SUNITINIB

SUTENT®
12.5 mg, 25 mg, 50 mg Capsules

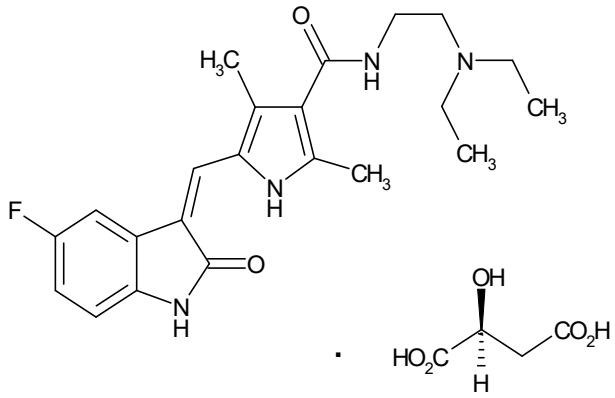
Rx

1.0 PHARMACOLOGIC CATEGORY

Antineoplastic Agent (Protein Kinase Inhibitor)

2.0 DESCRIPTION

Sunitinib malate (SUTENT®), an oral multi-kinase inhibitor targeting several receptor tyrosine kinases (RTK), 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 $C_{22}H_{27}FN_4O_2 \bullet C_4H_6O_5$ and the molecular weight is 532.6 Daltons. The chemical structure of sunitinib malate is:



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.

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.**

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.**

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.**

3.0 FORMULATION

Sunitinib malate (Sutent) 12.5 mg capsules: Each capsule contains 16.7 mg sunitinib malate (equivalent to 12.5 mg of sunitinib).

Sunitinib malate (Sutent) 25 mg capsules: Each capsule contains 33.4 mg sunitinib malate (equivalent to 25 mg of sunitinib).

Sunitinib malate (Sutent) 50 mg capsules: Each capsule contains 66.8 mg sunitinib malate (equivalent to 50 mg of sunitinib).

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Sunitinib is indicated for the treatment of gastrointestinal stromal tumor (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance (see Section **5.1 Pharmacodynamic Properties**).

Sunitinib is indicated for the treatment of treatment-naïve advanced and/or metastatic renal cell carcinoma (MRCC) (see Section **5.1 Pharmacodynamic Properties**).

Sunitinib is indicated for the treatment of advanced and/or MRCC after failure of cytokine-based therapy (see Section **5.1 Pharmacodynamic Properties**).

Sunitinib is indicated for the treatment of unresectable or metastatic; well-differentiated pancreatic neuroendocrine tumors (pNET) with disease progression (see Section **5.1 Pharmacodynamic Properties**).

4.2 Dosage and Method of Administration

For GIST and MRCC, the recommended dose of sunitinib is 50 mg taken orally once daily for 4 consecutive weeks, followed by a 2-week off period (Schedule 4/2) to comprise a complete cycle of 6 weeks.

For pNET, the recommended dose of sunitinib is 37.5 mg taken orally once daily without a scheduled rest period.

Sunitinib may be taken with or without food.

If a dose is missed, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

<u>Dose modifications</u>

Safety and Tolerability

For GIST and MRCC, dose modifications in 12.5 mg increments or decrements may be applied based on individual safety and tolerability up to 75 mg or down to 25 mg.

For pNET, dose modification in 12.5 mg increments or decrements may be applied based on individual safety and tolerability. The maximum dose administered in the Phase 3 pNET study was 50 mg daily.

Dose interruptions may be required based on individual safety and tolerability.

CYP3A4 Inhibition/Induction

Co-administration of sunitinib with strong CYP3A4 inducers, such as rifampin, should be avoided (see Section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**). If this is not possible, the dose of sunitinib may need to be increased in 12.5 mg increments to a maximum of 87.5 mg (GIST and RCC), or 62.5 mg (pNET) daily, based on careful monitoring of tolerability.

Co-administration of sunitinib with strong CYP3A4 inhibitors, such as ketoconazole, should be avoided (see Section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**). If this is not possible, the dose of sunitinib may need to be reduced in 12.5 mg decrements to a minimum of 37.5 mg (GIST and RCC), or 25 mg (pNET) daily.

Selection of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP3A4 is recommended.

Use in Pediatrics

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

Use in the Elderly

Dose adjustments are not required in elderly patients. Approximately 34% of the subjects in clinical studies of sunitinib were 65 years of age or over. No significant differences in safety or efficacy were observed between younger and older patients.

Hepatic Insufficiency

No dose adjustment is necessary when administering sunitinib to patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Sunitinib was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment (see Section **5.2 Pharmacokinetic Properties**).

Renal Insufficiency

No starting dose adjustment is required when administering sunitinib to patients with renal impairment (mild-severe) or with end-stage renal disease (ESRD) on hemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability.

4.3 Contraindications

Use of sunitinib is contraindicated in patients with hypersensitivity to sunitinib or to any of the excipients, namely mannitol, croscarmellose sodium, povidone and magnesium stearate.

4.4 Special Warnings and Precautions for Use

Skin and tissues

Skin discoloration, possibly due to the active substance color (yellow) was a very common adverse reaction reported in clinical trials. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with sunitinib. Other possible dermatologic effects may include dryness, thickness or cracking of the skin, blisters or occasional rash on the palms of the hands and soles of the feet.

The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.

Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM) and cases suggestive of Stevens-Johnson syndrome (SJS), some of which were fatal. If signs or symptoms of SJS or EM (e.g., progressive skin rash often with blisters or mucosal lesions) are present, Sunitinib malate (Sutent) treatment should be discontinued. If the diagnosis of SJS is confirmed, treatment must not be re-started. In some cases of suspected EM, patients tolerated the reintroduction of Sunitinib malate (Sutent) therapy at a lower dose after resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines.

Hemorrhagic events

Hemorrhagic events reported through postmarketing experience, some of which were fatal, have included gastrointestinal (GI), respiratory, tumor, urinary tract, and brain hemorrhages. In clinical trials, tumor hemorrhage occurred in approximately 2% of subjects with GIST. These events may occur suddenly, and in the case of pulmonary tumors, may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Cases of pulmonary hemorrhage some with a fatal outcome, have been observed in clinical trials and have been reported in postmarketing experience in patients treated with sunitinib for MRCC, GIST, and metastatic non-small cell lung cancer (NSCLC). Sunitinib is not approved for use in patients with NSCLC.

Treatment-emergent bleeding events occurred in 18% of subjects receiving sunitinib in the double-blind treatment phase of GIST Study compared to 17% of subjects receiving placebo. In subjects receiving sunitinib for treatment-naïve MRCC, 39% of patients had bleeding events compared with 11% of subjects receiving interferon-α (IFN-α). Seventeen (4.5%) subjects on sunitinib versus 5 (1.7%) of subjects on IFN-α experienced Grade 3 or greater bleeding events. Of subjects receiving sunitinib for cytokine-refractory MRCC, 26% experienced bleeding. Bleeding events, excluding epistaxis, occurred in 21.7% of subjects receiving sunitinib in the Phase 3 pNET study compared to 9.85% of subjects receiving placebo. Routine assessment of these events should include complete blood counts and physical examination.

Gastrointestinal tract

Serious, sometimes fatal GI complications including GI perforation have occurred in subjects with intra-abdominal malignancies treated with sunitinib.

Gastrointestinal events

Nausea, diarrhea, stomatitis, dyspepsia, and vomiting were the most commonly reported treatment-related GI events. Supportive care for GI adverse events requiring treatment may include anti-emetic or antidiarrheal medication.

Pancreatitis

Pancreatitis has been reported in clinical trials of sunitinib. Increases in serum lipase and amylase were observed in subjects with various solid tumors who received sunitinib. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumors. If symptoms of pancreatitis are present, patients should have sunitinib discontinued and be provided with appropriate supportive care.

Hepatotoxicity

Hepatotoxicity has been observed in patients treated with sunitinib. Cases of hepatic failure, some with a fatal outcome, were observed in <1% of solid tumor patients treated with sunitinib. Monitor liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) before initiation of treatment, during each cycle of treatment, and as clinically indicated. Sunitinib should be interrupted for Grade 3 or 4 hepatic-related adverse events and discontinued if there is no resolution.

Hematological

Decreased absolute neutrophil counts and decreased platelet counts were reported in clinical trials. Such events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. In addition, some cases of fatal hemorrhage associated with thrombocytopenia were reported through postmarketing experience.

Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with sunitinib.

Cardiovascular

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia and myocardial infarction, some of which were fatal, have been reported through postmarketing experience. Use sunitinib with caution in patients who are at risk for, or who have a history of, these events. In clinical trials, decreases in left ventricular ejection fraction (LVEF) of ≥20% and below the lower limit of normal (LLN) occurred in approximately 2% of sunitinib-treated GIST subjects, 4% of cytokine-refractory MRCC subjects and 2% of placebo-treated subjects. These LVEF declines do not appear to have been progressive and often improved as treatment continued.

In the treatment-naïve MRCC study, 27% and 15% of subjects on sunitinib and IFN-α, respectively, had an LVEF value below the LLN. Two (<1%) subjects who received sunitinib were diagnosed with congestive heart failure (CHF).

Cardiac failure, cardiac failure congestive, or left ventricular failure were reported in 0.8% of subjects with solid tumors[*] and 1% of subjects treated with placebo.

In the Phase 3 pNET study, 1 (1.2%) subject who received sunitinib had treatment-related fatal cardiac failure.

Subjects who presented with cardiac events, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism within 12 months prior to sunitinib administration, were excluded from sunitinib 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 sunitinib. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. The dose of sunitinib should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

QT interval prolongation

At approximately twice the therapeutic concentrations, sunitinib has been shown to prolong the QTcF (Fridericia's correction) interval (see Section **5.2 Pharmacokinetic Properties**). There were no patients with greater than Grade 2 Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) QT/QTc interval prolongation. QT interval prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. Torsade de pointes has been observed in <0.1% of sunitinib-exposed patients. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of sunitinib reduced (see Sections **4.2 Dosage and Method of Administration** and **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Hypertension

Hypertension was a very common adverse reaction reported in clinical trials in subjects with solid tumors, including primarily GIST and cytokine-refractory RCC[†]. Sunitinib dosing was reduced or temporarily delayed in approximately 2.7% of this patient population. None of these subjects were discontinued from treatment with sunitinib. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of this patient population. Hypertension was reported in approximately 33.9% of subjects receiving sunitinib for treatment-naïve MRCC compared to 3.6% of subjects

[*] From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.
[†] From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.

receiving IFN-α. Severe hypertension occurred in 12% of treatment-naïve subjects on sunitinib and <1% of patients on IFN-α. Hypertension was reported in 26.5% of subjects receiving sunitinib in a Phase 3 pNET study, compared to 4.9% of subjects receiving placebo. Severe hypertension occurred in 10% of pNET subjects on sunitinib and 3% of subjects on placebo. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

Aneurysms and artery dissections

The use of vascular endothelial growth factor (VEGF) pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating sunitinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

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 sunitinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on sunitinib 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.

Acquired hypothyroidism was noted in 6.2% of GIST subjects on sunitinib versus 1% on placebo. Hypothyroidism was reported as an adverse event in 16% of subjects on sunitinib in the treatment-naïve MRCC study and 3 subjects (<1%) in the IFN-α arm, and in 4% of subjects across the 2 cytokine-refractory MRCC studies. Additionally, thyroid stimulating hormone (TSH) elevations were reported in 2% of cytokine-refractory MRCC subjects. Overall, 7% of the cytokine-refractory MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. In the Phase 3 pNET study, hypothyroidism was reported in 6 (7.2%) subjects receiving sunitinib and in 1 (1.2%) subject on placebo.

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

Seizures

In clinical studies of sunitinib, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been rare (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness, should be controlled with medical management including control of hypertension. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Surgical procedures

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

Osteonecrosis of the Jaw (ONJ)

ONJ has been uncommonly observed in clinical trials and has been reported in postmarketing experience in patients treated with sunitinib. The majority of cases occurred in patients who had received prior or concomitant treatment with intravenous (IV) bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when sunitinib and IV bisphosphonates are used either simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor for ONJ. Prior to treatment with sunitinib, a dental examination and appropriate preventive dentistry should be considered. In patients being treated with sunitinib, who have previously received or are receiving IV bisphosphonates, invasive dental procedures should be avoided, if possible.

Tumor lysis syndrome (TLS)

Cases of TLS, some fatal, have been rarely observed in clinical trials and have been reported in postmarketing experience in patients treated with sunitinib. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

Necrotizing fasciitis

Rare cases of necrotizing fasciitis, including of the perineum, sometimes fatal, have been reported. Sunitinib therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated.

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in postmarketing experience of sunitinib as monotherapy and in combination with bevacizumab. Discontinue sunitinib in patients developing TMA. Reversal of the effects of TMA has been observed after treatment discontinuation.

Proteinuria

Cases of proteinuria and 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 sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue sunitinib in patients with nephrotic syndrome.

Hypoglycemia

Decreases in blood glucose, in some cases clinically symptomatic, have been reported during sunitinib treatment. Blood glucose levels in diabetic patients should be checked regularly in order to assess if anti-diabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Drugs that may increase sunitinib plasma concentrations

Concomitant administration of sunitinib with the strong CYP3A4 inhibitor ketoconazole resulted in a 49% and 51% increase of the complex [sunitinib + primary active metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib in healthy volunteers.

Administration of sunitinib with strong inhibitors of the CYP3A4 family (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations. Concomitant administration with inhibitors should therefore be avoided, or the selection of an alternate concomitant medication with no, or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dosage of sunitinib may need to be reduced (see Section **4.2 Dosage and Method of Administration**).

Drugs that may decrease sunitinib plasma concentrations

Concomitant use of sunitinib with the CYP3A4 inducer rifampin resulted in a 23% and 46% reduction of the complex [sunitinib + primary active metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib in healthy volunteers.

Administration of sunitinib with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or *Hypericum perforatum* also known as St. John's Wort) may decrease sunitinib concentrations. Concomitant administration with inducers should therefore be avoided, or selection of an alternate concomitant medication with no, or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dosage of sunitinib may need to be increased (see Section **4.2 Dosage and Method of Administration**).

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no studies in pregnant women using sunitinib.

Studies in animals have shown reproductive toxicity including fetal malformations (see Section **5.3 Preclinical Safety Data**). Sunitinib should not be used during pregnancy

or in any woman not employing adequate contraception unless the potential benefit justifies the potential risk to the fetus. If sunitinib is used during pregnancy, or if the patient becomes pregnant while receiving sunitinib, 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 sunitinib.

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and post-natal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at ≥1 mg/kg/day but no maternal reproductive toxicity was observed up to 3 mg/kg/day (estimate exposure ≥2.3 times the AUC in patients administered the recommended daily dose [RDD]). Reduced offspring body weights were observed during the pre-weaning and post-weaning periods at 3 mg/kg/day. No development toxicity was observed at 1 mg/kg/day (approximate exposure ≥0.9 times the AUC in patients administered the RDD).

Fertility

Based on non-clinical findings, male and female fertility may be compromised by treatment with sunitinib (see Section **5.3 Preclinical Safety Data**).

Lactation

Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite is excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should not breastfeed while taking sunitinib.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive or operate machinery have been performed. Patients should be advised that they may experience dizziness during treatment with sunitinib.

4.8 Undesirable Effects

Table 1 presents the adverse drug reactions (ADRs) by system organ class (SOC) from single-agent studies (N=7527) in advanced RCC, GIST, pNET, adjuvant treatment of RCC, and from the post-marketing experience. A dataset that pooled the 12 single-agent studies in the marketed indications was used to calculate causality. ADRs are listed within each SOC by decreasing medical seriousness or clinical importance.

Table 1. Adverse Drug Reactions Table

System Organ Class	Adverse Drug Reaction
Infections and infestations	Infections*

Blood and lymphatic system disorders	Thrombotic microangiopathy[a,**] Anemia Thrombocytopenia Neutropenia Leukopenia Lymphopenia
Immune system disorders	Hypersensitivity Angioedema
Endocrine disorders	Hyperthyroidism Hypothyroidism Thyroiditis
Metabolism and nutrition disorders	Dehydration[**] Hypoglycemia Tumor lysis syndrome[**] Decreased appetite
Psychiatric disorders	Insomnia Depression
Nervous system disorders	Cerebral hemorrhage[**] Cerebrovascular accident[**] Cerebral infarction Transient ischemic attack Posterior reversible encephalopathy syndrome Headache Dizziness Paresthesia Ageusia Dysgeusia
Eye disorders	Periorbital edema Eyelid edema Lacrimation increased
Cardiac disorders	Myocardial ischemia[b,**] Myocardial infarction[c,**] Cardiac failure[**] Cardiomyopathy[**] Left ventricular failure[**] Torsade de pointes Cardiac failure congestive
Vascular disorders	Aneurysms and artery dissections [d,**] Tumor hemorrhage[**] Hypertension Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism[**] Dyspnea Hemoptysis[e,**] Pleural effusion Epistaxis Oropharyngeal pain[f]

Gastrointestinal disorders	Gastrointestinal hemorrhage[**] Gastrointestinal perforation[g,**] Pancreatitis Esophagitis Abdominal distension Abdominal pain[h] Diarrhea Vomiting Nausea Gastro-esophageal reflux disease Dyspepsia Stomatitis[i] Constipation Oral pain Glossodynia Gingival bleeding Dry mouth Flatulence
Hepatobiliary disorders	Hepatic failure[**] Cholecystitis[j]
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome[**] Erythema multiforme[**] Pyoderma gangrenosum Dermatitis exfoliative Skin reaction Skin lesion Rash[k] Erythema Pruritus Skin exfoliation Palmar-plantar erythrodysesthesia syndrome Blister Skin discoloration[l] Hair color changes Alopecia Nail disorder Dry skin
Musculoskeletal and connective tissue disorders	Fistula[**] Rhabdomyolysis[**] Osteonecrosis of jaw Myopathy Arthralgia Myalgia Pain in extremity
Renal and urinary disorders	Renal failure[**] Nephrotic syndrome Renal impairment Hemorrhage urinary tract Proteinuria Chromaturia

General disorders and administration site conditions	Fatigue[m] Mucosal inflammation Edema[n] Pyrexia Chills Influenza like illness
Investigations	Electrocardiogram QT Prolonged Ejection fraction decreased[o] Hemoglobin decreased Platelet count decreased White blood cell count decreased Lipase increased Blood uric acid increased Amylase increased[p] Blood creatine phosphokinase increased Blood thyroid stimulating hormone increased Weight decreased

Abbreviation: ADR=adverse drug reaction.
* Infections and infestations are described in the subsection Description of Selected Adverse Reactions.
** Event may be fatal.
[a] Thrombotic microangiopathy: The following terms have been combined: Thrombotic microangiopathy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome.
[b] Myocardial ischemia: The following terms have been combined: Acute coronary syndrome, Angina pectoris, Angina unstable, Coronary artery occlusion, Myocardial ischemia.
[c] Myocardial infarction: The following terms have been combined: Acute myocardial infarction, Myocardial infarction, Silent myocardial infarction.
[d] Aneurysms and artery dissections: The following terms have been combined: Aneurysm ruptured, Aortic aneurysm, Aortic aneurysm rupture, and Aortic dissection.
[e] Hemoptysis: The following terms have been combined: Hemoptysis and pulmonary hemorrhage.
[f] Oropharyngeal pain: The following terms have been combined: Laryngeal pain and Oropharyngeal pain.
[g] Gastrointestinal perforation: The following terms have been combined: Gastrointestinal perforation and Intestinal perforation.
[h] Abdominal pain: The following terms have been combined: Abdominal pain, Abdominal pain lower, Abdominal pain upper.
[i] Stomatitis: The following terms have been combined: Stomatitis and Aphthous ulcer.
[j] Cholecystitis: The following terms have been combined: Cholecystitis and Acalculous cholecystitis.
[k] Rash: The following terms have been combined: Dermatitis psoriasiform, Exfoliative rash, Rash, Rash erythematous, Rash follicular, Rash generalized, Rash macular, Rash maculopapular, Rash papular, Rash pruritic.
[l] Skin discoloration: The following terms have been combined: Skin discoloration, Yellow skin, Pigmentation disorder.
[m] Fatigue: The following terms have been combined: Fatigue and Asthenia.
[n] Edema: The following terms have been combined: Face edema, Edema, Edema peripheral.
[o] Ejection fraction decreased: The following terms have been combined: Ejection fraction decreased and Ejection fraction abnormal.
[p] Amylase increased: The following terms have been combined: Amylase, Amylase increased.

ADR frequencies presented in this section represent the frequencies of the events that occurred in sunitinib-treated subjects regardless of causality assessment.

The most important serious adverse reactions associated with sunitinib treatment of patients with solid tumors[‡*] were pulmonary embolism; thrombocytopenia, tumor hemorrhage, febrile neutropenia, and hypertension (see Section **4.4 Special Warnings and Precautions for Use**).

The most common ADRs of any grade included: fatigue; gastrointestinal disorders, such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting; skin discoloration; rash; palmar plantar erythrodysesthesia; dry skin; hair color changes; mucosal inflammation;

[‡*] From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.

asthenia; dysgeusia; anorexia and hypertension. Fatigue, hypertension and neutropenia were the most common ADRs of Grade 3 maximum severity and increased lipase was the most frequently occurring ADR of Grade 4 maximum severity in subjects with solid tumors.

Epistaxis was the most frequent hemorrhagic ADR, having been reported for approximately half of the subjects with solid tumors[§*] who experienced hemorrhagic events (see Section **4.4 Special Warnings and Precautions for Use**).

In clinical studies of sunitinib, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been reports (<1%) some fatal, of subjects presenting with seizures and radiological evidence of RPLS (see Section **4.4 Special Warnings and Precautions for Use**).

Description of selected adverse reactions

Infections and Infestations

Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported. The infections observed with sunitinib treatment are infections typically seen in cancer patients, e.g., respiratory infections (e.g., pneumonia, bronchitis), urinary tract infections, skin infections (e.g., cellulitis), sepsis/septic shock, and abscess (e.g., oral, genital, anorectal, skin, limb, visceral). Infections may be bacterial, viral, or fungal. Rare cases of necrotizing fasciitis, including of the perineum, sometimes fatal, have been reported.

Blood and Lymphatic System Disorders

Rare cases of thrombotic microangiopathy, in some cases with fatal outcome, have been reported. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Vascular Disorders

Arterial thromboembolic events (ATE)

Cases of arterial thromboembolic events (ATE), sometimes fatal, have been reported in patients treated with sunitinib. The most frequent events included cerebrovascular accident, transient ischemic attack and cerebral infarction. Risk factors associated with ATE, in addition to the underlying malignant disease and age ≥65 years, included hypertension, diabetes mellitus, and prior thromboembolic disease.

Venous thromboembolic events (VTE)

In the double-blind treatment phase of GIST study, 7 patients (3%) on sunitinib and none on placebo experienced VTE; 5 of the 7 were Grade 3 deep vein thrombosis (DVT), and 2 were Grade 1 or 2. Four of these 7 GIST patients discontinued treatment following first observation of DVT. Thirteen patients (3%) receiving sunitinib for

[§*] From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.

treatment-naïve MRCC and 4 (2%) patients in the 2 cytokine-refractory MRCC studies had VTE reported. Nine of these patients had pulmonary embolism: 1 was Grade 2 and 8 were Grade 4. Eight patients had DVT: 1 with Grade 1, 2 with Grade 2, 4 with Grade 3, and 1 with Grade 4. One patient with pulmonary embolism in the cytokine-refractory MRCC study experienced dose interruption. In treatment-naïve MRCC patients receiving IFN-α, 6 (2%) VTE occurred; 1 (<1%) patient experienced a Grade 3 DVT and 5 (1%) patients had pulmonary embolism, all Grade 4. In the adjuvant treatment of RCC study, pulmonary embolism was reported in 2.0% of patients receiving sunitinib and 0.7% of patients receiving placebo. DVT was reported in 0.3% of patients receiving sunitinib and placebo.

Pulmonary embolism was reported in approximately 2.2% of patients with solid tumors [**] [‡] who received sunitinib. None of these events resulted in a patient discontinuing treatment with sunitinib; however, a dose reduction or temporary delay in treatment occurred in a few cases. There were no further occurrences of pulmonary embolism in these patients after treatment was resumed.

Musculoskeletal and Connective Tissue Disorders

Rare cases of myopathy and/or rhabdomyolysis with or without acute renal failure, in some cases with fatal outcome, have been reported. Most of these patients had pre-existing risk factors and/or were receiving concomitant medications known to be associated with these adverse reactions. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Long-term Safety in RCC

The long-term safety of sunitinib in patients with metastatic RCC was analyzed across 9 completed clinical studies conducted in the first-line, bevacizumab-refractory and cytokine-refractory treatment settings. The analysis included 5739 patients, of whom 807 (14%) were treated for ≥2 years up to 6 years. Prolonged treatment with sunitinib was not associated with new types or increased severity of treatment-related adverse events and except for hypothyroidism, toxicity was not cumulative.

4.9 Overdose and Treatment

There is no specific antidote for overdose with sunitinib and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed drug may be achieved by emesis or gastric lavage. Cases of overdose have been reported; some cases were associated with adverse reactions consistent with the known safety profile of sunitinib.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Sunitinib inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib

[**‡] From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.

was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), VEGF 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 in 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.*

Clinical studies

The clinical safety and efficacy of sunitinib has been studied in subjects with malignant GIST who were resistant to imatinib (i.e., those who experienced disease progression during or following treatment with imatinib); or intolerant to imatinib (i.e., those who experienced significant toxicity during treatment with imatinib that precluded further treatment); in subjects with metastatic renal cell carcinoma (MRCC); and in subjects with unresectable pNET.

Efficacy is based on time to tumor progression and an increase in survival in GIST.

Efficacy is based on progression-free survival (PFS) and objective response rates (ORR) for treatment-naïve and cytokine-refractory MRCC, respectively and on PFS for pNET.

Gastrointestinal Stromal Tumors (GIST)

An initial open-label, dose-escalation study was conducted in subjects with GIST after failure of imatinib (median maximum daily dose 800 mg) due to resistance or intolerance. Ninety-seven subjects were enrolled at various doses and schedules; 55 subjects received 50 mg at the recommended treatment schedule of 4 weeks on/2 weeks off (Schedule 4/2). In this study, the median TTP and PFS were 34.0 weeks (95% confidence interval [CI]: 22.0, 46.0).

A Phase 3, randomized, double-blind, placebo-controlled study of sunitinib was conducted in subjects with GIST who were intolerant to, or had experienced disease progression during or following treatment with imatinib (median maximum daily dose 800 mg). In this study, 312 subjects were randomized (2:1) to receive either 50 mg sunitinib or placebo, orally once daily on Schedule 4/2 until disease progression or withdrawal from the study for another reason (207 subjects received sunitinib and 105 subjects received placebo). The primary efficacy endpoint of the study was TTP (as assessed by the Independent Review), defined as the time from randomization to first documentation of objective tumor progression. Secondary objectives included PFS, ORR, and overall survival (OS).

At the time of the pre-specified interim analysis, the median TTP on sunitinib was 28.9 weeks (95% CI: 21.3, 34.1) as assessed by the Investigator and 27.3 weeks (95% CI: 16.0, 32.1) as assessed by the Independent Review and was statistically significantly longer than the TTP of 5.1 weeks (95% CI: 4.4, 10.1) as assessed by the Investigator and 6.4 weeks (95% CI: 4.4, 10.0) as assessed by the Independent Review. The difference in OS was statistically in favor of sunitinib (hazard ratio [HR]: 0.491 [95% CI 0.290, 0.831]); the risk of death was 2 times higher in subjects in the placebo arm compared to the sunitinib arm.

After the positive interim analysis of efficacy and safety, at the recommendation of the independent Data and Safety Monitoring Board (DSMB), the study was unblinded and subjects on the placebo arm were offered open-label sunitinib treatment.

A total of 255 subjects received sunitinib in the open-label treatment phase of the study, including 99 subjects who were initially treated with placebo. In this final analysis, the placebo arm included those subjects randomized to placebo who subsequently received open-label sunitinib treatment.

The final analyses of primary and secondary endpoints of the study reaffirmed the results obtained at the time of the interim analysis, as shown in Table 2 below:

Table 2. Summary of Efficacy Endpoints (ITT population)

	Double-Blind Treatment[a]				
	Median (95% CI)		Hazard Ratio (HR)		Placebo Cross-over Group
Endpoint	Sunitinib	Placebo	(95% CI)	p-value	Treatment[b]
Primary: TTP (weeks)					
Interim	27.3 (16.0,32.1)	6.4 (4.4, 10.0)	0.329 (0.233, 0.466)	<0.001	-
Final	26.6 (16.0, 32.1)	6.4 (4.4, 10.0)	0.339 (0.244, 0.472)	<0.001	10.4 (4.3, 22.0)

	Double-Blind Treatment[a]				
	Median (95% CI)		Hazard Ratio (HR)		Placebo Cross-over Group
Endpoint	Sunitinib	Placebo	(95% CI)	p-value	Treatment[b]
Secondary					
Interim					
PFS (weeks)[c]	24.1 (11.1, 28.3)	6.0 (4.4, 9.9)	0.333 (0.238, 0.467)	<0.001	-
ORR (%)[d]	6.8 (3.7, 11.1)	0 (-)	NA	0.006	-
OS (weeks)[e]	-	-	0.491 (0.290, 0.831)	0.007	-
Final					
PFS (weeks)	22.9 (10.9, 28.0)	6.0 (4.4, 9.7)	0.347 (0.253, 0.475)	<0.001	-
ORR (%)[d]	6.6 (3.8, 10.5)	0 (-)	NA	0.004	10.1 (5.0 17.8)
OS (weeks)	72.7 (61.3, 83.0)	64.9 (45.7, 96.0)	0.876 (0.679, 1.129)	0.306	-

Abbreviations: CI=confidence interval; ITT=intent-to-treat; NA=not applicable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TTP=time to tumor progression.

[a.] Results of double-blind treatment are from the ITT population and using central radiologist measurement, as appropriate.

[b.] Efficacy results for the 99 subjects who crossed over from placebo to sunitinib after unblinding. Baseline was reset at cross-over and efficacy analyses were based on investigators assessment.

[c.] The interim PFS numbers have been updated based on a recalculation of the original data.

[d.] Results for ORR are given as percent of subjects with confirmed response with the 95% CI.

[e.] Median not achieved because the data were not yet mature.

Of those subjects randomized to the sunitinib arm, 62.7% survived longer than 1 year, 35.5% survived longer than 2 years, and 22.3% survived longer than 3 years.

Overall the study demonstrated a statistically significant and clinically meaningful improvement in TTP, the primary endpoint, for sunitinib plus best supportive care compared with placebo plus best supportive care.

Pancreatic Neuroendocrine Tumors (pNET)

A Phase 2, open-label, multi-center study evaluated the efficacy and safety of single-agent Sunitinib malate (Sutent) 50 mg daily on Schedule 4/2 in subjects with advanced unresectable pNET. In a pancreatic islet cell tumor cohort of 66 subjects, a 17% ORR was observed.

A pivotal Phase 3, multi-center, international, randomized, double-blind placebo-controlled study of single-agent sunitinib was conducted in subjects with unresectable pNET.

Subjects were required to have documented progression, based on Response Evaluation Criteria in Solid Tumors (RECIST), within the prior 12 months and were randomized (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled off-treatment period (n=86), or placebo (n=85).

The primary objective was to compare PFS in subjects receiving sunitinib versus subjects receiving placebo. Other endpoints included OS, ORR, patient-reported outcomes (PRO), and safety. Demographics were comparable between the sunitinib and placebo groups. Additionally, 49% of sunitinib subjects had non-functioning tumors versus 52% of placebo subjects and 92% of subjects in both arms had liver metastases. Use of somatostatin analogs was allowed in the study. A total of 66% of sunitinib subjects received prior systemic therapy compared with 72% of placebo subjects. In addition, 24% of sunitinib subjects had received somatostatin analogs compared with 22% of placebo subjects.

A clinically significant advantage in investigator-assessed PFS for sunitinib over placebo was observed. The median PFS was 11.4 months for the sunitinib arm compared to 5.5 months for the placebo arm [HR: 0.418 (95% CI: 0.263, 0.662), p-value =0.0001]. Similar results were observed when derived tumor response assessments based upon application of RECIST to investigator tumor measurements were used to determine disease progression, as shown in Table 3. A hazard ratio favoring sunitinib was observed in all subgroups of baseline characteristics evaluated, including an analysis by number of prior systemic therapies. A total of 29 subjects in the sunitinib arm and 24 in the placebo arm had received no prior systemic treatment; among these subjects, the hazard ratio for PFS was 0.365 (95% CI: 0.156, 0.857), p=0.0156. Similarly, among 57 subjects in the sunitinib arm (including 28 with 1 prior systemic therapy and 29 with 2 or more prior systemic therapies), and 61 subjects in the placebo arm (including 25 with 1 prior systemic therapy and 36 with 2 or more prior systemic therapies), the hazard ratio for PFS was 0.456 (95% CI: 0.264, 0.787), p=0.0036.

A sensitivity analysis of PFS was conducted in which progression was based upon investigator-reported tumor measurements and in which all subjects censored for reasons other than study termination were treated as having PFS events. This analysis provided a conservative estimate of the treatment effect of sunitinib and supported the primary analysis, demonstrating a hazard ratio of 0.507 (95% CI: 0.350, 0.733), p=0.000193. The pivotal study in pNET was terminated prematurely at the recommendation of an independent Drug Monitoring Committee, and the primary endpoint was based upon investigator assessment, both of which may have affected the estimates of the treatment effect.

In order to rule out bias in the investigator-based assessment of PFS, a blinded independent central review (BICR) of scans was performed; this review supported the investigator assessment, as shown in Table 3. The Kaplan-Meier curve for PFS is in Figure 1.

Table 3. pNET Efficacy Results from the Phase 3 Study

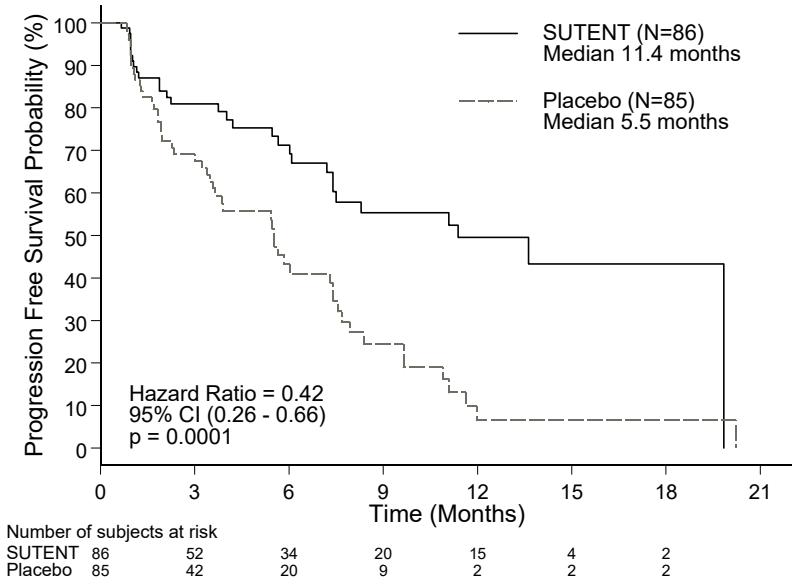
Efficacy Parameter	Sunitinib malate (Sutent) (n=86)	Placebo (n=85)	HR (95% CI)	p-value
PFS [median, months (95% CI)] by Investigator Assessment	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	0.418 (0.263, 0.662)	0.0001[a]
PFS [median, months (95% CI)] by derived response assessment based upon application of RECIST to investigator tumor assessments	12.6 (7.4, 16.9)	5.4 (3.5, 6.0)	0.401 (0.252, 0.640)	0.000066[a]
PFS [median, months (95% CI)] by blinded independent central review of tumor assessments	12.6 (11.1, 20.6)	5.8 (3.8, 7.2)	0.315 (0.181, 0.546)	0.000015[a]
OS [median, months (95% CI)]	20.6 (20.6, NR)	NR (15.5, NR)	0.409 (0.187, 0.894)	0.0204[a]
ORR [%, (95% CI)]	9.3 (3.2, 15.4)	0	NA	0.0066[b]

Abbreviations: CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; pNET= pancreatic neuroendocrine tumors; RECIST= Response Evaluation Criteria in Solid Tumors.

[a.] 2-sided unstratified log-rank test.

[b.] Fisher's exact test.

Figure 1. Kaplan-Meier Curve of PFS in the pNET Phase 3 Study



Abbreviations: CI=confidence interval; N=number of subjects; PFS=progression-free survival; pNET=pancreatic neuroendocrine tumors.

OS data were not mature at the time of the analysis. There were 9 deaths in the sunitinib arm and 21 deaths in the placebo arm. A statistically significant difference in ORR favoring sunitinib over placebo was observed.

Upon disease progression, subjects were unblinded and placebo subjects could have been offered access to open-label sunitinib in a separate extension study. As a result of the early study closure, remaining subjects were unblinded and offered access to open-

label sunitinib in an extension study. A total of 59 subjects from the placebo arm received Sunitinib malate (Sutent) in an extension study.

Results from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) showed that the overall global health-related quality of life and the five functioning domains (physical, role, cognitive, emotional and social) were maintained for subjects on sunitinib treatment as compared to placebo with limited adverse symptomatic effects.

Renal cell carcinoma

Treatment-naïve MRCC

A Phase 3 randomized study comparing single-agent sunitinib with IFN-α was conducted in subjects with treatment-naïve MRCC. The primary objective was to compare PFS in subjects receiving sunitinib versus subjects receiving IFN-α. Secondary objectives included TTP, ORR, OS, safety and PROs. Seven hundred fifty (750) subjects were randomized (1:1) to receive either 50 mg sunitinib once daily on Schedule 4/2 or to receive IFN-α administered subcutaneously at 9 MIU three times a week. Subjects were treated until disease progression or withdrawal from the study for another reason.

The ITT population included 750 subjects, 375 randomized to sunitinib and 375 randomized to IFN-α. Baseline age, gender, race and Eastern Cooperative Oncology Group (ECOG) performance status were comparable and balanced between the sunitinib and IFN-α groups. Demographics and patient characteristics are shown in Table 4. The most common site of metastases present at screening was the lung (78% versus 80%, respectively), followed by the lymph nodes (58% versus 53%, respectively), and bone (30% each arm). The majority of the subjects had multiple (2 or more) metastatic sites at baseline (80% versus 77%, respectively).

Table 4. Baseline Demographics in Treatment-naïve MRCC Study

	Treatment-naïve MRCC	
	Sunitinib (n=375)	IFN-α (n=375)
Gender [n (%)]		
Male	267 (71)	269 (72)
Female	108 (29)	106 (28)
Self-identified race [n (%)]		
White	354 (94)	340 (91)
Asian	7 (2)	12 (3)
Black	4 (1)	9 (2)
Not reported	10 (3)	14 (4)
Age group [n (%)]		
<65 years	223 (59)	252 (67)
≥65 years	152 (41)	123 (33)
Performance status [n (%)]		
0	231 (62)	229 (61)
1	144 (38)	142 (38)
2	0 (0)	4 (1)[a]

Prior treatment [n (%)]		
Nephrectomy	340 (91)	335 (89)
Radiotherapy	53 (14)	54 (14)
Abbreviations: ECOG= Eastern Cooperative Oncology Group; IFN-α=interferon-α MRCC=metastatic renal cell carcinoma; n=number of subjects. [a] Subjects had ECOG performance status of 1 at screening which changed to 2 at baseline.		

The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for sunitinib treatment and 4.1 months (range: 0.1 – 45.6) for IFN-α treatment. Dose interruptions occurred in 202 (54%) subjects on sunitinib and 141 (39%) subjects on IFN-α. Dose reductions occurred in 194 (52%) subjects on sunitinib and 98 (27%) subjects on IFN-α. Discontinuation rates due to adverse reactions were 20% for sunitinib and 23% for IFN-α. Subjects were treated until disease progression or withdrawal from the study. The primary efficacy endpoint was PFS. A planned interim analysis showed a statistically significant advantage for sunitinib over IFN-α in the primary endpoint of PFS, with PFS for sunitinib more than double that of IFN-α (47.3 weeks and 22.0 weeks, respectively). The secondary endpoint of ORR was more than four times higher for sunitinib than IFN-α (27.5% and 5.3%, respectively). Data were not mature enough to determine the overall survival benefit; at the time of the interim analysis, 374 of 750 (50%) subjects enrolled continued on study, 248 of 375 (66%) on the sunitinib arm and 126 of 375 (34%) on the IFN-α arm.

At the time of the final analysis there was a statistically-significant advantage for sunitinib over IFN-α in the endpoint of PFS (see Table 5 and Figure 2). In the pre-specified stratification factors of lactate dehydrogenase (LDH) (>1.5 ULN versus ≤1.5 ULN), ECOG performance status (0 versus 1), and prior nephrectomy (yes versus no), the HR favored sunitinib over IFN-α. Core radiology assessment was discontinued after the primary endpoint had been met. The ORR as determined by the investigator's assessment was 46% (95% CI: 41, 51) for the sunitinib arm and 12% (95% CI: 9, 16) for the IFN-α arm [$p < 0.001$] (see Table 5).

The results were similar in the supportive analyses and they were robust when controlling for demographic (age, gender, race and performance status) and known risk factors. For 262 of 750 subjects (35%) with no known risk factors, median PFS was 64.1 weeks in the sunitinib arm and 34.1 weeks in the IFN-α arm (HR: 0.447; 95% CI: 0.313, 0.640); for the 424 subjects (56%) with 1 or 2 risk factors, median PFS was 46.6 weeks in the sunitinib arm and 16.1 weeks in the IFN-α arm (HR: 0.547; 95% CI: 0.423, 0.707); and for the 47 subjects (6%) with ≥3 risk factors, median PFS was 12.1 weeks in the sunitinib arm and 5.7 weeks in the IFN-α arm (HR: 0.679; 95% CI: 0.330, 1.398).

As shown in Figure 3, sunitinib treatment was associated with longer survival compared to IFN-α. The median OS was 114.6 weeks for the sunitinib arm (95% CI: 100.1, 142.9) and 94.9 weeks for the IFN-α arm (95% CI: 77.7, 117.0) [HR: 0.821; 95% CI: 0.673, 1.001; p=0.0510 by log-rank test, p=0.013 by Wilcoxon test]. In the stratified analysis (LDH > versus ≤1.5 x ULN, ECOG performance status 0 versus ≥1, and absence or presence of prior nephrectomy), the HR was 0.818 (95% CI: 0.669, 0.999; p=0.049 by log-rank test). The median OS for the IFN-α arm included 25 subjects who discontinued IFN-α treatment because of disease progression and crossed over to treatment with sunitinib. Following discontinuation from the study, 213 subjects on the IFN-α arm received post-study cancer treatment, including 32% who received sunitinib; 182

subjects on the sunitinib arm received post-study cancer treatment, including 11% who received sunitinib. In post-hoc analyses censoring subjects who crossed over from IFN-α treatment to sunitinib treatment, median OS at the time of crossover was 114.6 versus 86.7 weeks (unstratified hazard ratio: 0.808; p=0.0361 by log-rank test; p=0.0081 by Wilcoxon test). When excluding subjects who received post-study anticancer therapy, median OS was 121.9 versus 61.3 weeks on sunitinib versus IFN-α (HR: 0.647; 95% CI: 0.482,0.867; p=0.0033 by log-rank test; p=0.0013 by Wilcoxon test).

Table 5. MRCC Efficacy Results

Efficacy Parameter	Treatment-naïve MRCC			
	Sunitinib (n=375)	IFN-α (n=375)	p-value (log-rank test)	HR (95% CI)
PFS[a] [median, weeks (95% CI)]	48.3 (46.4-58.3)	22.1 (17.1-24.0)	<0.000001	0.516 (0.419-0.635)
TTP[a] [median, weeks (95% CI)]	49.1 (46.6-59.1)	22.4 (21.9-31.3)	<0.0001	0.516 (0.419-0.635)
ORR[a] [%, (95% CI)]	38.7 (33.7-43.8)	7.7 (5.2-10.9)	<0.0001	NA
Efficacy Parameter	Cytokine-refractory MRCC			
	Study 1 (n = 106)		Study 2 (n = 63)	
Objective Response Rate [%, (95% CI)]	34.0[a] (25.0, 43.8)		36.5[b] (24.7, 49.6)	
Duration of Response [median, weeks (95% CI)]	* (42.0**)		54[b] (34.3, 70.1)	

Abbreviations: CI=confidence interval, DR=duration of response; HR=hazard ratio; IFN-α=interferon-α; MRCC=metastatic renal cell carcinoma; n=number of subjects; NA=not applicable; ORR=objective response rate; PFS=progression-free survival; RCC=renal cell carcinoma; TTP=time to tumor progression.

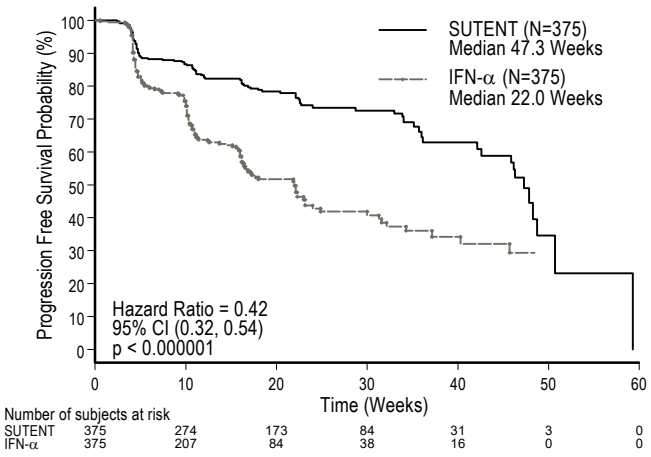
[a] Assessed by blinded core radiology laboratory: 90 subjects' scans had not been read at time of analysis.

[b] Assessed by investigators.

*Median DR has not yet been reached.

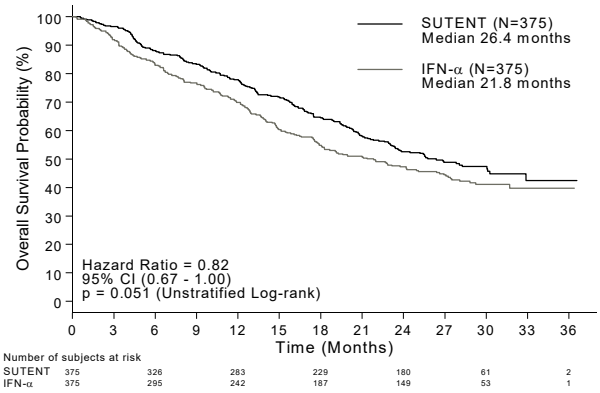
**Data not mature enough to determine upper confidence limit.

Figure 2. Kaplan-Meier Curve of PFS in Treatment-naïve MRCC Study (Intent-to-Treat Population)



Abbreviations: CI=confidence interval; IFN-α=interferon-α; MRCC=metastatic renal cell carcinoma; PFS=progression-free survival.

Figure 3. Kaplan-Meier Curve of OS in Treatment-naïve RCC Study (Intent-to-Treat Population)



Abbreviations: CI=confidence interval; IFN-α=interferon-α; OS=overall survival; RCC=renal cell carcinoma.

PRO were measured using the Functional Assessment of Cancer Therapy-Advanced Kidney Cancer Symptom Index (FKSI) and the Functional Assessment of Cancer Therapy-General (FACT-G). PRO endpoints include the FKSI score, its Disease Related Symptoms subscale (FKSI-DRS) score, the FACT-G total score and its four subscale scores (Physical Well-Being [PWB], Social/Family Well-Being [SWB], Emotional Well-Being [EWB] and Functional Well-Being [FWB]. The FKSI-DRS was pre-specified as the primary PRO endpoint and used to assess patient-reported kidney cancer related symptoms (lack of energy/fatigue, pain/bone pain, weight loss, shortness of breath, cough, fever, and hematuria) in 719 subjects. Subjects treated with sunitinib reported statistically significant better FKSI-DRS index scores ($p \leq 0.0071$), FKSI scores ($p \leq 0.0133$), FACT-G total scores ($p \leq 0.0244$), PWB ($p \leq 0.0208$), and FWB ($p \leq 0.0044$) than subjects treated with IFN-α at all post-baseline assessment time points up to 20 cycles of treatment. For PWB, SWB, and EWB, the statistical significance level increased above the 0.05 level after cycle 13, cycle 15 day 1, and cycle 10, respectively. Compared to the pre-established minimum clinically important differences for these endpoints, the between treatment differences for kidney cancer related symptoms (FKSI at all post-baseline timepoints and FKSI-DRS after cycle 3, day 1) and overall quality of life (FACT-G) at all post-baseline time points were considered clinically meaningful.

Cytokine-refractory MRCC

A Phase 2 study of sunitinib was conducted in subjects who were refractory to prior cytokine therapy with interleukin-2 or IFN-α. Sixty-three (63) subjects received a starting dose of 50 mg of sunitinib orally, once daily on Schedule 4/2. The primary efficacy endpoint was ORR based on RECIST. Secondary endpoints included assessment of TTP, PFS, duration of response (DR), and OS.

In this study the ORR was 36.5% (95% CI: 24.7%, 49.6%), the median TTP/PFS was 37.7 weeks (95% CI: 24.0, 46.4).

A confirmatory, open-label, single-arm, multi-center study evaluating the efficacy and safety of sunitinib was conducted in subjects with MRCC who were refractory to prior cytokine therapy. One hundred and six (106) subjects received at least one 50 mg dose of sunitinib on Schedule 4/2. The primary efficacy endpoint of this study was ORR. Secondary endpoints included TTP, PFS, DR, and OS.

In this study the ORR was 34.0% (95% CI: 25.0%, 43.8%). The median TTP, PFS, DR, and OS had not yet been reached.

5.2 Pharmacokinetic Properties

The pharmacokinetics of sunitinib and sunitinib malate were evaluated in 135 healthy volunteers and 266 subjects with solid tumors.

Absorption

Maximum plasma concentrations (C_{max}) are generally observed between 6 – 12 hours (T_{max}) following oral administration. Food has no effect on the bioavailability of sunitinib.

Distribution

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

Metabolism

The calculated *in vitro* Ki values for all CYP isoforms tested (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.

In vitro studies indicate that sunitinib neither induces nor inhibits major CYP enzymes, including CYP3A4 (see Section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

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

Excretion is primarily via feces (61%) with renal elimination of drug and metabolites 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 were not found in plasma. Total oral clearance (CL/F) ranged from 34-62 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 desethyl metabolite were approximately 40-60 hours, and 80 – 110 hours, respectively.

Pharmacokinetics in special patient groups

Hepatic Insufficiency

Sunitinib and its primary metabolite are mainly metabolized by the liver. Systemic exposures after a single dose of sunitinib 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. Sunitinib was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment.

Renal Insufficiency

Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in subjects with calculated creatinine clearances in the range of 42-347 mL/min. Systemic exposures after a single dose of Sunitinib malate (Sutent) were similar in subjects with severe renal impairment (CL_{cr} <30 mL/min) compared to subjects with normal renal function (CL_{cr} >80 mL/min). Although sunitinib and its primary metabolite were not eliminated through hemodialysis in subjects with ESRD, the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function.

Cardiac Electrophysiology

QT interval prolongation was investigated in a Phase 1 trial with 24 evaluable subjects, aged 20-87 years, with advanced malignancies. At therapeutic plasma concentrations, the maximum QTcF mean change from baseline was 9.6 msec (90% CI upper limit of 15.1 msec). At approximately twice the therapeutic concentrations, the maximum QTcF mean change from baseline was 15.4 msec (90% CI upper limit of 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 (CTCAE version 3.0). No patient presented with a cardiac arrhythmia (see Section **4.4 Special Warnings and Precautions for Use**).

Plasma Pharmacokinetics

Following administration of a single oral dose in healthy volunteers, the elimination half-lives of sunitinib and its primary active metabolite are approximately 40-60 hours, and 80-110 hours, respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary active 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 are 62.9-101 ng/mL which are target concentrations predicted from

preclinical data to inhibit receptor phosphorylation *in vitro* and result in tumor stasis/growth reduction *in vivo*. 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 all solid tumor populations tested and in healthy volunteers.

Population Pharmacokinetics

Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, gender, race or ECOG score on the pharmacokinetics of sunitinib or the primary active metabolite.

Weight, performance status: Population pharmacokinetic analyses of demographic data indicate that no starting dose adjustments are necessary for weight or ECOG performance status.

Gender: Available data indicate that females could have about 30% lower apparent clearance (CL/F) of sunitinib than males; this difference, however, does not necessitate starting dose adjustments.

5.3 Preclinical Safety Data

In rat and monkey repeated-dose toxicity studies up to 9-months duration, the primary target organ effects were identified in the gastrointestinal tract (emesis and diarrhea in monkeys); adrenal gland (cortical congestion and/or hemorrhage in rats and monkeys, with necrosis followed by fibrosis in rats); hemolymphopoietic system (bone marrow hypocellularity, and lymphoid depletion of thymus, spleen, and lymph node); exocrine pancreas (acinar cell degranulation with single-cell necrosis); salivary gland (acinar hypertrophy); bone joint (growth plate thickening); uterus (atrophy); and ovaries (decreased follicular development). All findings occurred at clinically relevant sunitinib plasma exposure levels. Additional effects, observed in other studies included: QTc interval prolongation, LVEF reduction, and testicular tubular atrophy, increased mesangial matrix in kidney, hemorrhage in GI tract and oral mucosa, and hypertrophy of anterior pituitary cells. Changes in the uterus (endometrial atrophy) and bone growth plate (physeal thickening or dysplasia of cartilage) are thought to be related to the pharmacological action of sunitinib. Most of these findings were reversible after 2 to 6 weeks without treatment.

Genotoxicity

The genotoxic potential of sunitinib was assessed *in vitro* and *in vivo*. Sunitinib was not mutagenic in bacteria using metabolic activation provided by rat liver. Sunitinib did not induce structural chromosome aberrations in human peripheral blood lymphocyte cells *in vitro*. Polyploidy (numerical chromosome aberrations) was observed in human peripheral blood lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Sunitinib was not clastogenic in rat bone marrow *in vivo.* The major active metabolite was not evaluated for genetic toxicity potential.

Carcinogenicity

In a 1-month, oral gavage dose-range finding study (0, 10, 25, 75, or 200 mg/kg/day) with continuous daily dosing in rasH2 transgenic mice, carcinoma and hyperplasia of Brunner's glands of the duodenum were observed at the highest dose (200 mg/kg/day) tested.

A 6-month, oral gavage carcinogenicity study (0, 8, 25, or 75 [reduced to 50] mg/kg/day), with daily dosing was conducted in rasH2 transgenic mice. Gastroduodenal carcinomas, an increased incidence of background hemangiosarcomas, and/or gastric mucosal hyperplasia were observed at doses of ≥25 mg/kg/day following 1- or 6-months duration (≥7.3 times the AUC in subjects administered the RDD).

In a 2-year rat carcinogenicity study (0, 0.33, 1, or 3 mg/kg/day), administration of sunitinib in 28-day cycles followed by 7-day dose-free periods resulted in increases in the incidence of pheochromocytomas and hyperplasia in the adrenal medulla of male rats given 3 mg/kg/day following >1 year of dosing (≥7.8 times the AUC in subjects administered the RDD). Brunner's glands carcinoma occurred in the duodenum at ≥1 mg/kg/day in females and at 3 mg/kg/day in males, and mucous cell hyperplasia was evident in the glandular stomach at 3 mg/kg/day in males, which occurred at ≥0.9, 7.8 and 7.8 times the AUC in subjects administered the RDD, respectively. The relevance to humans of the neoplastic findings observed in the mouse (rasH2 transgenic) and rat carcinogenicity studies with sunitinib treatment is unclear.

Reproductive and developmental toxicity

No effects on fertility were observed in male rats dosed for 58 days prior to mating with untreated females. No reproductive effects were observed in female rats treated for 14 days prior to mating with untreated males, at doses resulting in systemic exposures approximately 5 times the systemic exposure in humans. However, in repeated-dose toxicity studies performed in rats and monkeys, effects on female fertility were observed in the form of follicular atresia, degeneration of corpora lutea, endometrial changes in the uterus and decreased uterine and ovarian weights at clinically relevant systemic exposure levels. Moreover, in repeat-dose toxicity studies conducted in rats, effects on male fertility were observed in the form of tubular atrophy in the testes, reduction of spermatozoa in epididymides and colloid depletion in prostate and seminal vesicles at plasma exposure levels 25 times the systemic exposure in humans. Not all the effects observed in male rats were reversible at the end of the recovery period (6 weeks).

In rats, treatment-related embryo-fetal mortality was evident as significant reductions in the number of live fetuses, increased numbers of resorptions (early and total), corresponding increased post-implantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5 times the systemic exposure in humans. In rabbits, reductions in gravid uterine weights and number of live fetuses were due to increases in the number of resorptions (early and total), increases in post-implantation loss, and complete litter loss in 4 of 6 pregnant females at plasma exposure levels 3 times the systemic exposure in humans.

Sunitinib treatment in rats during organogenesis resulted in developmental effects at ≥5 mg/kg/day consisting of increased incidence of fetal skeletal malformations, predominantly characterized as retarded ossification of thoracic/lumbar vertebrae. Developmental effects in rats occurred at plasma exposure levels 6 times the systemic exposure in humans. In rabbits, developmental effects consisted of increased incidence of cleft lip at plasma exposure levels approximately equal to that observed in clinic, and cleft lip and cleft palate at plasma exposure levels 2.7 times the systemic exposure in humans.

A definitive rabbit embryo-fetal development toxicity study was not conducted as embryo-fetal effects were clearly demonstrated in the rat and reported in the preliminary study conducted in rabbits.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

See outer package for the expiry date.

6.2 Storage Condition

Sutent 12.5 mg, 25 mg & 50 mg Capsule (bottle): Store at temperatures not exceeding 25°C.
Sutent 12.5 mg, 25 mg & 50 mg Capsule (blister): Store at temperatures not exceeding 30°C.

6.3 Availability

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: HDPE bottle with polypropylene closure (Bottles of 28’s), Alu/PVC/Aclar Blister pack of 7’s (Box of 28’s)

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: HDPE bottle with polypropylene closure (Bottles of 28’s), Alu/PVC/Aclar Blister pack of 7’s (Box of 28’s)

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: HDPE bottle with polypropylene closure (Bottles of 28’s), Alu/PVC/Aclar Blister pack of 7’s (Box of 28’s)

6.4 Special Precautions for Disposal and Other Handling

No special requirements

7.0 FDA REGISTRATION NUMBER

Sutent 12.5 mg Capsule (bottle): DRP-2096
Sutent 25 mg Capsule (bottle): DRP-2095
Sutent 50 mg Capsule (bottle): DRP-2098

Sutent 12.5 mg Capsule (blister): DR-XY42990
Sutent 25 mg Capsule (blister): DR-XY42992
Sutent 50 mg Capsule (blister): DR-XY42991

8.0 DATE OF FIRST AUTHORIZATION

Sutent 12.5 mg Capsule (bottle): 30 June 2006
Sutent 25 mg Capsule (bottle): 30 June 2006
Sutent 50 mg Capsule (bottle): 27 June 2006

Sutent 12.5 mg Capsule (blister): 21 November 2013
Sutent 25 mg Capsule (blister): 21 November 2013
Sutent 50 mg Capsule (blister): 26 November 2013

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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