This guide will help you understand more about your treatment with SUTENT and an advanced form of kidney cancer called renal cell carcinoma (RCC). SUTENT is used to treat advanced RCC.

Please see important safety information on pages 8 and 9 of this booklet. Please see the patient Medication Guide and full prescribing information attached.
SUTENT is a medicine that treats cancer. It comes in 12.5-mg, 25-mg, and 50-mg capsules. You take SUTENT once per day by mouth. Do not open the capsules.

SUTENT is used to treat an advanced form of kidney cancer, known as renal cell carcinoma (RCC). SUTENT may slow or stop the growth of cancer. It may also help shrink tumors.

SUTENT is available by prescription only. Your healthcare provider has prescribed SUTENT because he or she believes it is the most appropriate treatment for you. SUTENT may not be appropriate for all patients with RCC and has not been studied in children. SUTENT may not work the same in every person.

Note: Words in bold type are defined on pages 34 and 35.
**What is cancer?**

The human body is made up of countless cells. Organs, such as the liver, kidneys, skin, or lungs, are made up of special types of cells that help these organs do their jobs. Most organs stay healthy by getting rid of old cells that can no longer work as they should. These old cells are then replaced by new cells. This process of new cells replacing old cells is well controlled. It takes place in the body all the time.

Cancer occurs when this controlled process goes out of control. This is caused by a breakdown in a cell’s genetic program. This breakdown makes the cell grow and divide when it is not supposed to. When this happens, it becomes a cancer cell. Soon a large mass of cancer cells forms. The mass is called a tumor. Some tumors can spread and threaten your health.

**What is RCC?**

RCC is cancer that starts in the kidneys. Often, a person who has RCC has had a change in one of his or her genes. That gene is called VHL, or the von Hippel-Lindau gene.

Some of the cancer cells may enter the bloodstream and spread to other parts of the body. New tumors may then develop in other organs. This is called metastasis. RCC may spread to your lungs, for example. If this happens, it is still called RCC (metastatic RCC), not lung cancer.

RCC often grows as a single tumor within one kidney. Sometimes, more than one tumor grows in one kidney. Less often, tumors grow in both kidneys at the same time.
How does SUTENT® (sunitinib malate) work?

SUTENT may slow or stop some cancers by blocking 2 basic processes that cause tumors to grow and spread. These processes are called proliferation and angiogenesis.

**Proliferation**
This is when a cell divides, creating 2 cells where there used to be only 1. Like the other cells in your body, cancer cells divide. The difference is that cancer cells divide more times than they should, forming a tumor. SUTENT may help slow down this process.

**Angiogenesis**
This is when new blood vessels form. These new blood vessels give tumors the nutrients and oxygen they need to grow. SUTENT may help stop this process.

SUTENT may help stop proliferation and angiogenesis by blocking the signals that cause them. Without these 2 processes, tumors cannot grow.

Please see important safety information on pages 8 and 9 of this booklet. Please see the patient Medication Guide and full prescribing information attached.
SUTENT can cause serious liver problems, including death.

Tell your healthcare provider right away if you develop any of the following during treatment with SUTENT: itching; yellow eyes or skin; dark urine; or 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.

SUTENT may cause heart problems. Heart problems may include heart failure, heart muscle problems (cardiomyopathy), or abnormal heart rhythm changes. Tell your healthcare provider if you feel dizzy, faint, very tired, have abnormal heartbeats, are short of breath, or have swollen feet and ankles while taking SUTENT.

SUTENT may cause high blood pressure. Your healthcare provider may check your blood pressure, and may treat you for high blood pressure.

SUTENT may cause bleeding sometimes leading to death. Tell your healthcare provider right away if you have any of the following during treatment with SUTENT: serious bleeding; painful swollen stomach (abdomen); vomiting blood; black, sticky stools; bloody urine; headache or change in your mental status.

SUTENT may cause 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.

SUTENT may harm an unborn baby (cause birth defects). Do not become pregnant while taking SUTENT. If you do, tell your healthcare provider right away. Stop taking SUTENT. Do not breastfeed while taking SUTENT.

Using SUTENT with other medicines can cause serious side effects. Tell your healthcare provider about all the medicines, vitamins, or herbal products you use.

You may have side effects or reactions to SUTENT. For most patients, these are moderate and may be managed, though some can be serious. Your healthcare provider may change your dose or stop your treatment. Some of the most common side effects include tiredness, weakness, fever, diarrhea, nausea, vomiting, mouth sores, upset stomach, abdominal pain, constipation, skin or hair changes, taste changes, swelling, loss of appetite, and bleeding, such as from the nose or cuts. Tell your healthcare provider if you have any swelling or bleeding. Be sure to tell your healthcare provider about any new side effects you have, as well as any change or increase in any side effect.
What should I tell my healthcare provider before taking SUTENT?

Before taking SUTENT, tell your healthcare provider if you:
- have any heart problems
- have high blood pressure
- have thyroid problems
- have kidney function problems (other than cancer)
- have liver problems
- have any bleeding problem
- have seizures
- have any other medical conditions
- are pregnant, could be pregnant, or plan to become pregnant. SUTENT may harm an unborn baby. You should not become pregnant while taking SUTENT. Tell your healthcare provider right away if you become pregnant while taking SUTENT
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take SUTENT or breastfeed. You should not do both

Using SUTENT with certain medicines can cause serious side effects. Tell your healthcare provider about all medicines you take. These include prescription medicines and nonprescription medicines, vitamins, and herbal supplements.

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

Please see important safety information on pages 8 and 9 of this booklet. Please see the patient Medication Guide and full prescribing information attached.

What are the possible side effects?

You may have side effects or reactions to SUTENT. Most patients have moderate side effects that can be managed, though some can be serious. In some cases, your healthcare provider may change your dose of SUTENT or stop treatment.

Be sure to talk to your healthcare provider about any side effects or concerns that you have.

Possible serious side effects

Some side effects are more serious than others. It is important that you know the signs of these side effects so you can tell your healthcare provider if any of these problems occur:

- **Serious liver problems.** SUTENT can cause serious liver problems, including death. Tell your healthcare provider right away if you develop any of the following symptoms of liver problems during treatment with SUTENT: itching; yellow eyes or skin; dark urine; or pain or discomfort in the right upper stomach area

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

Side effects continued on following page.
What are the possible side effects? (continued)

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

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

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

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

- **Hormone problems, including thyroid and adrenal gland problems.** Your healthcare provider may do tests to check your thyroid and adrenal gland function during SUTENT treatment. Tell your healthcare provider if you have any of the following signs and symptoms during treatment with SUTENT:
  - tiredness that worsens or does not go away
  - loss of appetite
  - intolerance to heat
  - 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**
Patients who take SUTENT have these side effects more often than other side effects:
- tiredness
- weakness
- fever

Please see important safety information on pages 8 and 9 of this booklet. Please see the patient Medication Guide and full prescribing information attached.
What are the possible side effects? (continued)

- **gastrointestinal** symptoms, including diarrhea, nausea, vomiting, mouth sores, upset stomach, abdominal pain, and constipation
- changes in color of hair or skin. The medicine in SUTENT is yellow, and it may make your skin look yellow. Your skin and hair may get lighter in color
- yellow eyes or skin. Yellow eyes or skin may also be a sign of serious liver problems. Call your healthcare provider right away if you develop these symptoms
- 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

**Be sure to tell your healthcare provider if there is any change or increase in your side effects. Do not wait until your symptoms become worse.**

There are also steps you can take on your own to ease some of these problems. See pages 15-18 of this booklet for some tips.

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**How to manage side effects**

You may have had some of these common side effects before starting treatment with SUTENT, and you may take steps on your own to ease some of these problems. **Always talk to your healthcare provider about any side effects you have as soon as you notice them. Do not wait until they become more serious to tell your healthcare provider.**

**FEELING TIRED/FATIGUE.** While you are taking SUTENT, you may feel less desire to do normal activities or you may feel tired, weary, or exhausted.

If you feel tired or fatigued, these tips may help:

- Stay as active as possible, setting short-term goals
- Try to maintain normal work and social schedules
- Take naps or rest when you can
- Inform your doctor or nurse when your fatigue begins to keep you from doing your normal activities

**DIARRHEA.** You may have changes in bowel habits and stool consistency while you are taking SUTENT.

How to manage side effects continued on following page.
How to manage side effects (continued)

These tips may help relieve your diarrhea:
✓ Take antidiarrheal medicine as recommended
✓ Drink fluids often, in small sips
✓ Add bananas and rice to your diet
✓ Choose high-protein foods, skim or low-fat milk, and desserts low in fat and lactose

NAUSEA OR VOMITING. While taking SUTENT, you may throw up or feel as if you are about to throw up.
If you experience nausea or vomiting, these tips may help:
✓ Be sure you are drinking enough fluids
✓ Find out from your healthcare provider if there are any other medicines you may be taking that might be adding to your nausea
✓ Eat and drink slowly and have small meals throughout the day
✓ Avoid sweet, fried, or fatty foods, as well as foods with strong odors

TASTE CHANGES. You may notice that foods you usually enjoy taste bland, different, or bad while you are taking SUTENT. This is common in people who are being treated for cancer.
If you have taste changes, these tips may help:
✓ Cold foods may taste better than hot foods
✓ Flavor your food with herbs, seasonings, sugar, lemon, or sauces

MOUTH SORES/STOMATITIS. You may have sores or redness in your mouth while taking SUTENT. You may also have mouth pain, bleeding gums, trouble swallowing, or cracks on the corner of the mouth.
If you have mouth sores or stomatitis, these tips may help:
✓ Avoid hot, spicy, or acidic foods
✓ Eat foods that are soft
✓ Use a straw to drink liquids
✓ Use an alcohol-free mouthwash
✓ Use mild toothpaste
✓ Keep a clean and healthy mouth by brushing and flossing often

UPSET STOMACH. While taking SUTENT, you may have an upset stomach or indigestion.
If you have an upset stomach, these tips may help:
✓ Avoid heavy meals, coffee, and alcohol
✓ Reduce your stress
✓ Sleep in a more upright position, propped up on a pillow
✓ Take antacids as recommended

How to manage side effects continued on following page.
How to manage side effects (continued)

SKIN OR HAIR CHANGES. While taking SUTENT, you may have changes in your skin or hair color. Yellow eyes or skin may also be a sign of serious liver problems. Call your healthcare provider right away if you develop these symptoms.

You may also experience dryness, thickening, or cracking of the palms of your hands and/or soles of your feet or other body parts. Some patients may have blisters or a rash. This is called hand-foot syndrome.

Tell your healthcare provider if you develop these problems. He or she may give you specific treatments.

If you have skin or hair changes, these tips may help:

✔ Use a sunscreen daily
✔ Wear rubber or cotton-lined gloves to do household chores
✔ Moisturize frequently
✔ Take short, lukewarm showers using a moisturizing soap
✔ Use an over-the-counter cream or ointment

Photo courtesy of Cleveland Clinic Taussig Institute.

Your healthcare provider can talk with you about any side effects or concerns you have. You may use the space below to note which side effects you have and when you have them. Bring this list with you to your next visit with your healthcare provider.
How to take SUTENT® (sunitinib malate)

- SUTENT is taken by mouth
  - Your healthcare provider 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
- 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
- Continue taking SUTENT as directed by your healthcare provider—do not open the capsules
- 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 the missed dose

- Call your healthcare provider right away if you take too much SUTENT
- Do not drink grapefruit juice or eat grapefruit while taking SUTENT
- Make sure to tell your doctor or nurse if you are taking any other medicines, vitamins, or herbal products
  - This includes any supplements or over-the-counter products

![Cycle chart]

Do not take SUTENT for 2 weeks (14 days). Then start the cycle again.

SUTENT 50 mg  SUTENT 25 mg  SUTENT 12.5 mg
Capsules shown are not actual size.
For more information about SUTENT, talk with your healthcare providers.

The resources listed below can offer you support and information about cancer. You may find that learning more about your disease and treatment or talking with other patients is helpful. These resources may also help your family and caregivers.

**SUTENT.com**
This single Web destination for everything SUTENT provides you with:
- Information about RCC
- Facts about SUTENT treatment
- Resources for you and your caregivers
- Assistance obtaining SUTENT

If you want to receive updates about RCC or SUTENT, sign up by clicking on “Get e-mail updates.”

**The Kidney Cancer Association (KCA)**
800-850-9132, [www.curekidneycancer.org](http://www.curekidneycancer.org)
The KCA is a group of patients, families, doctors, and healthcare providers who are all involved with kidney cancer. On the KCA Web site, you can learn about:
- Kidney cancer and treatments
- Simple ways to make living with kidney cancer easier
- Finding and meeting other kidney cancer patients and survivors

**The American Cancer Society (ACS)**
800-227-2345, [www.cancer.org](http://www.cancer.org)
The ACS is a resource for patients and healthcare providers alike. The ACS Web site has news, facts, and useful tips for you and your family, including:
- News about cancer studies
- Facts about treatments
- Stories about cancer survivors
- Helpful advice about RCC
- Links to support groups

Resources continued on following page.
Resources for you (continued)

Cancercare
800-813-4673, www.cancercare.org
The Cancercare Web site provides support services to people affected by cancer with:
- Helpful cancer advice and counseling
- Facts about cancer
- Free financial services

The National Cancer Institute (NCI)
The NCI Web site has many facts about cancer, treatments, and clinical trials. You can also find other useful topics, such as:
- How to pay for cancer treatment
- Choosing hospice and home care
- Finding support groups

The National Comprehensive Cancer Network (NCCN)
215-690-0300, www.nccn.com
The NCCN Web site has information for patients and their caregivers and families about cancer. On the NCCN Web site, you can find:
- Treatment summaries and guidance
- Advice on obtaining financial assistance
- Tips for living with cancer

SUTENT Patient Call Center
877-578-8368
The call center is a free service open Monday to Friday from 8 AM to 11 PM ET. The call center is staffed by trained oncology certified nurses who can:
- Answer your questions about RCC, SUTENT treatment, and possible side effects
- Make outgoing calls to check in on you at key times during your treatment

Note: Service does not provide medical advice.
What is the First Resource program?
Pfizer First Resource is a program that can help patients access Pfizer Oncology medicines. Enrollment is easy. A simple phone call can start the process.

How can First Resource help?
Pfizer First Resource is a program designed to help you obtain the Pfizer Oncology medicines you need. It can also provide you with information about coverage options and alternate funding sources, if needed.

First Resource offers:
- **Reimbursement Support Services**
  A First Resource counselor can help you and your healthcare providers understand coverage and reimbursement options. This includes benefit verification, in which the counselor will review your benefits to see how you are covered for the medicine you need. The counselor will research and verify benefits, explain coverage options and policies, and investigate and explain the prior authorization process.

- **Alternate Funding Assistance**
  First Resource can help you find alternate sources of funding if you need them. These may include state pharmaceutical assistance programs (SPAPs), Medicaid, Medicare Part D, low-income subsidies, and charitable foundations.

  You may also be able to receive a temporary supply of medicine from Pfizer while a counselor seeks alternate funding.

- **Appeals Process Information**
  If a claim is underpaid or denied, First Resource will investigate and explain the appeals process.

- **Access to Pfizer Oncology Medicines**
  You may be able to get your Pfizer Oncology medicines for free through the First Resource patient assistance program. You may also be able to receive co-pay assistance for certain medicines. A First Resource counselor will help determine your eligibility and help you complete the enrollment process.

  To be eligible, you must:
  - Have no prescription coverage or not enough coverage.

First Resource continued on following page.
Meet specific income guidelines, adjusted for family size
Reside in the United States, US Virgin Islands, or Puerto Rico
Be treated by a licensed physician in the United States or Puerto Rico

Patients with prescription coverage who demonstrate significant financial or medical hardship can apply for Hardship Assistance.* If you are eligible, you can access certain Pfizer Oncology medicines through the First Resource program. Eligibility varies by product.

To apply for any First Resource program, call 1-877-744-5675. Once a First Resource counselor determines your needs and eligibility,† you will need to complete an enrollment form. Your eligibility can be determined over the phone and an initial supply of medicine sent to your healthcare provider. The completed enrollment form can be faxed to 1-800-708-3430 or mailed to the address on the next page.

*Hardship Assistance is available for oral products.
†Proof of income includes items such as the most recent federal income tax return, W-2 form(s), Social Security check, or a copy of the most recent pay stub. Proof of income is required within 30 days of enrollment.

The following information is required for the application:
- Name and address
- Date of birth
- Household size and monthly income†
- Insurance information
- Healthcare provider’s name

How do I contact First Resource?
By phone: Call 1-877-744-5675, Monday to Friday, 9 AM to 8 PM ET. You may speak to a live operator in English or Spanish.

By fax: Fax your enrollment application or other correspondence to 1-800-708-3430.


Mail: Send correspondence to:
Pfizer First Resource
PO Box 220582
Charlotte, NC 28222-0582
First Resource® is a part of the Pfizer Helpful Answers® family of patient assistance programs—a joint program of Pfizer Inc and the Pfizer Patient Assistance Foundation™.
While you are taking SUTENT, you may have questions or concerns about your treatment. Listed here are a few common questions about SUTENT and answers you may find useful.

Remember: Your healthcare provider can talk with you about any questions or concerns you have.

Q: What is SUTENT?
A: SUTENT is a prescription medicine that you take by mouth. SUTENT is used to treat kidney cancer that has spread to other parts of the body. This is called advanced renal cell carcinoma (RCC). It is not known if SUTENT is safe and effective in children.

Q: What are the benefits of taking SUTENT?
A: SUTENT may slow or stop the growth of your cancer. SUTENT may not work the same for every person.

Q: How do I know if SUTENT is working?
A: When you visit your healthcare provider, you will have special scans or tests to check the size of your tumors. Your healthcare provider will discuss these with you. The scans and tests may show if the tumors are growing, staying the same size, or shrinking.

Q: What side effects might I have while taking SUTENT?
A: Some of the most common side effects include tiredness, weakness, fever, diarrhea, nausea, vomiting, mouth sores, upset stomach, abdominal pain, constipation, skin or hair changes, taste changes, swelling, loss of appetite, and bleeding, such as from the nose or cuts. For most patients, the side effects of SUTENT are moderate and may be managed. Some side effects are more serious. SUTENT can cause serious liver problems, including death. SUTENT may cause heart problems, high blood pressure, or hormone problems, including thyroid and adrenal gland problems. SUTENT may cause bleeding, sometimes leading to death. See pages 8 and 9 for more information.

Tell your healthcare provider if you have a change or increase in side effects.

Q: Will my skin and/or hair change color?
A: If you have light or fair skin, you may see a yellow tint in your skin. If your skin is darker, it may lighten all over or in patches. Your hair may lighten in patches.

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

Answers to your questions continued on following page.
Answers to your questions (continued)

Yellow eyes or skin may also be a sign of serious liver problems. Call your healthcare provider right away if you develop these symptoms.

Q: Will my natural skin and hair color come back?
A: Your natural skin or hair color will usually return after stopping treatment with SUTENT.

Q: What signs or symptoms should I watch for?
A: You should call your healthcare provider as soon as possible if you have any of these symptoms:
- Sweating and/or intolerance to heat
- Feeling very tired or short of breath; having swollen feet and ankles
- Feeling dizzy or faint; having abnormal heartbeats
- Painful, swollen stomach; vomiting blood; black, sticky stools; bloody urine; headache or change in your mental status
- Itching; yellow eyes or skin; dark urine; pain or discomfort in the right upper stomach area

See pages 11-15 for more information.

Q: Will SUTENT react with any other drugs I’m taking or products I’m using?
A: Using SUTENT with certain medicines can cause serious side effects. Tell your healthcare provider about all medicines you take. These include prescription medicines and nonprescription medicines, vitamins, and herbal supplements.

Grapefruit may affect the way SUTENT works in your body. Do not eat it or drink grapefruit juice while taking SUTENT. See pages 8-10 and 20-21 for more information.

Q: Where can I find information about access to SUTENT?
A: First Resource® can help make the access process easier for you. First Resource is a free program from Pfizer. If you have questions about or problems with access to SUTENT, you can call First Resource at 1-877-744-5675.
Angiogenesis (anjee-o-JEN-ih-sis)
The growth of new blood vessels from existing ones. Tumors use this process to receive nutrients from the bloodstream and to metastasize.

Cardiomyopathy (CAR-di-o-my-O-pathy)
A disease of the heart muscle.

Gastrointestinal (GASS-tro-in-TESS-tin-nul)
Relating to your stomach and intestines.

Hand-foot syndrome (hand-foot-SIN-drome)
Dryness, thickening, or cracking of the skin on the palms of the hands and soles of the feet. It can sometimes include blisters or a rash.

Metastasis (muh-TAHS-tuh-sis)
The spread of cancer from one part of the body to another through the lymphatic system or bloodstream.

Proliferation (pro-liff-er-AY-shun)
When cells divide and multiply quickly. Tumors form when cancer cells proliferate.

Renal cell carcinoma (RCC)
(REE-null SELL kar-sin-O-muh)
The most common form of cancer that starts in the kidneys.

Stomatitis (stow-muh-TIE-tiss)
Sores or swelling on the lining of the mouth; often a side effect of cancer therapy.

Tumor (TOO-mor)
A mass of cancer cells.

VHL
A gene that helps to prevent tumor growth. If the VHL gene is not working properly, RCC can develop. VHL stands for von Hippel-Lindau.

For more information, visit SUTENT.com
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUTENT safely and effectively. See full prescribing information for SUTENT.

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

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

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

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INDICATIONS AND USAGE
SUTENT is a kinase inhibitor indicated for the treatment of:
- Gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. (1.1)
- Advanced renal cell carcinoma. (1.2)

DOSSAGE AND ADMINISTRATION
- 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off. (2.1)
- Dose interruptions and/or dose adjustments of 12.5 mg recommended based on individual safety and tolerability. (2.2)

DOSE FORMS AND STRENGTHS
- Capsules: 12.5 mg, 25 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)
- Left ventricular ejection fraction declines to below the lower limit of normal 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)
- 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. (5.7)
- Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma or severe infection. (5.8)

ADVERSE REACTIONS
- The most common adverse reactions (≥20%) are fatigue, anemia, 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: 7/2010

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

1 INDICATIONS AND USAGE
   1.1 Gastrointestinal Stromal Tumor (GIST)
   SUTENT is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.
   1.2 Advanced Renal Cell Carcinoma (RCC)
   SUTENT is indicated for the treatment of advanced renal cell carcinoma.

2 DOSAGE AND ADMINISTRATION
   2.1 Recommended Dose
   The recommended dose of SUTENT for gastrointestinal stromal tumor (GIST) and advanced renal cell carcinoma (RCC) is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUTENT may be taken with or without food.
   2.2 Dose Modification
   Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability.
   Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for SUTENT to a minimum of 37.5 mg daily should be considered if SUTENT must be co-administered with a strong CYP3A4 inhibitor [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].
   CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS
   12.5 mg capsules
   Hard gelatin capsule with orange cap and orange body, printed with white ink “Pfizer” on the cap and “STN 12.5 mg” on the body.

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

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

4 CONTRAINDICATIONS
   None

5 WARNINGS AND PRECAUTIONS
   5.1 Hepatotoxicity
   SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include
jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

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

5.2 Pregnancy

Pregnancy Category D

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. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

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 through post-marketing experience. More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving either placebo or interferon-α (IFN-α). In the double-blind treatment phase of GIST Study A, 22/209 patients (11%) on SUTENT and 3/102 patients (3%) on placebo had treatment-emergent LVEF values below the lower limit of normal (LLN). Nine of 22 GIST patients on SUTENT with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction: one patient; addition of antihypertensive or diuretic medications: four patients). Six patients went off study without documented recovery. Additionally, three patients on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF <40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. In the double-blind treatment phase of GIST Study A, 1 patient on SUTENT and 1 patient on placebo died of diagnosed heart failure; 2 patients on SUTENT and 2 patients on placebo died of treatment-emergent cardiac arrest.

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

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

5.4 QT Interval Prolongation and Torsade de Pointes

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

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

5.5 Hypertension

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

Of patients receiving SUTENT for treatment-naive RCC, 127/375 patients (34%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 50/375 treatment-naive RCC patients (13%) on SUTENT compared to 1/360 patients (<1%) on IFN-α. While all-grade hypertension was similar in GIST patients on SUTENT compared to placebo, Grade 3 hypertension was reported in 9/202 GIST patients on SUTENT (4%), and none of the GIST patients on placebo. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) on the treatment-naive RCC study. Four treatment-naive RCC patients, including one with malignant hypertension, 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%), and in 32/375 treatment-naive RCC patients (9%) on SUTENT and 3/360 patients (1%) on IFN-α.

5.6 Hemorrhagic Events

Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. In patients receiving SUTENT in a clinical trial for treatment-naive RCC, 140/375 patients (37%) had bleeding events compared with 35/360 patients (10%) receiving IFN-α. Bleeding events occurred in 37/202 patients (18%) receiving SUTENT in the double-blind treatment phase of GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in GIST or RCC patients included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. In the double-blind treatment phase of GIST Study A, 14/202 patients (7%) receiving SUTENT and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in GIST Study A taking placebo had a fatal gastrointestinal bleeding event during Cycle 2. Most events in RCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment-naive patient.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC. Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5/202 patients (3%) with GIST receiving SUTENT on Study A. Tumor hemorrhages were observed as early as Cycle 1 and as late as Cycle 6. One of these five patients received no further drug following tumor hemorrhage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the Study A placebo arm were
observed to undergo intratumoral hemorrhage. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

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

5.7 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 on SUTENT treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Treatment-emergent acquired hypothyroidism was noted in eight GIST patients (4%) on SUTENT versus 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-α arm.

Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

5.8 Adrenal Function

Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

5.9 Laboratory Tests

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.

6 ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 577 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)] or an active-controlled trial (n=375) for the treatment of RCC [see Clinical Studies (14.2)]. The patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.

The most common adverse reactions (≥20%) in patients with GIST or RCC 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. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in Warnings and Precautions (5). Other adverse reactions occurring in GIST and RCC studies are described below.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adverse Reactions in GIST Study A

Median duration of blinded study treatment was two cycles for patients on SUTENT (mean 3.0, range 1-9) and one cycle (mean 1.8, range 1-6) for patients on placebo at the time of the interim analysis. Dose reductions occurred in 23 patients (11%) on SUTENT and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUTENT and 31 patients (30%) on placebo. The rates of treatment-emergent, non-fatal adverse
reactions resulting in permanent discontinuation were 7% and 6% in the SUTENT and placebo groups, respectively.

Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 56% versus 51% of patients on SUTENT versus placebo, respectively, in the double-blind treatment phase of the trial. Table 1 compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT and reported more commonly in patients receiving SUTENT than in patients receiving placebo.

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

<table>
<thead>
<tr>
<th>Adverse Reaction, n (%)</th>
<th>GIST</th>
<th>SUTENT (n=202)</th>
<th>Placebo (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any</td>
<td></td>
<td>114 (56)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81 (40)</td>
<td>9 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>58 (29)</td>
<td>2 (1)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Constipation</td>
<td>41 (20)</td>
<td>0 (0)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (15)</td>
<td>9 (4)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Dermatology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>61 (30)</td>
<td>0 (0)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Rash</td>
<td>28 (14)</td>
<td>2 (1)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>28 (14)</td>
<td>9 (4)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered taste</td>
<td>42 (21)</td>
<td>0 (0)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia/limb pain</td>
<td>28 (14)</td>
<td>1 (1)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Metabolism/Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia\textsuperscript{a}</td>
<td>67 (33)</td>
<td>1 (1)</td>
<td>30 (29)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>45 (22)</td>
<td>10 (5)</td>
<td>11 (11)</td>
</tr>
</tbody>
</table>

* Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
\textsuperscript{a} Includes decreased appetite

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

Table 2 provides common (≥10%) treatment-emergent laboratory abnormalities.
<table>
<thead>
<tr>
<th>Laboratory Parameter, n (%)</th>
<th>GIST</th>
<th>Placebo (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SUTENT (n=202)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All Grades*</td>
<td>Grade 3/4a</td>
</tr>
<tr>
<td>Any</td>
<td>68 (34)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST / ALT</td>
<td>78 (39)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Lipase</td>
<td>50 (25)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>48 (24)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Amylase</td>
<td>35 (17)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>32 (16)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>20 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased LVEF</td>
<td>22 (11)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Renal/Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>25 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>24 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sodium increased</td>
<td>20 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>107 (53)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>76 (38)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Platelets</td>
<td>76 (38)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>52 (26)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

LVEF=Left ventricular ejection fraction

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

a Grade 4 laboratory abnormalities in patients on SUTENT included alkaline phosphatase (1%), lipase (2%), creatinine (1%), potassium decreased (1%), neutrophils (2%), hemoglobin (2%), and platelets (1%).

b Grade 4 laboratory abnormalities in patients on placebo included amylase (1%), lipase (1%), and hemoglobin (2%).

After an interim analysis, the study was unblinded, and patients on the placebo arm were given the opportunity to receive open-label SUTENT treatment [see Clinical Studies (14.1)]. For 241 patients randomized to the SUTENT arm, including 139 who received SUTENT in both the double-blind and open-label treatment phases, the median duration of SUTENT treatment was 6 cycles (mean 8.5, range 1 – 44). For the 255 patients who ultimately received open-label SUTENT treatment, median duration of study treatment was 6 cycles (mean 7.8, range 1 – 37) from the time of the unblinding. A total of 118 patients (46%) required dosing interruptions, and a total of 72 patients (28%) required dose reductions. The incidence of treatment-emergent adverse reactions resulting in permanent discontinuation was 20%. The most common Grade 3 or 4 treatment-related adverse reactions experienced by patients receiving SUTENT in the open-label treatment phase were fatigue (10%), hypertension (8%), asthenia (5%), diarrhea (5%), hand-foot syndrome (5%), nausea (4%), abdominal pain (3%), anorexia (3%), mucositis (2%), vomiting (2%), and hypothyroidism (2%).

6.2 Adverse Reactions in the Treatment-Naive RCC Study

The as-treated patient population for the treatment-naive RCC study included 735 patients, 375 randomized to SUTENT and 360 randomized to IFN-α. The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for SUTENT treatment and 4.1 months (range: 0.1 – 45.6) for IFN-α treatment. Dose interruptions occurred in 202 patients (54%) on SUTENT and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on SUTENT and 98 patients (27%) on IFN-α. Discontinuation rates due to adverse reactions were 20% for SUTENT and 24% for IFN-α. Most treatment-emergent adverse reactions in both study arms
were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 77% versus 55% of patients on SUTENT versus IFN-α, respectively.

Table 3 compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT versus IFN-α.
<table>
<thead>
<tr>
<th>Adverse Reaction, n (%)</th>
<th>Treatment-Naïve RCC</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4*</td>
<td>All Grades</td>
</tr>
<tr>
<td><strong>Any</strong></td>
<td>372 (99)</td>
<td>290 (77)</td>
<td>355 (99)</td>
</tr>
<tr>
<td><strong>Constitutional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>233 (62)</td>
<td>55 (15)</td>
<td>202 (56)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>96 (26)</td>
<td>42 (11)</td>
<td>81 (22)</td>
</tr>
<tr>
<td>Fever</td>
<td>84 (22)</td>
<td>3 (1)</td>
<td>134 (37)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>60 (16)</td>
<td>1 (&lt;1)</td>
<td>60 (17)</td>
</tr>
<tr>
<td>Chills</td>
<td>53 (14)</td>
<td>3 (1)</td>
<td>111 (31)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>50 (13)</td>
<td>7 (2)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>18 (5)</td>
<td>0 (0)</td>
<td>54 (15)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>246 (66)</td>
<td>37 (10)</td>
<td>76 (21)</td>
</tr>
<tr>
<td>Nausea</td>
<td>216 (58)</td>
<td>21 (6)</td>
<td>147 (41)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>178 (47)</td>
<td>13 (3)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>148 (39)</td>
<td>19 (5)</td>
<td>62 (17)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>128 (34)</td>
<td>8 (2)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Abdominal painc</td>
<td>113 (30)</td>
<td>20 (5)</td>
<td>42 (12)</td>
</tr>
<tr>
<td>Constipation</td>
<td>85 (23)</td>
<td>4 (1)</td>
<td>49 (14)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>50 (13)</td>
<td>0 (0)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>GERD/reflux</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>esophagitis</td>
<td>47 (12)</td>
<td>1 (&lt;1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>52 (14)</td>
<td>0 (0)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Oral pain</td>
<td>54 (14)</td>
<td>2 (&lt;1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>40 (11)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>38 (10)</td>
<td>0 (0)</td>
<td>6 (2)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (34)</td>
<td>50 (13)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>91 (24)</td>
<td>7 (2)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>61 (16)</td>
<td>10 (3)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dermatology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>109 (29)</td>
<td>6 (2)</td>
<td>39 (11)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>108 (29)</td>
<td>32 (8)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Skin discoloration/</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yellow skin</td>
<td>94 (25)</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>85 (23)</td>
<td>1 (&lt;1)</td>
<td>26 (7)</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>75 (20)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>51 (14)</td>
<td>0 (0)</td>
<td>34 (9)</td>
</tr>
<tr>
<td>Erythema</td>
<td>46 (12)</td>
<td>2 (&lt;1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>44 (12)</td>
<td>1 (&lt;1)</td>
<td>24 (7)</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Altered taste*</td>
<td>178 (47)</td>
<td>1 (&lt;1)</td>
<td>54 (15)</td>
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<tr>
<td>Headache</td>
<td>86 (23)</td>
<td>4 (1)</td>
<td>69 (19)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>43 (11)</td>
<td>2 (&lt;1)</td>
<td>50 (14)</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>105 (28)</td>
<td>19 (5)</td>
<td>52 (14)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>111 (30)</td>
<td>10 (3)</td>
<td>69 (19)</td>
</tr>
<tr>
<td>Adverse Reaction, n (%)</td>
<td>Treatment-Naïve RCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SUTENT (n=375)</td>
<td>IFN-α (n=360)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>All Grades</td>
</tr>
<tr>
<td>Pain in extremity/limb discomfort</td>
<td>150 (40)</td>
<td>19 (5)</td>
<td>107 (30)</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>61 (16)</td>
<td>6 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>100 (27)</td>
<td>3 (1)</td>
<td>51 (14)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>99 (26)</td>
<td>24 (6)</td>
<td>71 (20)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>54 (14)</td>
<td>0 (0)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>51 (14)</td>
<td>2 (&lt;1)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>43 (11)</td>
<td>2 (&lt;1)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Metabolism/Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>182 (48)</td>
<td>11 (3)</td>
<td>153 (42)</td>
</tr>
<tr>
<td>Hemorrhage/Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding, all sites</td>
<td>140 (37)</td>
<td>16 (4)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>35 (10)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>57 (15)</td>
<td>3 (&lt;1)</td>
<td>37 (10)</td>
</tr>
<tr>
<td>Depression&lt;sup&gt;g&lt;/sup&gt;</td>
<td>40 (11)</td>
<td>0 (0)</td>
<td>51 (14)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
<sup>b</sup>Grade 4 ARs in patients on SUTENT included back pain (1%), arthralgia (<1%), dyspnea (<1%), asthenia (<1%), fatigue (<1%), limb pain (<1%) and rash (<1%).
<sup>c</sup>Grade 4 ARs in patients on IFN-α included dyspnea (1%), fatigue (1%), abdominal pain (<1%) and depression (<1%).
<sup>d</sup>Includes flank pain
<sup>e</sup>Includes ageusia, hypogeusia and dysgeusia
<sup>f</sup>Includes decreased appetite
<sup>g</sup>Includes depressed mood

Treatment-emergent Grade 3/4 laboratory abnormalities are presented in Table 4.
<table>
<thead>
<tr>
<th>Laboratory Parameter, n (%)</th>
<th>Treatment-Naive RCC</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SUTENT (n=375)</td>
<td>All Grades*</td>
<td>Grade 3/4</td>
<td>All Grades*</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>211 (56)</td>
<td>6 (2)</td>
<td>136 (38)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>ALT</td>
<td>192 (51)</td>
<td>10 (3)</td>
<td>144 (40)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Lipase</td>
<td>211 (56)</td>
<td>69 (18)</td>
<td>165 (46)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>171 (46)</td>
<td>7 (2)</td>
<td>132 (37)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Amylase</td>
<td>130 (35)</td>
<td>22 (6)</td>
<td>114 (32)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>75 (20)</td>
<td>3 (1)</td>
<td>8 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>49 (13)</td>
<td>4 (1)</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Renal/Metabolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>262 (70)</td>
<td>2 (&lt;1)</td>
<td>183 (51)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>183 (49)</td>
<td>9 (2)</td>
<td>40 (11)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>173 (46)</td>
<td>54 (14)</td>
<td>119 (33)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>156 (42)</td>
<td>4 (1)</td>
<td>145 (40)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>116 (31)</td>
<td>22 (6)</td>
<td>87 (24)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Albumin</td>
<td>106 (28)</td>
<td>4 (1)</td>
<td>72 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>86 (23)</td>
<td>21 (6)</td>
<td>55 (15)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>75 (20)</td>
<td>31 (8)</td>
<td>55 (15)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>65 (17)</td>
<td>0 (0)</td>
<td>43 (12)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>61 (16)</td>
<td>13 (3)</td>
<td>61 (17)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Calcium increased</td>
<td>50 (13)</td>
<td>2 (&lt;1)</td>
<td>35 (10)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>49 (13)</td>
<td>3 (1)</td>
<td>7 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Sodium increased</td>
<td>48 (13)</td>
<td>0 (0)</td>
<td>38 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>289 (77)</td>
<td>65 (17)</td>
<td>178 (49)</td>
<td>31 (9)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>298 (79)</td>
<td>29 (8)</td>
<td>250 (69)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Platelets</td>
<td>255 (68)</td>
<td>35 (9)</td>
<td>85 (24)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>256 (68)</td>
<td>66 (18)</td>
<td>245 (68)</td>
<td>93 (26)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>293 (78)</td>
<td>29 (8)</td>
<td>202 (56)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

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

Grade 4 laboratory abnormalities in patients on SUTENT included uric acid (14%), lipase (3%), neutrophils (2%), lymphocytes (2%), hemoglobin (2%), platelets (1%), amylase (1%), ALT (<1%), creatinine (<1%), creatinine (<1%), glucose increased (<1%), calcium decreased (<1%), phosphorous (<1%), potassium increased (<1%), and sodium decreased (<1%).

Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (8%), lymphocytes (2%), lipase (1%), neutrophils (1%), amylase (<1%), calcium increased (<1%), glucose decreased (<1%), potassium increased (<1%), and hemoglobin (<1%).

### 6.3 Venous Thromboembolic Events

Seven patients (3%) on SUTENT and none on placebo in the double-blind treatment phase of GIST Study A experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT), and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Thirteen (3%) patients receiving SUTENT for treatment-naive RCC had venous thromboembolic events reported. Seven (2%) of these patients had pulmonary embolism, one was Grade 2 and six were Grade 4, and six (2%) patients had DVT, including three 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.

### 6.4 Reversible Posterior Leukoencephalopathy Syndrome

There have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. 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.

### 6.5 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. Hepatotoxicity was observed in patients receiving SUTENT [See Boxed Warning and Warnings and Precautions (5.1)].

### 6.6 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.

Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported.

Cases of myopathy and/or rhabdomyolysis with or without acute renal failure, in some cases with fatal outcome, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Thrombotic microangiopathy has been reported in patients on SUTENT. Suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Cases of fatal hemorrhage associated with thrombocytopenia have been reported.

Pulmonary embolism, in some cases with fatal outcome, has been reported.

Cases of renal impairment and/or failure, in some cases with fatal outcome, have been reported.

Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUTENT in patients with nephrotic syndrome.

Hypersensitivity reactions, including angioedema, have been reported.

Cases of fistula formation, sometimes associated with tumor necrosis and/or regression, in some cases with fatal outcome, have been reported.

### 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 inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C\textsubscript{max} and AUC\textsubscript{0-\textinfty} 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, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors [see Dosage and Administration (2.2)].

#### 7.2 CYP3A4 Inducers

CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in
the combined (sunitinib + primary active metabolite) Cmax and AUC0-∞ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John’s Wort) may decrease sunitinib concentrations. St. John’s Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John’s Wort concomitantly. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers [see Dosage and Administration (2.2)].

7.3 In Vitro Studies of CYP Inhibition and Induction

In vitro studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The in vitro studies in human liver microsomes and hepatocytes of the activity of CYP isoforms 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)].

8.3 Nursing Mothers

Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether sunitinib or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, 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 [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

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

 Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for ≥ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were > 0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at ≥5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤ 2 mg/kg/day.

8.5 Geriatric Use

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

8.6 Hepatic Impairment

No dose adjustment is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

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 attempted suicide was reported without adverse reaction. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m²) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

11 DESCRIPTION

SUTENT, an oral multi-kinase inhibitor, is the malate salt of sunitinib. Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S), compound with N-[2-(diethylamino)ethyl]-5-[[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1). The molecular formula is C_{22}H_{27}FN_{4}O_{7} • C_{4}H_{6}O_{3} and the molecular weight is 532.6 Daltons.

The chemical structure of sunitinib malate is:

![Chemical structure of sunitinib malate](image_url)

Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2.

SUTENT (sunitinib malate) capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

The orange gelatin capsule shells contain titanium dioxide, and red iron oxide. The caramel gelatin capsule shells contain titanium dioxide, red iron oxide, yellow iron oxide and black iron oxide. The white printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets in vivo and demonstrated inhibition of tumor growth or tumor regression and/or inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) in vitro and to inhibit PDGFRβ- 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 ($C_{\text{max}}$) of sunitinib are generally observed between 6 and 12 hours ($T_{\text{max}}$) following oral administration. Food has no effect on the bioavailability of sunitinib. SUTENT may be taken with or without food.

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

Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23 to 37% of the total exposure. Elimination is primarily via feces. In a human mass balance study of $[^{14}\text{C}]$sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/hr with an inter-patient variability of 40%.

Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively. With repeated daily administration, sunitinib accumulates 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 of demographic 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:** No clinical studies of SUTENT were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in patients with calculated creatinine clearances in the range of 42 – 347 mL/min.

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

12.4 Cardiac Electrophysiology

*See Warnings and Precautions (5.4).*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Although definitive carcinogenicity studies with sunitinib have not been completed, carcinoma and hyperplasia of the Brunner’s gland of the duodenum have been observed at the highest dose tested in H2ras transgenic mice administered doses of 0, 10, 25, 75, or 200 mg/kg/day for 28 days. Sunitinib did not cause genetic damage when tested in in vitro assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an in vivo rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (approximately 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 approximately 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

Although fertility was not affected in rats, 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 approximately 5 times the AUC in patients administered the RDD], however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (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 approximately 25.8 times the AUC in patients administered the RDD).

14 CLINICAL STUDIES

The clinical safety and efficacy of SUTENT have been studied in patients with gastrointestinal stromal tumor (GIST) after progression on or intolerance to imatinib mesylate, and in patients with renal cell carcinoma (RCC).

14.1 Gastrointestinal Stromal Tumor

GIST Study A

Study A was a two-arm, international, randomized, double-blind, placebo-controlled trial of SUTENT in patients with GIST who had disease progression during prior imatinib mesylate (imatinib) treatment or who were intolerant of imatinib. The objective was to compare 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: 4% both arms, remainder not reported), and Performance Status (ECOG 0: 44% vs. 46%, ECOG 1: 55% vs. 52%, and ECOG 2: 1% vs. 2%). Prior treatment included surgery (94% vs. 93%) and radiotherapy (8% vs. 15%). Outcome of prior imatinib treatment was also comparable between arms with intolerance (4% vs. 4%), progression within 6 months of starting treatment (17% vs. 16%), or progression beyond 6 months (78% vs. 80%) balanced.

The planned interim efficacy and safety analysis was performed after 149 TTP events had occurred. There was a statistically significant advantage for SUTENT over placebo in TTP, meeting the primary endpoint. Efficacy results are summarized in Table 5 and the Kaplan-Meier curve for TTP is in Figure 1.
Table 5. 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(^a) [median, 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(^b) [median, weeks (95% CI)]</td>
<td>24.1 (11.1, 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 (PR) [% (95% CI)]</td>
<td>6.8 (3.7, 11.1)</td>
<td>0 (0, 0)</td>
<td>0.006(^c)</td>
<td></td>
</tr>
</tbody>
</table>

CI=Confidence interval, HR=Hazard ratio, PR=Partial response
\(^a\)A comparison is considered statistically significant if the p-value is < 0.00417 (O’Brien Fleming stopping boundary)
\(^b\)Time from randomization to progression; deaths prior to documented progression were censored at time of last radiographic evaluation
\(^c\)Pearson chi-square test

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

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. After the primary endpoint was met at the interim analysis, the study was unblinded, and patients on the placebo arm were offered open-label SUTENT treatment. Ninety-nine of the patients initially randomized to placebo crossed over to receive SUTENT in the open-label treatment phase. At the protocol specified final analysis of OS, the median OS was 72.7 weeks for the SUTENT arm and 64.9 weeks for the placebo arm [HR= 0.876, 95% CI (0.679, 1.129)].

Study B
Study B was an open-label, multi-center, single-arm, dose-escalation study conducted in patients with GIST following progression on or intolerance to imatinib. Following identification of the recommended Phase 2 regimen (50 mg once daily on Schedule 4/2), 55 patients in this study received the 50 mg dose of SUTENT on treatment Schedule 4/2. Partial responses were observed in 5 of 55 patients [9.1% PR rate, 95% CI (3.0, 20.0)].

14.2 Renal Cell Carcinoma
Treatment-Naive RCC
A multi-center, international randomized study comparing single-agent SUTENT with IFN-α was conducted in patients with treatment-naive RCC. The objective was to compare Progression-Free Survival (PFS) in patients receiving SUTENT versus patients receiving IFN-α. Other endpoints included Objective Response Rate (ORR), Overall Survival (OS) and safety. Seven hundred fifty (750) patients were randomized (1:1) to
receive either 50 mg SUTENT once daily on Schedule 4/2 or to receive IFN-α administered subcutaneously at 9 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 6 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 6).

Table 6. Treatment-Naïve RCC Efficacy Results (interim analysis)

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=375)</th>
<th>P-value (log-rank test)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-Free Survival(^a) [median, weeks (95% CI)]</td>
<td>47.3 (42.6, 50.7)</td>
<td>22.0 (16.4, 24.0)</td>
<td>&lt;0.000001(^b)</td>
<td>0.415 (0.320, 0.539)</td>
</tr>
<tr>
<td>Objective Response Rate(^a) [% (95% CI)]</td>
<td>27.5 (23.0, 32.3)</td>
<td>5.3 (3.3, 8.1)</td>
<td>&lt;0.001(^c)</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI=Confidence interval, NA=Not applicable
\(^a\) Assessed by blinded core 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 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 post-study cancer treatment with SUTENT.

**Cytokine-Refractory RCC**

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

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

The baseline malignancy and prior treatment history of the patients were comparable between Studies 1 and 2. Across the two studies, 95% of the pooled population of patients had at least some component of clear-cell histology. All patients in Study 1 were required to have a histological clear-cell component. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in Study 1. All patients had received one previous cytokine regimen. Metastatic disease present at the time of study entry included lung metastases in 81% of patients. Liver metastases were more common in Study 1 (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 7. There were 36 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 34.0% (95% CI 25.0, 43.8). There were 23 PRs in Study 2 as assessed by the investigators for an ORR of 36.5% (95% CI 24.7, 49.6). The majority (>90%) of objective disease responses were observed during the first four cycles; the latest reported response was observed in Cycle 10. DR data from Study 1 is premature as only 9 of 36 patients (25%) responding to treatment had experienced disease progression or died at the time of the data cutoff.
**Table 7. Cytokine-Refractory RCC Efficacy Results**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study 1 (N=106)</th>
<th>Study 2 (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate</td>
<td>34.0&lt;sup&gt;a&lt;/sup&gt; (25.0, 43.8)</td>
<td>36.5&lt;sup&gt;b&lt;/sup&gt; (24.7, 49.6)</td>
</tr>
<tr>
<td>Duration of Response (DR)</td>
<td>*</td>
<td>54&lt;sup&gt;b&lt;/sup&gt; (34.3, 70.1)</td>
</tr>
</tbody>
</table>

CI = Confidence interval  
* Median DR has not yet been reached  
** Data not mature enough to determine upper confidence limit  
<sup>a</sup> Assessed by blinded core radiology laboratory  
<sup>b</sup> Assessed by investigators

### 16 HOW SUPPLIED/STORAGE AND HANDLING

**12.5 mg Capsules**  
Hard gelatin capsule with orange cap and orange body, printed with white ink “Pfizer” on the cap, “STN 12.5 mg” on the body; available in:  
Bottles of 28: NDC 0069-0550-38  
25 mg Capsules  
Hard gelatin capsule with caramel cap and orange body, printed with white ink “Pfizer” on the cap, “STN 25 mg” on the body; available in:  
Bottles of 28: NDC 0069-0770-38  
50 mg Capsules  
Hard gelatin capsule with caramel cap and caramel body, printed with white ink “Pfizer” on the cap, “STN 50 mg” on the body; available in:  
Bottles of 28: NDC 0069-0980-38  
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

### 17 PATIENT COUNSELING INFORMATION

*See 17.5 for FDA-Approved Patient Labeling.*

#### 17.1 Gastrointestinal Disorders

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

#### 17.2 Skin Effects

Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet.

#### 17.3 Other Common Events

Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

#### 17.4 Concomitant Medications

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

#### 17.5 FDA-Approved Patient Labeling

LAB-0317-14.0
MEDICATION GUIDE

SUTENT (su TENT)  
(sunitinib malate)

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

2. Advanced kidney cancer (advanced renal cell carcinoma or RCC).

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

What should I tell my healthcare provider before taking SUTENT?  
Before taking SUTENT tell your healthcare provider if you:

- have any heart problems
- have high blood pressure
- have thyroid problems
- have kidney function problems (other than cancer)
- have liver problems
- have any bleeding problem
- have seizures
- have any other medical conditions
- are pregnant, could be pregnant or plan to become pregnant. SUTENT may harm an unborn baby. You should not become pregnant while taking SUTENT. Tell your healthcare provider right away if you become pregnant while taking SUTENT.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take SUTENT or breastfeed. You should not do both.

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

How should I take SUTENT?  
- Take SUTENT exactly the way your healthcare provider tells you.
- Take SUTENT 1 time each day with or without food.
- Do not open the SUTENT capsules.
- Do not drink grapefruit juice or eat grapefruit during your treatment with SUTENT. They may cause you to have too much SUTENT in your body.

SUTENT is usually taken for 4 weeks (28 days) and then stopped for 2 weeks (14 days). This is 1 cycle of treatment.

- You will repeat this cycle of taking SUTENT for 4 weeks and then stopping it for 2 weeks, as long as your healthcare provider tells you to.
• Your healthcare provider may do blood tests before each cycle of treatment.
• If you miss a dose, take it as soon as you remember. Do not take it if it is close to your next dose. Just take the next dose at your regular time. Do not take more than 1 dose of SUTENT at a time. Tell your healthcare provider about any missed dose.
• Call your healthcare provider right away, if you take too much SUTENT.

What are possible side effects of SUTENT?
SUTENT may cause serious side effects including:
• See “What is the most important information I should know about SUTENT?”
• Heart problems. Heart problems may include heart failure and heart muscle problems (cardiomyopathy). 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.
  o painful, swollen stomach (abdomen)
  o vomiting blood
  o black, sticky stools
  o bloody urine
  o headache or change in your mental status
Your healthcare provider can tell you other symptoms to watch for.
• 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:
  o tiredness that worsens and does not go away
  o loss of appetite
  o heat intolerance
  o feeling nervous or agitated, tremors
  o sweating
  o nausea or vomiting
  o diarrhea
  o fast heart rate
  o weight gain or weight loss
  o feeling depressed
  o irregular menstrual periods or no menstrual periods
  o headache
  o 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 and 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

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