SUTENT® (sunitinib malate) is indicated 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.

STARTING PATIENTS ON SUTENT® (sunitinib malate)

A GUIDE TO DISCUSSING DOSING AND POTENTIAL ARs

Please see Important Safety Information on page 3. Please see patient Medication Guide and full Prescribing Information, including Boxed Warning, starting on page 10.
GUIDING PATIENT TREATMENT EXPECTATIONS

Educating patients
This guide has been provided to help you speak with new patients about the dosing schedule of SUTENT and tips to help manage certain ARs. Effective patient education is critical, since SUTENT is a self-administered agent.1

1. Consider the following when reviewing common ARs:
   - Include symptoms to watch for and how to manage them
   - Encourage your patients to communicate openly about their ARs
   - Be alert to possible serious ARs
2. Give the patient a copy of pages 4-9, as well as a copy of the full Prescribing Information, which includes the patient Medication Guide
   - Instruct your patients to read the patient Medication Guide
   - Note that pages 4-9 include self-management tips
   - Encourage your patients to keep track of their ARs by requesting a free journal from the In Touch program (1-877-578-8368)
   - Consider attaching a business card with your contact information

Talking points

• Remind patients to communicate any ARs that they may have as soon as possible
  - Early intervention and ongoing evaluation of AR management strategies are an important part of the patient treatment experience1,2
• Remind patients to always disclose all prescription and nonprescription medicines they may be taking, including vitamins and herbal supplements. Patients may have an increased risk of osteonecrosis if they take SUTENT and a bisphosphonate medicine. Patients should especially inform their healthcare provider if they are taking or have taken any of the following:
  - Actonel — Fosamax
  - Aredia — Reclast
  - Boniva — Skelid
  - Didronel — Zometa
• Remind patients that they should not become pregnant or breastfeed while taking SUTENT
• Remind patients to disclose to all other doctors and dentists they may see that they are taking SUTENT
  - Patients should talk to the healthcare provider who prescribed SUTENT before any surgery, or medical or dental procedure
• Be prepared to listen to your patients’ concerns on each visit1
  - Changes in a patient’s appearance, physical condition, and capabilities can affect his/her self-image and quality of life
  - Physical changes are perhaps the most visible signs of a patient’s disease and the effects of treatment

Possible serious ARs

• 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
• Please be alert to the following ARs and inform patients about their corresponding symptoms:
  - Hepatotoxicity
    » Advise patients to contact you right away if they develop any of the following signs or symptoms of liver problems: itching, yellow eyes or skin; dark urine; or pain or discomfort in the right upper stomach area
  - Cardiac events
    » Advise patients to contact you if they feel very tired, have shortness of breath, or have swollen feet and ankles, feel dizzy, faint, or have abnormal heartbeats
  - Hypertension
    » Monitor patients’ blood pressure regularly and treat as appropriate
  - Serious bleeding
    » Patients should contact you if they experience symptoms such as a painful swollen abdomen; vomiting blood; black sticky stools; bloody urine; headache; or a change in their mental status
  - Osteonecrosis of the jaw (ONJ)
    » Advise patients to consider preventive dentistry prior to treatment with SUTENT. Advise patients to avoid invasive dental procedures if possible, particularly in patients receiving bisphosphonates
  - Tumor lysis syndrome (TLS)
    » Monitor patients, especially those with high tumor burden, closely and treat as clinically indicated
  - Hormone problems
    » Monitor thyroid and adrenal function and advise patients to contact you if they experience fatigue, diarrhea, fast heart rate, loss of appetite, weight gain or weight loss, heat intolerance, depression, nervousness or agitation, tremors, dysmenorrhea, sweating, nausea or vomiting, headache, or hair loss
  - Impaired wound healing
    » Patients should inform you if they are planning to have any surgery or medical or dental procedure
  - Proteinuria
    » Advise patients that you will check protein levels in their urine
  - Dermatologic toxicities
    » Advise patients to contact you immediately if they develop skin symptoms, including: rash, widespread blistering or peeling of skin, and peeling on the inside of their mouth


Please see Important Safety Information on page 3. Please see patient Medication Guide and full Prescribing Information, including Boxed Warning, starting on page 10.
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 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, myocardial disorders, and cardiomyopathy, some of which were fatal, have been reported. 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.

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

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.

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

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.

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 administered with CYP3A4 inhibitors or inducers.

The most common ARs occurring in ≥20% of patients receiving SUTENT for treatment-naïve 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 (25% 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%).

For more information, please visit www.SUTENThcp.com.

Please see patient Medication Guide and full Prescribing Information, including Boxed Warning, starting on page 10.
TAKING SUTENT® (sunitinib malate) capsules

Your doctor has prescribed SUTENT® (sunitinib malate) because he or she believes it is the most appropriate treatment for you. SUTENT may not be appropriate for all patients. SUTENT is available by prescription only.

SUTENT is used to treat advanced kidney cancer (advanced renal cell carcinoma or RCC).

SUTENT is used to treat GIST (gastrointestinal stromal tumor). This is a rare cancer of the stomach, bowel, or esophagus. SUTENT is used to treat GIST when the medicine Gleevec® (imatinib mesylate) does not stop the cancer from growing or when you cannot take Gleevec.

SUTENT is used to treat people with a rare type of pancreatic cancer known as pancreatic neuroendocrine tumors (pNET) that has progressed and cannot be treated with surgery.

Important Safety Information

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
- 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.

Pregnancy and breastfeeding:

- 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
- Do not breastfeed while taking SUTENT

Tell your healthcare provider about all the medicines you take, including prescription medicines and nonprescription 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 (Actonel, Aredia, Boniva, Didronel, Fosamax, Reclast, Skelax, or Zometa). Talk with your healthcare provider before starting any new medicines.

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.

HOW TO TAKE SUTENT

- SUTENT is taken by mouth
  - Your doctor will choose the dose that is most appropriate for you
  - He or she may change or hold your dose from time to time
  - Depending on the dose, you may need to take 1 or more capsules
  - You may take SUTENT with or without food
  - Do not open the SUTENT capsules
  - Continue taking SUTENT as directed by your doctor

- Do not drink grapefruit juice or eat grapefruit during your treatment with SUTENT
- Do not take St John’s Wort during your treatment with SUTENT
- Your doctor may check your blood before each dosing cycle
- If you miss a dose, take it as soon as you remember. Do not take it if it is close to your next dose. Just take the next dose at your regular time.
- Do not take more than 1 dose of SUTENT at a time. Tell your doctor or nurse about the missed dose
- Call your doctor right away if you take too much SUTENT

Capsules shown are not actual size.

Gleevec® is a registered trademark of Novartis Pharmaceuticals Corp.

Please see Important Safety Information on pages 8 and 9.

Full Prescribing Information, including Boxed Warning regarding serious liver problems and Medication Guide, is available from your healthcare professional.
Recommended dosing schedule for patients with **advanced RCC or certain patients with GIST**

### TAKE SUTENT EVERY DAY FOR 4 WEEKS (28 DAYS).

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### DO NOT TAKE SUTENT FOR 2 WEEKS (14 DAYS).

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Then start the cycle again.

- SUTENT is taken in 6-week cycles
  - Take SUTENT every day for the first 4 weeks (days 1 to 28) of this cycle
  - Stop taking SUTENT for the next 2 weeks (days 29 to 42) to complete the cycle
  - Then begin the next 6-week cycle

*GIST (gastrointestinal stromal tumor) is a rare cancer of the stomach, bowel, or esophagus. SUTENT is used when the medicine Gleevec (imatinib mesylate) did not stop the cancer from growing or when you cannot take Gleevec.*

Recommended dosing schedule for patients with **advanced pNET**

- Take SUTENT one time each day until your healthcare provider tells you to stop
  - There is no scheduled break in treatment, unless otherwise directed by your doctor

### TIPS FOR SIDE EFFECT MANAGEMENT

- During treatment with SUTENT, many patients have side effects. Some can be managed, but others are more serious and may not be manageable. In some cases, your doctor may change your dose of SUTENT or stop treatment
- Always talk to your doctor or nurse about any side effects you have as soon as you notice them. Do not wait until they become more serious to tell your doctor or nurse
- Use a journal, which is available for free by enrolling in the In Touch program, to help keep track of your side effects and the tips you use to try to manage them

Please see Important Safety Information on pages 8 and 9.
Full Prescribing Information, including Boxed Warning regarding serious liver problems and Medication Guide, is available from your healthcare professional.
Always talk to your doctor or nurse about any side effects you have as soon as you notice them. Do not wait until they become more serious.

### TIPS FOR SIDE EFFECT MANAGEMENT (cont'd)

#### Fatigue
- Less desire to do normal activities
- Feeling tired, weak, or exhausted

- Take short naps or breaks
- Eat well and drink plenty of fluids
- Take short walks or do light exercise if you feel up to it
- Do things that are relaxing, such as listening to music or reading
- Ask your doctor if there are over-the-counter or prescription medications that may help you manage your condition

#### Diarrhea
- 3 or more loose or watery stools/bowel movements in 1 day

- It is important for you and your doctor to try to manage diarrhea as soon as it begins
- Ask your doctor or nurse if you can be treated with over-the-counter medications
- Avoid spicy foods, fatty foods, caffeine, and fruit
- Eat only mild foods
- Drink water often, but only in small sips

#### Nausea or vomiting
- Throwing up or feeling as if you are about to throw up

- It is best to call your doctor or nurse at the first sign of nausea or vomiting
- This is especially important if these symptoms keep you from taking your oral medications
- Your healthcare provider may prescribe a medicine for these symptoms
- Eat small meals
- Avoid foods that are sweet, fried, or fatty
- Drink lots of fluids, but in small amounts
- If you vomit, start with small amounts of water, broth, or other clear liquids when you are ready to eat again
  - If that stays down, then try soft foods, such as gelatin, plain cornstarch pudding, yogurt, strained soup, or strained cooked cereal
  - Slowly work up to eating solid food
  - Make sure that you do not eat any food that you are allergic to

#### Mouth pain
- Sores or redness in the mouth
- A white coating of the tongue
- Bleeding gums
- Trouble swallowing
- Cracks on corner of the mouth

- Avoid hot, spicy, or acidic foods
- Eat foods that are soft
- Use a straw for drinking liquids
- Use an alcohol-free mouthwash, and rinse your mouth often with water
- Avoid toothpastes with whiteners (ie, peroxide) and use a soft toothbrush
- Ask your doctor if there are over-the-counter or prescription medications that may help you manage your condition

#### Upset stomach
- General stomach upset
- Indigestion

- Avoid heavy meals, coffee, and alcohol
- Reduce your stress with meditation, yoga, or music
- Sleep in a more upright position, propped up on a pillow
- Ask your doctor if there are over-the-counter or prescription medications that may help you manage your condition

#### Skin or hair changes
- Changes in skin or hair color
- Rash or dry skin
- Blisters
- Dryness, thickening, calluses, or cracking of the skin on the palms of your hands and soles of your feet
  - This is called hand-foot syndrome

- In most cases, color change does not require treatment
- Wear thick cotton gloves and/or socks
- Avoid constrictive footwear and excessive friction
- Avoid hot water
- Your doctor or nurse may give you specific treatments, which may include lotions, moisturizers, or pain medicines such as ibuprofen or acetaminophen
- Yellow eyes or skin may be a sign of serious liver problems. Patients should contact their healthcare provider right away if these conditions develop

While this side effect usually poses no health risks, blistering and peeling on the inside of your mouth can be a sign of a more serious side effect. Discuss this side effect with your doctor so he or she can perform a full evaluation.

#### Taste changes
- Foods you usually enjoy taste bland, different, or bad

- Cold or frozen foods may taste better than hot foods
- Flavor your food with herbs, seasonings, sugar, or sauces
- Keep a clean and healthy mouth by brushing and flossing often

#### Increased blood pressure
- SUTENT may cause your blood pressure to rise

- You may receive treatment for high blood pressure (hypertension)
- Tell your doctor or nurse if you have high blood pressure or a history of heart disease
- If you already have high blood pressure and are receiving treatment, your doctor may change it as needed
- Your doctor may also ask you to track your blood pressure regularly in a diary

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For more information, including full Prescribing Information and Boxed Warning regarding serious liver problems and Medication Guide, please visit www.SUTENT.com or contact your healthcare professional.

Please see Important Safety Information on pages 8 and 9.

Full Prescribing Information, including Boxed Warning regarding serious liver problems and Medication Guide, is available from your healthcare professional.
A free program to support you during treatment

SUTENT In Touch is a free personalized support program that connects patients and caregivers to relevant information, tips, and tools throughout SUTENT treatment.

By joining In Touch today, you will gain access to many useful resources, including:
• A partnership with a trained oncology certified nurse who is ready to answer your questions and provide helpful information about SUTENT, possible side effects, and your type of cancer
• Personalized mail and e-mail communications, with relevant, timely information about treatment
• E-mails to help keep your SUTENT medication cycles on schedule
• A free treatment journal to track your experiences and to help you make the most of follow-up visits with your healthcare team

Think of the In Touch Call Center as a complement to your treatment team. Our oncology certified nurses are here to provide you with added support. They are even available to check in and call you at key points along your treatment path.

*SUTENT In Touch does not replace the advice of your healthcare professional. Be sure to call your doctor or nurse right away if you have side effects or questions about your treatment.*

REQUEST YOUR FREE JOURNAL WHEN CALLING TO JOIN IN TOUCH

When you call, request a free treatment journal. The journal offers more tools and information, including:
• Tips on managing your condition
• Organizational tools for your treatment
• Additional information you may find helpful

To enroll, speak to one of our oncology certified nurses by calling **1-877-5-SUTENT (1-877-578-8368)**.

Nurses are available from 9:30 AM to 7 PM ET, Monday through Friday.

For more information, including full Prescribing Information and Boxed Warning regarding serious liver problems and Medication Guide, please visit www.SUTENT.com or contact your healthcare professional.

*Please see Important Safety Information on pages 8 and 9.*
Important Safety Information (cont'd)

SUTENT is a prescription medicine used to treat people with:

- a rare cancer of the stomach, bowel, or esophagus called GIST (gastrointestinal stromal tumor) and when:
  - the medicine Gleevec® (imatinib mesylate) did not stop the cancer from growing, or
  - you cannot take Gleevec
- advanced kidney cancer (advanced renal cell carcinoma or RCC)
- a type of pancreatic cancer known as pancreatic neuroendocrine tumors (pNET), that has progressed and cannot be treated with surgery

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

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

Pregnancy and breastfeeding:

- 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
- Do not breastfeed while taking SUTENT

Tell your healthcare provider about all the medicines you take, including prescription medicines and nonprescription 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 (Actonel, Aredia, Boniva, Didronel, Fosamax, Reclast, Skelid, or Zometa). Talk with your healthcare provider before starting any new medicines.

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.

SUTENT may cause serious side effects, including:

- Serious liver problems, including death
- Heart problems—Heart problems may include heart failure 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
- 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:
  - Painful, swollen stomach (abdomen)
  - Bloody urine
  - 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.

Please see additional Important Safety Information on page 9.

For more information, including full Prescribing Information and Boxed Warning regarding serious liver problems and Medication Guide, please visit www.SUTENT.com or contact your healthcare professional.
Important Safety Information (cont’d)

• Jaw-bone problems (osteonecrosis)—Severe jaw bone problems may happen. 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.

• 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 doctor if you have any of the following signs and symptoms:

  - 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

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
• Blisters or a rash on the palms of your hands and soles of your feet
• Taste changes
• 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.

Full Prescribing Information, including Boxed Warning regarding serious liver problems and Medication Guide, is available from your healthcare professional.
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, Thyroid Dysfunction (5.9) 08/2013
- Warnings and Precautions, Proteinuria (5.11) 06/2014
- Warnings and Precautions, Dermatologic Toxicities (5.12) 06/2014

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)
- 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)
- Cardiac toxicity including 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)
- Osteonecrosis of the jaw has been reported. Consider preventative dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving intravenous bisphosphonate therapy. (5.7)
- 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. (5.8)
- 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. (5.9)
- Wound Healing: Impaired wound healing has occurred with SUTENT. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures. (5.10)
- 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. (5.11)
- Discontinue SUTENT if necrotizing fasciitis, erythema multiforme, Stevens-Johnson Syndrome or toxic epidermal necrolysis occurs. (5.12)
- Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma or severe infection. (5.13)

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: 06/2014
1 INDICATIONS AND USAGE

1.1 Gastrointestinal Stomal 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 patients with unresectable locally advanced or metastatic disease.

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 capsule 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.

3 DOSAGE FORM 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 caramel 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 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. Severe 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 enzyme induction potential should be considered. A dose increase for SUTENT to a maximum of 56.5 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)].

5.2 Pregnancy
SUTENT induces warfarin may decrease warfarin 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 37.5 mg (GIST and RCC) or 25 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 for bleeding [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)].

5.3 Left Ventricular Dysfunction
In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Cardiovascular events, including heart failure, myocardial disorders and cardiomyopathy, some of which were fatal, have been reported in post-marketing experience. 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 an antihypertensive or diuretic medication: 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 heart failure. Twenty-six 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 held for >4 weeks. Left ventricular dysfunction was reported in four patients (1%) on SUTENT 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.

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 induction potential is recommended. A dose increase for SUTENT to a maximum 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)].

5.4 QT Interval Prolongation and Torsade de Pointes
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 should be aware of 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.

5.5 Hypertension
Events for which dose modification may be required 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.

5.6 Hemorrhagic Events
Hemorrhagic events reported during post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinay tract and brain hemorrhages. In patients with metastatic renal cell carcinoma (mRCC), 8/121 patients (7%) receiving SUTENT for mRCC patients (33%) had bleeding events compared with 35/360 patients (10%) receiving placebo. 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, including epistaxis, occurred in 17/102 patients receiving SUTENT in the GIST Study A (17%) compared to 2/36 patients (6%) on placebo. In pNET patients, 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-naïve RCC study and 7/783 pNET patients (8%). Four percent of treatment-naïve RCC patients, one percent of pNET patients receiving SUTENT 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 32/737 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 2/66 pNET patients (3%) on placebo.

5.7 Peripheral Vascular Events
Peripheral vascular events were reported in 21/375 patients (6%) receiving SUTENT for RCC (20/202 patients on SUTENT and 1/173 patients on placebo). Epistaxis was the most common hemorrhagic adverse event reported. Bleeding events, including epistaxis, occurred in 8/121 patients receiving SUTENT for mRCC patients (33%) had bleeding events compared with 35/360 patients (10%) receiving placebo. 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, including epistaxis, occurred in 17/102 patients receiving SUTENT in the GIST Study A (17%) compared to 2/36 patients (6%) on placebo. In pNET patients, 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-naïve RCC study and 7/783 pNET patients (8%). Four percent of treatment-naïve RCC patients, one percent of pNET patients receiving SUTENT 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 32/737 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 2/66 pNET patients (3%) on placebo.

5.8 Other Events
The most frequent events in post-marketing experience are described in table 18. Additional events that have been reported during post-marketing experience are described in table 19.
Cycle 6. One of these five patients received no further drug following tumor hemorrage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrage. No patients with GIST in the Study A placebo arm were observed to undergo intratumoral hemorrage. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations. Serious, treatment-emergent gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

5.7 Osteonecrosis of the Jaw (ONJ)

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

5.8 Tumor Lysis Syndrome (TLS)

Cases of TLS, such as 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.

5.9 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 be monitored and thyroid function performed and be treated as per standard medical practice.

Treatment-emergent acquired hypothyroidism was noted in eight GIST patients (4%) on SUTENT versus one (1%) on placebo. Hypothyroidism was reported as an adverse reaction in sixty-one patients (16%) on SUTENT in the treatment-naive RCC study and in three patients (1%) in the IFN arm. Hypothyroidism was reported as an adverse reaction in 6/83 patients (7%) on SUTENT in the Phase 3 pNET study and in 1/82 patients (1%) in the placebo arm.

5.10 Wound Healing

Cases of impaired wound healing have been observed during SUTENT therapy. Temporary interruption of SUTENT therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of non-clinical major surgical follow-up. Therefore, the decision to resume SUTENT therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

5.11 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. Perform baseline 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 grams. Discontinue SUTENT for patients with nephrotic syndrome or urine protein ≥ 3 grams despite dose reductions. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

5.12 Dermatologic Toxicities

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

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

5.13 Adrenal Function

Serum potassium and mineralocorticoid function tests were normal in patients receiving SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection. Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical trials and through post-marketing experience. Clinical trials and through post-marketing experience.

6 ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 660 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of GIST [see Clinical Studies (14.1)], an active-controlled trial (n=375) for the treatment of RCC, [see Clinical Studies (14.2)] or a placebo-controlled trial (n=83) for the treatment of pNET [see Clinical Studies (14.3)]. The GIST and RCC patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles, and the pNET patients received a starting oral dose of 37.5 mg daily without scheduled off-treatment periods. The most common adverse reactions (≥20% in patients with GIST, RCC or pNET) are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspnea, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in Warnings and Precautions.

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

The data described below reflect exposure to SUTENT in 660 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of GIST. 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.

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.

6.2 Laboratory Abnormalities

Table 2 provides common (≥10%) treatment-emergent laboratory abnormalities.

Table 2. Laboratory Abnormalities Reported in Study A in at Least 10% of GIST Patients Who Received SUTENT or Placebo in the Double-Blind Treatment Phase*
Table 3. Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α*

<table>
<thead>
<tr>
<th>Adverse Reaction, n (%)</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>372 (99)</td>
<td>290 (77)</td>
</tr>
<tr>
<td>Constitutional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>233 (62)</td>
<td>55 (15)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>96 (26)</td>
<td>42 (12)</td>
</tr>
<tr>
<td>Fever</td>
<td>84 (22)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>60 (16)</td>
<td>1 (60)</td>
</tr>
<tr>
<td>Chills</td>
<td>53 (14)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>50 (13)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>18 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>246 (66)</td>
<td>37 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>216 (58)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>178 (47)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>148 (39)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>128 (34)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Abdominal painc</td>
<td>113 (30)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>85 (23)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>50 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>esophagitis</td>
<td>47 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Flatulencen</td>
<td>52 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Oral pain</td>
<td>54 (14)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>40 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>38 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (34)</td>
<td>50 (13)</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>91 (24)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
<td>61 (16)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Dermatology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>109 (29)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>108 (29)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Skin discoloration/yellow skin</td>
<td>94 (25)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>85 (23)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>75 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>51 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Erythema</td>
<td>46 (12)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>44 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered taste</td>
<td>178 (47)</td>
<td>54 (15)</td>
</tr>
<tr>
<td>Headache</td>
<td>86 (23)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>43 (11)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>105 (28)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>111 (30)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Pain in extremity/limb discomfort</td>
<td>150 (40)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>61 (16)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>100 (27)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>99 (26)</td>
<td>24 (6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>54 (14)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Laboratory Parameter, n (%)</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades*</td>
<td>220 (77)</td>
<td>65 (17)</td>
</tr>
<tr>
<td>Grade 3/4*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>211 (56)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>ALT</td>
<td>192 (51)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Lipase</td>
<td>211 (56)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>171 (46)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Amylase</td>
<td>130 (35)</td>
<td>26 (7)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>75 (20)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>49 (13)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Renal/Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>262 (70)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>183 (49)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>156 (42)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>116 (31)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Albumin</td>
<td>106 (28)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>75 (20)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>86 (23)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>61 (16)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Calcium increased</td>
<td>50 (13)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>49 (13)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Sodium increased</td>
<td>48 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>289 (77)</td>
<td>65 (17)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>298 (79)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Platelets</td>
<td>255 (68)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>256 (68)</td>
<td>66 (18)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>293 (78)</td>
<td>29 (8)</td>
</tr>
</tbody>
</table>

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

6.3 Adverse Reactions in the Phase 3 pNED 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-naive 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 have been 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. Temporary suspension of 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-naive 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: thrombotic microangiopathy; 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, skin infections, sepsis/septic shock.

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 is recommended. Concomitant administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and AUC_{inf} 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, nefazodone, ritonavir, saquinavir, telithromycin, voriconazole) may result in increased 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) C_{max} and AUC_{inf} 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, 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 concurrently. 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 SUTENT does not inhibit or induce major CYP enzymes. The in vitro studies were performed on microsomal hepatocytes of the activity of CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, 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 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,
Sunitinib systemic exposure after a single dose of SUTENT was approximately 5,500 mg·h/mL in healthy volunteers and in patients with solid tumors. The terminal half-life of sunitinib was approximately 11 hours in healthy volunteers and in patients with solid tumors. Sunitinib systemic exposure was increased in patients with renal impairment compared to patients with normal renal function. The terminal half-life of sunitinib was longer in patients with renal impairment compared to patients with normal renal function.

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 can be administered with or without food.

Binding of sunitinib and its primary active metabolite to human plasma protein is approximately 95% for each compound. Sunitinib is primarily renally excreted. The renal clearance of sunitinib is approximately 20 mL/min, which is similar to the glomerular filtration rate. Sunitinib is not removed by hemodialysis or peritoneal dialysis.

Following administration of a single oral dose of sunitinib, the terminal half-life of sunitinib is approximately 20 hours. Sunitinib is primarily renally excreted. The renal clearance of sunitinib is approximately 20 mL/min, which is similar to the glomerular filtration rate. Sunitinib is not removed by hemodialysis or peritoneal dialysis.

Pharmacokinetics in Special Populations

Ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postnatal development study in C57BL/6J mice. Sunitinib and its metabolites were observed at concentrations up to 12-fold higher than in plasma. It is not known whether this drug or its primary active metabolite is 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.

3.4 Pediatric Use

The efficacy and safety of SUTENT in pediatric patients have not been established.

3.5 Geriatric Use

Of 825 GIST and RCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. In the Phase 3 PNET study, 22 (27%) patients who received SUTENT were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

6. Hepatic Impairment

No dose adjustment to the starting dose is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are extensively metabolized by the liver. Sunitinib systemic exposure after a single dose of SUTENT was similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. Sunitinib was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >3.0 x ULN.

6.7 Renal Impairment

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

10. OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdose with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. A few 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 1,500 mg of SUTENT in an adult subject with no adverse reaction.

12.1 Mechanism of Action

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, angiogenesis, and metastasis 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 PDGFβR), 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 observed in several preclinical models in vitro and in vivo. Sunitinib also inhibits a number of other related kinases, and its primary active metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

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

12.3 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 can be administered with or without food.

Binding of sunitinib and its primary active metabolite to human plasma protein is approximately 95% for each compound. Sunitinib is primarily renally excreted. The renal clearance of sunitinib is approximately 20 mL/min, which is similar to the glomerular filtration rate. Sunitinib is not removed by hemodialysis or peritoneal dialysis.

Following administration of a single oral dose of sunitinib, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite ranged from 62.9 – 101 ng/mL. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

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

Pharmacokinetics in Special Populations

Population pharmacokinetic analyses in clinical data indicate that there are no clinically relevant effects of age, body 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 (Ccr<30 mL/min) compared to subjects with normal renal function (Ccr>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.
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of sunitinib has been evaluated in two species; rath2 transgenic mice and Sprague-Dawley rats. There were similar positive findings in both species. In rath2 transgenic mice gastrointestinal adenomas 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 and 6 months duration. No proliferative changes were observed in rath2 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 finding of duodenal adenomas 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 cell 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 in an in vivo rat bone marrow micronucleus test.

In female rats, the female reproductive system were identified in a 3-month repeat dose 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 were reproduced at 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 dose produced a mean AUC that was >8.0 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, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day ([0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was ≥5 times the AUC in patients administered the RDD), however significant embryolethality was observed at ≥1.0 mg/kg/day. No reproductive effects were observed for 1, 3 or 10 mg/kg/day for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10 mg/kg/day dose produced a mean AUC that was ≥25.8 times the AUC in patients administered the RDD).

14 CLINICAL STUDIES

14.1 Gastrintestinal Stromal Tumor

GIST Study A

Study A was a two-arm, international, randomized, double-blind, placebo-controlled trial of SUTENT in patients with GIST who had disease progression during prior imatinib mesylate (imatinib) treatment or who were intolerant of imatinib. The objective was to compare Time-to-Tumor Progression (TTP) in patients receiving SUTENT plus best supportive care versus patients receiving placebo plus best supportive care. Other objectives included Progression-Free Survival (PFS), Objective Response Rate (ORR), and Overall Survival (OS). Patients were randomized (2:1) to receive either 50 mg SUTENT or placebo orally, once daily, on Schedule 4:2 until disease progression or withdrawal from the study for another reason. Treatment was unblinded at the time of disease progression. Patients randomized to placebo were then offered crossover to open-label SUTENT, and patients randomized to SUTENT were permitted to continue treatment per investigator judgment.

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: 5% both arms, remainder not reported), and Performance Status (ECOG 0: 62% vs. 61%; ECOG 1: 38% each arm). Prior treatment included surgery (94% vs. 91%), and radiotherapy (8% vs. 4% respectively), with 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 Tables 7 and the Kaplan-Meier curve for TTP is Figure 1. 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. Among the 243 patients initially randomized to SUTENT, 99 crossed over to receive IFN-α when progression was noted. 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, 1.299]).

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 (25 mg/kg on Schedule 4:2), 55 patients in this study received the 50 mg dose of SUTENT on treatment Schedule 4:2. Partial responses were observed in 5 of 55 patients [9.1% PR rate, 95% CI (3.0, 20.0)].

14.2 Renal Cell Carcinoma

Treatment-Naïve RCC

A multi-center, international randomized study comparing single-agent SUTENT with IFN-α was conducted in patients with treatment-naïve RCC. The objective was to compare Progression-Free Survival (PFS) in patients receiving SUTENT versus patients receiving IFN-α. Other endpoints included Objective Response Rate (ORR), Overall Survival (OS) and safety. Seven hundred fifty (750) patients were randomized (1:1) to receive either 50 mg SUTENT or placebo 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 SUTENT and 375 randomized to IFN-α. Demographics were comparable between the SUTENT and IFN-α groups with regard to age (59% vs. 67% <65 years for SUTENT vs. IFN-α, respectively), gender (Male: 71% vs. 72%), race (White: 94% vs. 91%, Asian: 2% vs. 3%, Black: 1% vs. 2%, remainder not reported), and Performance Status (ECOG 0: 62% vs. 61%, ECOG 1: 38% each arm, ECOG 2: 0 vs. 1%). Prior treatment included nephrectomy (91% vs. 89%) and radiotherapy (14% each arm). The most common site of metastases present at screening was the lung (78% vs. 80%, 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 SUTENT over IFN-α in the endpoint of PFS (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 7. GIST Efficacy Results from Study A (Double-blind Treatment Phase)

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>SUTENT (n=207)</th>
<th>Placebo (n=105)</th>
<th>p-value (log-rank test)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Tumor Progression (weeks, 95% CI)</td>
<td>27.3 (16.0, 32.1)</td>
<td>6.4 (4.4, 10.0)</td>
<td>&lt;0.0001*</td>
<td>0.33 (0.23, 0.47)</td>
</tr>
<tr>
<td>Progression-free Survival (median, weeks, 95% CI)</td>
<td>24.1 (10.1, 28.3)</td>
<td>6.0 (4.4, 9.9)</td>
<td>&lt;0.0001</td>
<td>0.33 (0.24, 0.47)</td>
</tr>
<tr>
<td>Objective Response Rate (%) (95% CI)</td>
<td>8.6 (3.7, 11.1)</td>
<td>0</td>
<td>0.0066*</td>
<td></td>
</tr>
</tbody>
</table>

* A comparison is considered statistically significant if the p-value is ≤0.00417 (O'Brien Fleming stopping boundary).

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>Value (log-rank test)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-Free Survival (weeks, 95% CI)</td>
<td>47.3 (42.6, 50.7)</td>
<td>22.0 (16.4, 24.0)</td>
<td>&lt;0.000001*</td>
<td>0.415 (0.320, 0.539)</td>
</tr>
<tr>
<td>Objective Response Rate (%) (95% CI)</td>
<td>27.5 (23.0, 32.3)</td>
<td>5.3 (3.8, 8.1)</td>
<td>&lt;0.001*</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

a Assessed by blind radiology laboratory; 90 patients' scans had not been read at time of analysis
b A comparison is considered statistically significant if the p-value is ≤0.0042 (O'Brien Fleming stopping boundary)
c Pearson chi-square test

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

Figure 2. Kaplan-Meier Curve of PFS in Treatment-Naïve RCC Study (Intent-to-Treat Population)
At the protocol-specified final analysis of OS, the median OS was 114.6 weeks for the SUTENT arm and 94.9 weeks for the IFN-α arm (HR = 0.821, 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 treatment with SUTENT as well as 121 patients (32%) on the IFN-α arm who received prior 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 radiographic evidence of disease progression defined by RECIST or World Health Organization (WHO) criteria occurring within 9 months of completion of 1 cytokine therapy treatment (IFN-α, interleukin-2, or IFN-α plus interleukin-2; patients who were treated with IFN-α alone must have received treatment for at least 28 days). In Study 2, failure of prior cytokine therapy was defined as disease progression or unacceptable treatment-related toxicity. The endpoint for both studies was ORR. Duration of Response (DR) was also evaluated.

One hundred six patients (106) were enrolled into Study 1, and 63 patients were enrolled into Study 2. Patients received 50 mg SUTENT on Schedule 4/2. Therapy was continued until the patients met withdrawal criteria or had progressive disease. The baseline age, gender, race and ECOG performance statuses of the patients were comparable between Studies 1 and 2. Approximately 86-94% of patients in the two studies were White. Men comprised 65% of the pooled population. The median age was 57 years and ranged from 24 to 87 years in the studies. All patients had an ECOG performance status <2 at the screening visit.

The baseline malignancy and prior treatment history of the patients were comparable between Studies 1 and 2. Across the two studies, 95% of the pooled population of patients had at least some component of clear-cell histology. All patients in Study 1 were required to have a histological clear-cell component. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in Study 2. All patients in Study 1 received one previous cytokine regimen. Metastatic disease present at the time of study entry included lung metastases in 81% of patients. Liver metastases were more common in Study 1 (27% vs. 16% in Study 2) and bone metastases were more common in Study 2 (51% vs. 25% in Study 1); 52% of patients in the pooled population had at least 3 metastatic sites. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

The ORR and DR data from Studies 1 and 2 are provided in Table 9. There were 36 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 36.5% (95% CI 24.7, 49.6). 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.

The baseline malignancy and prior treatment history of the patients were comparable between Studies 1 and 2. Across the two studies, 95% of the pooled population of patients had at least some component of clear-cell histology. All patients in Study 1 were required to have a histological clear-cell component. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in Study 2. All patients in Study 1 received one previous cytokine regimen. Metastatic disease present at the time of study entry included lung metastases in 81% of patients. Liver metastases were more common in Study 1 (27% vs. 16% in Study 2) and bone metastases were more common in Study 2 (51% vs. 25% in Study 1); 52% of patients in the pooled population had at least 3 metastatic sites. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

The ORR and DR data from Studies 1 and 2 are provided in Table 9. There were 36 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 36.5% (95% CI 24.7, 49.6). 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.

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14.3 Pancreatic Neuroendocrine Tumors

The Phase 3 study was a multi-center, international, randomized, double-blind placebo-controlled study of single-agent 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 Progression-Free Survival (PFS) in patients receiving SUTENT versus patients receiving placebo. Other endpoints included Overall Survival (OS), Objective Response Rate (ORR), and safety. Use of somatostatin analogs was allowed in the study. Demographics were comparable between the SUTENT and placebo groups. Additionally, 49% of SUTENT patients had non-functioning tumors vs 52% of placebo patients, and 92% patients in both arms had liver metastases. A total of 66% of SUTENT patients received prior systemic therapy compared with 72% of placebo patients and 35% of SUTENT patients had received somatostatin analogs compared with 36% 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 prior to the planned final 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. A statistically significant difference in ORR favoring SUTENT over placebo was observed. Efficacy results are summarized in Table 10 and the Kaplan-Meier curve for PFS is in Figure 3.
SUTENT (su TENT)
(sunitinib malate) capsules

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

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

SUTENT can cause serious liver problems, including death.

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

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

What is SUTENT?

SUTENT is a prescription medicine used to treat people with:

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

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

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

SUTENT can cause serious liver problems, including death.

• Call your healthcare provider right away, if you take too much SUTENT.

• 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.

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 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.

• 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.

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.
• **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 doctor 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

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.
  - blisters or a rash on the palms of your hands and soles of your feet.
  - taste changes
  - 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.