131 (34)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

### 6.3 Adverse Reactions in the Phase 3 pNET Study

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

Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 54% versus 50% of patients on SUTENT versus placebo, respectively. Table 5 compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT and reported more commonly in patients receiving SUTENT than in patients receiving placebo.
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 patients (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 25 Grade 1 events, one Grade 3 event, and one Grade 4 event. No patients had Grade 5 events reported. Reversible posterior leukoencephalopathy syndrome (RPLS) is a rare, reversible, and potentially fatal condition with a characteristic clinical picture of headaches, altered mental status, seizures, and brain imaging changes. Treatment discontinuation is recommended after the first episode to prevent future events. The presence of antinuclear antibodies increases the risk of developing RPLS. The condition is more common in patients with RCC. The management of RPLS includes support, symptomatic treatment, and discontinuation of the drug that precipitated the condition. For patients with RPLS, a multidisciplinary approach, including neurologists and intensivists, is recommended to provide comprehensive care.

### 6.6 Pancreatic and Hepatic Function

A single patient (<1%) on SUTENT had Grade 4 acute pancreatitis. A single patient (<1%) on SUTENT had Grade 3 hepatic enzyme increase. There were no Grade 5 hepatic enzymes increases reported. Acute pancreatitis is a clinical syndrome characterized by acute inflammation of the pancreas, resulting in significant pain, fever, and laboratory abnormalities. The condition can be caused by various factors, including sunitinib. Management includes supportive care and discontinuation of the drug. Hepatic enzyme increases, on the other hand, are common with sunitinib treatment and are usually mild and transient. Monitoring liver function tests is recommended during treatment with sunitinib. If increases are observed, treatment discontinuation should be considered.

### 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*.

Surgical site infections: incisional hernia. Vascular disorders: arterial thromboembolic events. The most frequent events included cerebrovascular accident, transient ischemic attack and cerebral infarction.

### 7 DRUG INTERACTIONS

#### 7.1 CYP3A4 Inhibitors

Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of strong inhibitors of the CYP3A4 is recommended to avoid drug-drug interactions.

#### 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 strong inducers of the CYP3A4 is recommended to avoid drug-drug interactions.

### 7.3 In Vitro Studies of CYP Inhibition and Induction

In vitro studies indicated that sunitinib does not inhibit major CYP enzymes. The in vitro finding indicated that sunitinib is not 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 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 abortifacient.
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 receiving this treatment, SUTENT should not be administered to breastfeeding women. The safety and effectiveness in children under 18 were not established; therefore, use in children under 18 is not recommended. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Cases of accidental overdosage with SUTENT have occurred, and have been managed with supportive measures. There have been no deaths associated with SUTENT overdosage.

Sunitinib was evaluated for safety and efficacy in a variety of human malignant tumors. Sunitinib has a Cmax of 0.94-8.1 ng/mL with a Tmax of 6-24 hours, depending on the dose. The mean terminal half-life (t1/2) of Sunitinib in patients with Advanced RCC is 62 L/hr with an inter-patient variability of 40% . Sunitinib and its metabolites are eliminated primarily via the urine, representing 91.5% , 86.4% and 73.8% of radioactivity in urine, respectively. Minor metabolites were identified in urine and feces, representing 91.5%, 86.4% and 73.8% of radiolabeled metabolites, respectively. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/hr with an inter-patient variability of 40% .

10. Overdosage
Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of SUTENT, or without adverse reactions. A case of intentional overdose involving the ingestion of 1,300 mg of SUTENT was reported where the patient survived the ingestion. The patient was peritoneal dialysis dependent for end-stage renal disease (ESRD) on hemodialysis, and the starting dose was required. However, compared to subjects with normal renal function, the sunitinib exposure is 47% lower in subjects with ESRD on hemodialysis. Therefore, the subsequent doses may be increased gradually up to 2 fold based on safety and tolerability.

11. Description
SUTENT, an oral multi-kinase inhibitor, is the malate salt of sunitinib. Sunitinib malate is formulated as a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2. The chem汲取ical structure of sunitinib malate is:

\[
\text{CH}_3\text{CO}_2\text{H} + \text{F}_{3}\text{N} = \text{O} + \text{NH}_2 + \text{CH}_2 - \text{CH} = \text{CH} - \text{C} - \text{H}_2 + \text{C}_6\text{H}_5\text{O}_2 + \text{C}_2\text{H}_4\text{N}_3 + \text{O}_2 + \text{CH}_3
\]

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\[
\text{H} + \text{CH}_3\text{CO}_2\text{H} + \text{F}_{3}\text{N} = \text{O} + \text{NH}_2 + \text{CH}_2 - \text{CH} = \text{CH} - \text{C} - \text{H}_2 + \text{C}_6\text{H}_5\text{O}_2 + \text{C}_2\text{H}_4\text{N}_3 + \text{O}_2 + \text{CH}_3
\]

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (~80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been correlated with the chem汲取ical structure and reversible inhibition of the activity of these RTKs. Sunitinib exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRα, VEGFR2, KIT) in tumor xenografts expressing RTK targets in vivo and demonstrated inhibition of tumor growth in vivo. Sunitinib also inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated RTK targets (PDGFR, RET, or KIT) in vitro and to inhibit PDGFR- and VEGFR2-dependent tumor angiogenesis in vivo.

12. Mechanism of Action
Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (~80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been correlated with the chem汲取ical structure and reversible inhibition of the activity of these RTKs. Sunitinib exhibits similar potency compared to sunitinib in biochemical and cellular assays.

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13. 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 can be taken with or without food.

Binding of sunitinib and its primary active metabolite to human plasma protein in vitro was 95% and 90%, respectively, with no concentration dependence in the range of 100 to 4000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was 2230 L. In the dosing range of 25 - 150 mg, the area under the plasma concentration-time curve (AUC) was proportional to the dose.

Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23 to 37% of the total exposure. Elimination is primarily via feces. In a human mass balance study of [14C]sunitinib, 61% of the dose was recovered in feces, 13% in urine and the remaining 26% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/hr with an inter-patient variability of 40% . Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively. With repeated daily administration, sunitinib accumulates to 3- to 4-fold with the primary metabolite accumulating 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite ranged from 62.9 – 101 ng/mL. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

The pharmacokinetics were similar in healthy volunteers and in the solid tumor patient populations tested, including patients with GIST and RCC.

Pharmacokinetics in Special Populations
Population pharmacokinetic analyses of demographic data indicate that there are no clinical relevant effects of age, weight, creatinine clearance, race, gender, or ECOG score on the pharmacokinetics of SUTENT or the primary active metabolite.

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

Renal Insufficiency: Sunitinib systemic exposure after a single dose of SUTENT was similar in subjects with severe renal impairment (Clcr<30 mL/min) compared to subjects with normal renal function (Clcr>80 mL/min). Although sunitinib was not eliminated through hemodialysis, the sunitinib systemic exposure was 47% lower in subjects with ESRD on hemodialysis compared to subjects with normal renal function.

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

15. Side Effects
The most common adverse reactions reported during treatment with SUTENT were as follows: Fatigue, taste perversion, and diarrhea were the most common adverse reactions that were reported during treatment with SUTENT. The most common adverse reactions reported during treatment with SUTENT were as follows: Fatigue, taste perversion, and diarrhea were the most common adverse reactions that were reported during treatment with SUTENT. The most common adverse reactions reported during treatment with SUTENT were as follows: Fatigue, taste perversion, and diarrhea were the most common adverse reactions that were reported during treatment with SUTENT.
12.4 Cardiac Electrophysiology
See Warnings and Precautions (5.4).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of sunitinib has been evaluated in two species; rasH2 transgenic mice and Sprague-Dawley rats. There were similar positive findings in both species. In rasH2 transgenic mice gastroduodenal carcinomas and/or gastric mucosal hyperplasia, as well as an increased incidence of background hemangiosarcomas were observed at doses of ≥25 mg/kg/day following daily dose administration of sunitinib in studies of 1 or 6 months duration. No proliferative changes were observed in rasH2 transgenic mice at 8 mg/kg/day. Similarly, in a 2-year rat carcinogenicity study, administration of sunitinib in 28-day cycles followed by 7-day dose-free periods resulted in development of duodenal carcinoma at doses as low as 1 mg/kg/day (approximately 0.9 times the AUC in patients given the RDD of 50 mg/day). At the high dose of 3 mg/kg/day (approximately 7.8 times the AUC in patients at the RDD of 50 mg/day) the incidence of duodenal tumors was increased and was accompanied by findings of gastric mucosal hyperplasia and by an increased incidence of pheochromocytoma and hyperplasia of the adrenal. Sunitinib did not cause genetic damage when tested in in vitro assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an in vivo rat bone marrow micronucleus test.

The planned interim efficacy and safety analysis was performed after 149 TTP events had occurred. There was a statistically significant advantage for SUTEN over placebo in TTP, meeting the primary endpoint. Efficacy results are summarized in Table 7 and the Kaplan-Meier curve in Figure 1.

The final ITT population enrolled in the double-blind treatment phase of the study included 243 patients randomized to the SUTEN arm and 118 patients randomized to the placebo arm. Among the 118 patients, the primary endpoint was met at the interim analysis, the study was unblinded, and patients on the placebo arm were offered open-label SUTEN treatment. Ninety-nine of the patients initially randomized to placebo crossed over to receive SUTEN in the open-label treatment phase. At the protocol-specified final analysis of OS, the median OS was 72.7 weeks for the SUTEN arm and 64.9 weeks for the placebo arm (HRs: 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 (95% confidence interval on Schedule 4/2), 55 patients in this study received the 50 mg dose of SUTEN on treatment Schedule 4/2. Partial responses were observed in 5 of 55 patients [9.1% PR rate, 95% CI (3.0, 20.0)].

14.2 Renal Cell Carcinoma

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

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

There was a statistically significant advantage for SUTEN 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 SUTEN over IFN-α. The OHR was higher in the SUTEN arm (see Table 8).

Table 8. Treatment-Naive RCC Efficacy Results (interim analysis)

- **Efficacy Parameter**
- **SUTEN (n=375)**
  - Progression-Free Survival (median, weeks (95% CI))
    - 47.3 (42.6, 50.7)
  - IFN-α (n=375)
    - 22.0 (16.4, 24.0)
  - P-value (log-rank test)
    - <0.00001<sup>a</sup>
  - HR (95% CI)
    - 0.415 (0.320, 0.539)

- **Objective Response Rate [% (95% CI)]**
  - SUTEN
    - 27.5 (23.0, 32.3)
  - IFN-α
    - 5.3 (3.1, 8.1)
  - P-value (log-rank test)
    - <0.001<sup>b</sup>
  - HR (95% CI)
    - NA

<sup>a</sup> Confidence interval, NA: Not applicable
<sup>b</sup> Assessed by blinded core radiology laboratory; 90% patients’ scans had not been read at time of analysis
<sup>c</sup> A comparison is considered statistically significant if the p-value is ≤ 0.0042 (O’Brien Reming stopping boundary)

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

- **Efficacy Parameter**
- **SUTEN (n=207)**
  - Time to Tumor Progression* (median, weeks (95% CI))
    - 27.2 (16.0, 32.1)
  - IFN-α (n=105)
    - 14.6 (4.4, 10.0)
  - P-value (log-rank test)
    - <0.001<sup>c</sup>
  - HR (95% CI)
    - 0.33 (0.23, 0.47)

- **Progression-Free Survival [median, weeks (95% CI)]**
  - SUTEN
    - 47.3 (42.6, 50.7)
  - IFN-α
    - 22.0 (16.4, 24.0)
  - P-value (log-rank test)
    - <0.00001<sup>a</sup>
  - HR (95% CI)
    - 0.415 (0.320, 0.539)

- **Objective Response Rate [% (95% CI)]**
  - SUTEN
    - 27.5 (23.0, 32.3)
  - IFN-α
    - 5.3 (3.1, 8.1)
  - P-value (log-rank test)
    - <0.001<sup>b</sup>
  - HR (95% CI)
    - NA

<sup>a</sup> Confidence interval, NA: Not applicable
<sup>b</sup> Assessed by blinded core radiology laboratory; 90% patients’ scans had not been read at time of analysis
<sup>c</sup> A comparison is considered statistically significant if the p-value is ≤ 0.0042 (O’Brien Reming stopping boundary)

<sup>* A comparison is considered statistically significant if the p-value is ≤ 0.0041 (O’Brien Reming stopping boundary)
At the protocol-specified final analysis of OS, the median OS was 114.6 weeks for the SUTENT arm and 94.3 weeks for the IFN-α arm (HR= 0.821, 95% CI (0.673, 1.001)). The median OS for the IFN-α arm included 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.

Cytokine-Refractory RCC

The use of single agent SUTENT in the treatment of cytokine-refractory RCC was investigated in two single-arm, multi-center studies. All patients enrolled into these studies experienced failure of prior cytokine-based therapy. In Study 1, failure of prior cytokine therapy was based on radio graphic evidence of disease progression defined by RECIST or World Health Organization (WHO) criteria during or within 9 months of completion of 1 cytokine therapy treatment (IFN-α, interleukin-2, or IFN-α plus interleukin-2; patients who were treated with IFN-α alone must have received treatment for at least 28 days). In Study 2, failure of prior cytokine therapy was defined as disease progression or unacceptable treatment-related toxicity. The endpoint for both studies was ORR. Duration of Response (DR) was also evaluated.

One hundred six patients (106) were enrolled into Study 1, and 63 patients were enrolled into Study 2. Patients in the SUTENT arm were followed for 24 and 87 weeks in Study 1 and 2, respectively. Therapy was continued until the patients met withdrawal criteria or had progressive disease. The baseline age, gender, race and ECOG performance statuses of the patients were comparable between Studies 1 and 2. Approximately 86-94% of patients in the two studies were Black. Men comprised 65% of the pooled population. The median age was 57 years and ranged from 24 to 87 years in the studies. All patients had an ECOG performance status ≤2 at the screening visit.

The baseline malignancy and prior treatment history of the patients were comparable between Studies 1 and 2. Across the two studies, 85% of the pooled population of patients had at least some component of clear-cell histology. All patients in Study 1 were required to have a histological clear-cell component. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in Study 1. All patients had received one previous cytokine regimen. Metastatic disease was defined as at least one lesion at the time of study entry included lung metastases in 61% of patients. Liver metastases were more common in Study 1 (27% vs. 16% in Study 2) and bone metastases were more common in Study 2 (51% vs. 25% in Study 1); 52% of patients in the pooled population had at least 3 metastatic sites. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

The ORR and DR data from Studies 1 and 2 are provided in Table 9. There were 36 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 34.0% (95% CI 25.0, 43.8). There were 23 PRs in Study 2 as assessed by the investigators for an ORR of 36.5% (95% CI 24.7, 49.6). The majority (>90%) of objective disease responses were observed during the first four cycles; the latest reported response was observed in Cycle 10. DR data from Study 1 is premature as only 9 of 36 patients (25%) responding to treatment had experienced disease progression or died at the time of the data cutoff.

### Table 9. Cytokine-Refractory RCC Efficacy Results

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study 1 (N=106)</th>
<th>Study 2 (N=63)</th>
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<tbody>
<tr>
<td>Objective Response Rate</td>
<td>34.0% (95% CI)</td>
<td>36.5% (95% CI)</td>
</tr>
<tr>
<td>Duration of Response (DR)</td>
<td>9.3 weeks (95% CI)</td>
<td>5.4 weeks (95% CI)</td>
</tr>
</tbody>
</table>

**Objective Response Rate** (95% CI) = 9.3% (3.2, 15.4) vs. 0% (Fisher's Exact test, NA)

**Duration of Response (DR)** median (95% CI) = 9.3 weeks (3.2, 15.4) vs. 5.4 weeks (2.3, 15.4)

At the protocol-specified final analysis of OS, the median OS was 114.6 weeks for the SUTENT arm and 94.3 weeks for the IFN-α arm (HR= 0.821, 95% CI (0.673, 1.001)). The median OS for the IFN-α arm included 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.

Cytokine-Refractory RCC

The use of single agent SUTENT in the treatment of cytokine-refractory RCC was investigated in two single-arm, multi-center studies. All patients enrolled into these studies experienced failure of prior cytokine-based therapy. In Study 1, failure of prior cytokine therapy was based on radio graphic evidence of disease progression defined by RECIST or World Health Organization (WHO) criteria during or within 9 months of completion of 1 cytokine therapy treatment (IFN-α, interleukin-2, or IFN-α plus interleukin-2; patients who were treated with IFN-α alone must have received treatment for at least 28 days). In Study 2, failure of prior cytokine therapy was defined as disease progression or unacceptable treatment-related toxicity. The endpoint for both studies was ORR. Duration of Response (DR) was also evaluated.

One hundred six patients (106) were enrolled into Study 1, and 63 patients were enrolled into Study 2. Patients in the SUTENT arm were followed for 24 and 87 weeks in Study 1 and 2, respectively. Therapy was continued until the patients met withdrawal criteria or had progressive disease. The baseline age, gender, race and ECOG performance statuses of the patients were comparable between Studies 1 and 2. Approximately 86-94% of patients in the two studies were Black. Men comprised 65% of the pooled population. The median age was 57 years and ranged from 24 to 87 years in the studies. All patients had an ECOG performance status ≤2 at the screening visit.

The baseline malignancy and prior treatment history of the patients were comparable between Studies 1 and 2. Across the two studies, 85% of the pooled population of patients had at least some component of clear-cell histology. All patients in Study 1 were required to have a histological clear-cell component. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in Study 1. All patients had received one previous cytokine regimen. Metastatic disease was defined as at least one lesion at the time of study entry included lung metastases in 61% of patients. Liver metastases were more common in Study 1 (27% vs. 16% in Study 2) and bone metastases were more common in Study 2 (51% vs. 25% in Study 1); 52% of patients in the pooled population had at least 3 metastatic sites. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

The ORR and DR data from Studies 1 and 2 are provided in Table 9. There were 36 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 34.0% (95% CI 25.0, 43.8). There were 23 PRs in Study 2 as assessed by the investigators for an ORR of 36.5% (95% CI 24.7, 49.6). The majority (>90%) of objective disease responses were observed during the first four cycles; the latest reported response was observed in Cycle 10. DR data from Study 1 is premature as only 9 of 36 patients (25%) responding to treatment had experienced disease progression or died at the time of the data cutoff.

### Table 9. Cytokine-Refractory RCC Efficacy Results

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study 1 (N=106)</th>
<th>Study 2 (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate</td>
<td>34.0% (95% CI)</td>
<td>36.5% (95% CI)</td>
</tr>
<tr>
<td>Duration of Response (DR)</td>
<td>9.3 weeks (95% CI)</td>
<td>5.4 weeks (95% CI)</td>
</tr>
</tbody>
</table>

**Objective Response Rate** (95% CI) = 9.3% (3.2, 15.4) vs. 0% (Fisher's Exact test, NA)

**Duration of Response (DR)** median (95% CI) = 9.3 weeks (3.2, 15.4) vs. 5.4 weeks (2.3, 15.4)
**MEDICATION GUIDE**

**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 looseness of a tooth
- have any other medical conditions
- are pregnant, could be pregnant or plan to become pregnant. SUTENT may harm an unborn baby. You should not become pregnant while taking SUTENT. Tell your healthcare provider right away if you become pregnant while taking SUTENT.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take SUTENT or breastfeed. You should not do both. Tell all of your healthcare providers and dentists that you are taking SUTENT. They should talk to the healthcare provider who prescribed SUTENT for you, before you have any surgery, or medical or dental procedure.

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

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

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

**How should I take SUTENT?**

- Take SUTENT exactly the way your healthcare provider tells you.
- Take SUTENT 1 time each day with or without food.
- If you take SUTENT for GIST or RCC, you will usually take your medicine for 4 weeks (28 days) and then stop for 2 weeks (14 days). This is 1 cycle of treatment. You will repeat this cycle for as long as your healthcare provider tells you to.
- If you take SUTENT for 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 phosphorous levels and low calcium levels in the blood) that can lead to changes in kidney function and acute kidney failure. Your healthcare provider may do blood tests to check you for TLS.
Common side effects of SUTENT include:

• rash or other skin changes, including drier, thicker, or cracking skin
• protein in your urine. Your healthcare provider will check you for this problem. If there is too much protein in your urine, your healthcare provider may tell you to stop taking SUTENT.
• serious skin and mouth reactions. SUTENT can cause serious skin reactions that can cause death. This can include rash, widespread blistering or peeling of the skin and blistering and peeling on the inside of your mouth. If you develop a rash or these skin symptoms, tell your healthcare provider immediately. Your healthcare provider may tell you to stop taking SUTENT.
• hormone problems, including thyroid and adrenal gland problems. Your healthcare provider may do tests to check your thyroid and adrenal gland function during SUTENT treatment. Tell your healthcare provider if you have any of the following signs and symptoms during treatment with SUTENT:
  • tiredness that worsens and does not go away
  • loss of appetite
  • heat intolerance
  • feeling nervous or agitated, tremors
  • sweating
  • nausea or vomiting
  • diarrhea
  • fast heart rate
  • weight gain or weight loss
  • feeling depressed
  • irregular menstrual periods or no menstrual periods
  • headache
  • hair loss
• low blood sugar (hypoglycemia). Low blood sugar can happen with SUTENT, and may cause you to become unconscious, or you may need to be hospitalized. Low blood sugar with SUTENT may be worse in people who have diabetes and take anti-diabetic medicines. Your healthcare provider should check your blood sugar levels regularly during treatment with SUTENT and may need to adjust the dose of your anti-diabetic medicines. Signs and symptoms of low blood sugar may include:
  • headache
  • drowsiness
  • weakness
  • dizziness
  • confusion
  • irritability
  • hunger
  • fast heart beat
  • sweating
  • feeling jittery

Common side effects of SUTENT include:

• 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