ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SUTENT 12.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains sunitinib malate, equivalent to 12.5 mg of sunitinib.
Excipient(s): 80.0 mg of mannitol
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.
Gelatin capsules with orange cap and orange body, printed with white ink “Pfizer” on the cap, “STN 12.5 mg” on the body, and containing yellow to orange granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.
SUTENT is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy.
Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC. (see section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the treatment of renal cell carcinoma or GIST.

The recommended dose of SUTENT is one 50 mg dose orally, taken daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks.

Dose modifications in 12.5-mg steps may be applied based on individual safety and tolerability. Daily dose should not exceed 87.5 mg nor be decreased below 37.5 mg.

Co-administration of potent CYP3A4 inducers such as rifampin, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of SUTENT may need to be increased in 12.5 mg increments (up to 87.5 mg per day) based on careful monitoring of tolerability.
Co-administration of SUTENT with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see sections 4.4 and 4.5). If this is not possible the doses of SUTENT may need to be reduced to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability
Selection of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP3A4 should be considered.

Paediatric use**:** The safety and efficacy of SUTENT in paediatric patients have not been established. SUTENT should not be used in paediatric population until further data become available.

Elderly patients use: Approximately 25% of the subjects in clinical studies of SUTENT were 65 or over. No significant differences in safety or effectiveness were observed between younger and older patients.

Hepatic Insufficiency: No clinical studies have been performed in patients with impaired hepatic function. (see section 5.2).

Renal Insufficiency: No clinical studies have been performed in patients with impaired renal function.(see section 5.2).

SUTENT 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.

4.3 Contraindications

Hypersensitivity to sunitinib malate or to any of the excipients.

4.4 Special warnings and precautions for use

Co-administration of potent CYP3A4 inducers such as rifampin, may **decrease** sunitinib plasma concentrations. Combination with inducers should therefore be avoided. If this is not possible, the dosage of SUTENT may need to be increased (see sections 4.2 and 4.5)

Co-administration of strong CYP3A4 inhibitor such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. If this is not possible, the dosage of SUTENT may need to be reduced (see sections 4.2 and 4.5).

*Skin and tissue*s
Skin discolouration, possibly due to the active substance colour (yellow) is a common treatment-related adverse event occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with SUTENT. 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.
Mouth pain/irritation was reported in approximately 14% of patients. Dysgeusia (taste disturbance) was reported in approximately 28% of patients.
The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.

Gastrointestinal events
Nausea, diarrhoea, stomatitis, dyspepsia and vomiting were the most commonly reported treatment-related gastrointestinal events.
Supportive care for gastrointestinal adverse events requiring treatment may include medication with an anti-emetic or anti-diarrhoeal medication.

Haemorrhage
Treatment-related tumour haemorrhage occurred in approximately 2% of patients with GIST. These events may occur suddenly, and in the case of pulmonary tumours, may present as severe and life-threatening haemoptysis or pulmonary haemorrhage. Fatal pulmonary haemorrhage 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. Routine assessment of this event should include complete blood counts and physical examination.
Epistaxis was the most common treatment-related haemorrhagic adverse event, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. None of these events was serious.

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

Hypertension
Treatment-related hypertension was reported in approximately 16% of patients with solid tumours. SUTENT dosing was reduced or temporarily delayed in approximately 2.7% of this patient population. None of these patients were discontinued from treatment with SUTENT. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of this patient population. 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.

Haematological
Decreased absolute neutrophil counts of grade 3 and 4 severity were reported in 13.1% and 0.9% patients, respectively. Decreased platelet counts of grade 3 and 4 severity were reported in 4% and 0.5% patients respectively. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.
Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

Cardiovascular
Decreases in left ventricular ejection fraction (LVEF) of ≥ 20% and below the lower limit of normal occurred in approximately 2% of SUTENT-treated GIST patients and of 4% MRCC patients and 2% of placebo-treated patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued.
Treatment-related adverse events of 'cardiac failure', 'cardiac failure congestive' or 'left ventricular failure' were reported in 0.7% of patients with solid tumours and 1% of patients treated with placebo. All patients had GIST. The relationship, if any, between receptor tyrosine kinase (RTK) inhibition and cardiac function remains unclear.
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 congestive heart failure (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 the patient is receiving SUTENT. 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 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.

QT Interval prolongation
QT interval prolongation was investigated in a trial in 24 patients, aged 20-87 years, with advanced malignancies. At approximately twice therapeutic concentrations, SUTENT has been shown to prolong the QTcF interval (Frederica's Correction) . There were no patients with greater than grade 2 (CTCAE v3.0) QT/QTc interval prolongation and no patient presented with a cardiac arrhythmia. The clinical relevance of the effects observed is unclear and will depend on individual patient risk factors and

susceptibilities present. SUTENT 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 potent CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of SUTENT reduced (see Section 4.5).

Venous Thromboembolic Events
Four patients (2%) on the two MRCC studies had venous thromboembolic events reported; two patients with pulmonary embolism (both grade 4) and two patients with deep venous thrombosis (DVT) (both grade 3). Dose interruption occurred in one of these cases. Seven patients (3%) on SUTENT and none on placebo in the pivotal GIST study experienced venous thromboembolic events; five of the seven were grade 3 DVTs, and two were grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Pulmonary Embolism
Treatment-related pulmonary embolism was reported in approximately 1.1% patients with solid tumours who received SUTENT. None of these events resulted in a patient discontinuing treatment with SUTENT; 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.

Hypothyroidism
Hypothyroidism was reported as an adverse event in 7 patients (4%) across the two MRCC studies. Additionally, TSH elevations were reported in 4 patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Treatment-emergent acquired hypothyroidism was noted in 8 GIST patients (4%) on SUTENT *versus* 1 (1%) on placebo. Patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Pancreatic Function
Increases in serum lipase and amylase activities were observed in patients with various solid tumours who received SUTENT. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours. Pancreatitis was observed in 0.4% of patients with solid tumours. If symptoms of pancreatitis are present, patients should have proper medical follow-up.

Seizures
In clinical studies of SUTENT, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, 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.

4.5 Interaction with other medicinal products and other forms of interaction

*Drugs that may **increase** sunitinib plasma concentrations.*
Concomitant administration of sunitinib malate with the potent CYP3A4 inhibitor, ketoconazole, resulted in a 49% and 51% increase of the complex [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib malate in healthy volunteers.
Administration of SUTENT with potent inhibitors of the CYP3A4 family (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations
Combination 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 SUTENT may need to be reduced to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability (see section 4.2)

*Drugs that may **decrease** sunitinib plasma concentrations:*
Concomitant use of SUTENT with the CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction of the complex [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers.
Administration of SUTENT with potent inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or *Hypericum perforatum* known also as St. John's Wort) may decrease sunitinib concentrations. Combination 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 SUTENT may need to be increased in 12.5 mg increments (up to 87,5 mg per day) based on careful monitoring of tolerability. (see section 4.2).
To maintain sunitinib target concentrations, selection of co-medications with less enzyme induction potential, should be considered. If this is not possible, dose-adjustments of SUTENT may be necessary (see section 4.2).

Haemorrhage has been observed rarely in patients treated with SUTENT (see section 4.4). Patients receiving concomitant treatment with anti-coagulants (e.g. warfarin; acenocumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR), and physical examination

4.6 Pregnancy and lactation

Pregnancy
There are no studies in pregnant women using SUTENT. Studies in animals have shown reproductive toxicity including foetal malformations (see section 5.3). SUTENT should not be used during pregnancy or in any woman not employing adequate contraception unless the potential benefit justifies the potential risk to the foetus. 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 foetus.
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Based on non-clinical findings, male and female fertility may be compromised by treatment with SUTENT (see section 5.3)

Lactation
Sunitinib and/or its metabolites are excreted in rat milk. 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, women should not breast feed while taking SUTENT.

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 SUTENT.

4.8 Undesirable effects

The most important treatment-related serious adverse events associated with SUTENT treatment of patients with solid tumours were pulmonary embolism (1%), thrombocytopoenia (1%), tumour haemorrhage (0.9%), febrile neutropoenia (0.4%), and hypertension (0.4%). The most common treatment-related adverse events (experienced by at least 20% of the patients) of any grade included: fatigue; gastrointestinal disorders, such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting; skin discolouration; dysgeusia and anorexia. Fatigue, hypertension and neutropoenia were the most common treatment-related adverse events of Grade 3 maximum severity and increased lipase was the most frequently occurring treatment-related adverse event of Grade 4 maximum severity in patients with solid tumours.

Treatment-related adverse reactions that were reported in >5% of solid tumour patients are listed below, by system organ class, frequency and grade of severity. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Frequencies are defined as: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to <1//100), rare (≥1/10,000 to 1/1,000), very rare (< 1/10,000).

Adverse Reactions reported in GIST studies

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Blood and the lymphatic system disorders	Very common	Anaemia	33 (12.8%)	13 (5.1%)	1 (0.4%)
	Common	Neutropoenia	24 (9.3%)	15 (5.8%)	1 (0.4%)
	Common	Thrombocytopoenia	23 (8.9%)	6 (2.3%)	1 (0.4%)
Endocrine disorders	Common	Hypothyroidism	15 (5.8%)	0 (0.0%)	1 (0.4%)
Metabolism and nutrition disorders	Common	Anorexia	44 (7.1%)	1 (0.4%)	0 (0.0%)
Nervous system disorders	Very common	Dysgeusia	48 (18.7%)	0 (0.0%)	0 (0.0%)
	Very common	Headache	27 (10.5%)	2 (0.8%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	43 (16.7%)	18 (7.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	17 (6.6%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	Common	Chromaturia	13 (5.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Diarrhoea	90 (35.0%)	13 (5.1%)	0 (0.0%)
	Very common	Nausea	69 (26.8%)	2 (0.8%)	0 (0.0%)
	Very common	Stomatitis	49 (19.1%)	2 (0.8%)	0 (0.0%)
	Very common	Vomiting	46 (17.9%)	1 (0.4%)	0 (0.0%)
	Very common	Dyspepsia	32 (12.5%)	2 (0.8%)	0 (0.0%)
	Common	Glossodynia	17 (6.6%)	0 (0.0%)	0 (0.0%)
	Common	Constipation	13 (5.1%)	1 (0.4%)	0 (0.0%)
	Very common	Abdominal pain*	30 (11.7%)	5 (1.9%)	1 (0.4%)
	Common	Oral pain	16 (6.2%)	0 (0.0%)	0 (0.0%)
	Common	Flatulence	15 (5.8%)	0 (0.0%)	0 (0.0%)
	Common	Dry mouth	15 (5.8%)	0 (0.0%)	0 (0.0%)
	Common	Gastro-oesophageal reflux disease	15 (5.8%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Very common	Skin discolouration	65 (25.3%)	0 (0.0%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	55 (21.4%)	14 (5.4%)	0 (0.0%)
	Very common	Rash***	39 (15.2%)	2 (0.8%)	0 (0.0%)
	Common	Hair colour changes	22 (8.6%)	0 (0.0%)	0 (0.0%)
	Common	Dry skin	15 (5.8%)	0 (0.0%)	0 (0.0%)
Muscoloskeletal, connective tissue	Common	Pain in extremity	21 (8.2%)	1 (0.4%)	0 (0.0%)
	Common	Arthralgia	15 (5.8%)	2 (0.8%)	0 (0.0%)

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
and bone disorders	Common	Myalgia	13 (5.1%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions	Very common	Fatigue/Asthenia	135 (52.5%)	25 (9.7%)	0 (0.0%)
	Very common	Mucosal Inflammation	30 (11.7%)	0 (0.0%)	0 (0.0%)
	Common	Oedema**	21 (8.2%)	1 (0.4%)	0 (0.0%)
Investigations	Common	Haemoglobin decreased	16 (6.2%)	2 (0.8%)	0 (0.0%)
	Common	Blood creatinine phosphokinase increased	14 (5.4%)	0 (0.0%)	0 (0.0%)
	Common	Ejection fraction decreased	13 (5.1%)	1 (0.4%)	0 (0.0%)
	Common	Lipase increased	13 (5.1%)	5 (1.9%)	4 (1.6%)
	Common	Platelet count decreased	13 (5.1%)	2 (0.8%)	1 (0.4%)
		Any adverse event	222 (86.4%)	88 (34.2%)	24 (9.3%)

*The following terms have been combined: *abdominal pain*, *abdominal pain upper*, and *abdominal pain lower*.
**The following terms have been combined: oedema and oedema peripheral.
***The following terms have been combined: rash, rash erythematous, rash macular and rash scaly

Adverse Reactions reported in MRCC studies

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Blood and lymphatic system disorders	Very common	Neutropoenia	17 (10.1%)	8 (4.7%)	1 (0.6%)
	Common	Anaemia	16 (9.5%)	6 (3.6%)	0 (0.0%)
	Common	Thrombocytopoenia	15 (8.9%)	5 (3.0%)	2 (1.2%)
	Common	Leucopoenia	14 (8.3%)	7 (4.1%)	0 (0.0%)
Eye disorders	Common	Lacrimation increased	9 (5.3%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	Very common	Anorexia	47 (27.8%)	1 (0.6%)	0 (0.0%)
	Common	Dehydration	12 (7.1%)	4 (2.4%)	0 (0.0%)
	Common	Decreased appetite	11 (6.5%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	Very common	Dysgeusia	71 (42%)	0 (0.0%)	0 (0.0%)
	Very common	Headache	25 (14.8%)	1 (0.6%)	0 (0.0%)
	Common	Dizziness	13 (7.7%)	2 (1.2%)	0 (0.0%)
	Common	Paraesthesia	9 (5.3%)	0 (0.0%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	28 (16.6%)	7 (4.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	16 (9.5%)	0 (0.0%)	0 (0.0%)
	Common	Dyspnoea	9 (5.3%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Diarrhoea	83 (49.1%)	5 (3.0%)	0 (0.0%)
	Very common	Nausea	84 (49.7%)	2 (1.2%)	0 (0.0%)

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
	Very common	Stomatitis	70 (41.4%)	6 (3.6%)	0 (0.0%)
	Very common	Dyspepsia	69 (40.8%)	1 (0.6%)	0 (0.0%)
	Very common	Vomiting	52 (30.8%)	2 (1.2%)	0 (0.0%)
	Very common	Constipation	34 (20.1%)	0 (0.0%)	0 (0.0%)
	Very common	Glossodynia	25 (14.8%)	0 (0.0%)	0 (0.0%)
	Very common	Abdominal pain*	17 (10.1%)	2 (1.2%)	0 (0.0%)
	Common	Flatulence	16 (9.5%)	0 (0.0%)	0 (0.0%)
	Common	Abdominal distension	9 (5.3%)	0 (0.0%)	0 (0.0%)
	Common	Dry mouth	9 (5.3%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Very common	Skin discolouration	54 (32.0%)	0 (0.0%)	0 (0.0%)
	Very common	Rash**	46 (27.2%)	0 (0.0%)	0 (0.0%)
	Very common	Hair colour changes	24 (14.2%)	0 (0.0%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	21 (12.4%)	6 (3.6%)	0 (0.0%)
	Common	Alopecia	13 (7.7%)	0 (0.0%)	0 (0.0%)
	Common	Dermatitis exfoliative	10 (5.9%)	2 (1.2%)	0 (0.0%)
	Common	Periorbital oedema	9 (5.3%)	0 (0.0%)	0 (0.0%)
	Very common	Dry skin	22 (13.0%)	0 (0.0%)	0 (0.0%)
	Very common	Erythema	20 (11.8%)	0 (0.0%)	0 (0.0%)
Muscoloskeletal, connective tissue and bone disorders	Very common	Pain in extremity	21 (12.4)	1 (0.6%)	0 (0.0%)
	Common	Myalgia	15 (8.9%)	1 (0.6%)	0 (0.0%)
General disorders and administration site conditions	Very common	Fatigue/Asthenia	108 (63.9%)	19 (11.2%)	0 (0.0%)
	Very common	Mucosal Inflammation	30 (17.8%)	1 (0.6%)	0 (0.0%)
Injury, poisoning, and procedural complications	Very common	Blister	7 (11.1%)	2 (3.2%)	0 (0.0%)
Investigations	Very common	Lipase increased	17 (10.1%)	12 (7.1%)	3 (1.8%)
	Common	Ejection fraction abnormal	16 (9.5%)	1 (0.6%)	0 (0.0%)
	Common	Blood amylase increased	9 (5.3%)	6 (3.6%)	0 (0.0%)
	Common	Weight decreased	11 (6.5%)	0 (0.0%)	0 (0.0%)
	Common	WBC decreased	10 (5.9%)	3 (1.8%)	0 (0.0%)
	Common	Platelet count decreased	9 (5.3%)	3 (1.8%)	2 (1.2%)
		Any adverse event	166 (98.2%)	77 (45.6%)	14 (8.3%)

*The following terms have been combined: *abdominal pain*, *abdominal pain upper*, and *abdominal pain lower*.
**The following terms have been combined: rash, rash erythematous, rash follicular, rash generalized, rash papular and rash pruritic

4.9 Overdose

There is no experience of acute overdosage with SUTENT. There is no specific antidote for overdosage with SUTENT and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed drug may be achieved by emesis or gastric lavage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Protein-tyrosine kinase inhibitor,
ATC Code :LO1XE04

Sunitinib malate inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib- was identified as a~~n~~ 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 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

CLINICAL STUDIES
The clinical safety and efficacy of SUTENT has been studied in the treatment of patients with malignant gastrointestinal stromal tumour (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) and the treatment of patients with metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy.
Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC.

Gastrointestinal Stromal Tumours
An initial open-label, dose-escalation study was conducted in patients with GIST after failure of imatinib (Median maximum daily dose 800 mg) due to resistance or intolerance. Ninety-seven patients were enrolled at various doses and schedules; 55 patients received 50 mg at the recommended treatment schedule 4 weeks on /2 weeks off ("schedule 4/2").
In this study the median Time To Progression (TTP) was 34.0 weeks (95% CI = 22.0 – 46.0 weeks).

A phase 3, randomized, double-blind, placebo-controlled study of SUTENT was conducted in patients 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 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 (207 patients received SUTENT and 105 patients received placebo). The primary efficacy endpoint of the study was TTP, defined as the time from randomization to first documentation of objective tumour progression.
The median TTP on SUTENT was 28.9 weeks (95% CI = 21.3-34.1 weeks) and was statistically significantly longer than the TTP of 5.1 weeks (95% CI = 4.4-10.1 weeks) on placebo. The difference in overall survival was statistically in favour of SUTENT [hazard ratio: 0.491 95%(C.I. 0.290- 0.831)]; the risk of death was 2 times higher in patients in the placebo arm compared to the SUTENT arm. The percentages of deaths were 14% for SUTENT *vs* 25% for placebo. Median overall survival had not yet been reached in either treatment arm at the time of analysis.

Cytokine-Refractory Metastatic Renal Cell Carcinoma (MRCC)
A phase 2 study of SUTENT was conducted in patients who were refractory to prior cytokine therapy with interleukin-2 or interferon-α. Sixtythree patients received a starting dose of 50 mg of SUTENT orally, once daily for 4 consecutive weeks followed by a 2-week rest period, to comprise a complete

cycle of 6 weeks (schedule 4/2). The primary efficacy endpoint was objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumours (RECIST).
In this study the objective response rate was 36.5% (95% C.I. 24.7% - 49.6%) and the median time to progression (TTP) was 37.7 weeks (95% C.I. 24.0 - 46.4 weeks).

A confirmatory, open-label, single-arm, multi-centre study evaluating the efficacy and safety of SUTENT was conducted in patients with MRCC who were refractory to prior cytokine therapy. One hundred and six patients received at least one 50 mg dose of SUTENT on schedule 4/2.

The primary efficacy endpoint of this study was Objective Response Rate (ORR). Secondary endpoints included TTP, duration of response (DR) and overall survival (OS).
In this study the ORR was 38% (95% C.I. 26.8% – 47.5 %) The median DR and OS had not yet been reached.

This medicinal product has been authorised under a "conditional approval" scheme. This means that further evidence on this medicinal product is awaited, in particular about the effect of SUTENT in terms of progression-free survival in patients with MRCC. A study is being conducted to investigate this. The European Medicines Agency (EMEA) will review new information on the product every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and 266 patients with solid tumours.

Absorption
After oral administration of sunitinib, maximum concentrations (C_{max}) are generally observed from 6 to 12 hours (T_{max}) post-dose.
Food has no effect on the bioavailability of sunitinib.

Distribution
Binding of sunitinib and its primary active metabolite to human plasma protein in *in vitro* assays was 95% and 90%, respectively, with no apparent concentration dependence. The apparent volume of distribution (V/F) for sunitinib was large - 2230 l -, indicating distribution into the tissues.

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 inhibit metabolism, to any clinically relevant extent, of drugs that may be metabolized by these enzymes.
In-vitro studies also indicate that SUTENT neither induces nor inhibits major CYP enzymes, including CYP3A4.

Biotransformation
Sunitinib is metabolized primarily by CYP3A4, the cytochrome P450 enzyme, which produces its primary active metabolite, which is then further metabolized by CYP3A4.
Concurrent administration of SUTENT with the potent CYP3A4 inducer, rifampin, resulted approximately in 56% and 78% reduction in sunitinib C_{max} and $AUC_{0-\infty}$, values respectively, after a single dose of SUTENT in healthy volunteers. Administration of SUTENT with other inducers of the CYP3A4 family /(e.g. dexamethasone, phenytoin, carbamazepine, phenobarbital or *Hypericum perforatum*, known also as St. John's Wort) may decrease sunitinib concentrations.

Elimination
Excretion is primarily via faeces (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 faeces, representing 91.5%, 86.4% and 73.8% of

radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and faeces, but generally were not found in plasma. Total oral clearance (CL/F) was 34-62 l/hr.

Organ Functions impairment
Hepatic insufficiency: No clinical studies have been performed in patients with impaired hepatic function
Studies excluded patients with ALT or AST >2.5 x ULN (Upper Limit of Normal) or, if due to underlying disease > 5.0 x ULN.
Renal insufficiency: No clinical studies have been performed in patients with impaired renal function
Studies excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses indicated that sunitinib apparent clearance (CL/F) was not affected by creatinine clearance within the range evaluated (42-347 ml/min).

Plasma Pharmacokinetics
Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40 - 60 hours, and 80 - 110 hours, respectively. In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its 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 is 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 tumour stasis/growth reduction *in vivo*. The primary active metabolite comprises 23 to 37% of the total exposure. No significant changes in the pharmacokinetics of sunitinib or the primary, active metabolite are observed with repeated daily administration or with repeated cycles in the dosing regimens tested. The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers.

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for weight or ECOG score.
Available data indicate that females could have about 30% lower apparent clearance (CL/F) of sunitinib than males: this difference however does not necessitate 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 diarrhoea in monkeys), adrenal gland (cortical congestion and/or haemorrhage in rats and monkeys, with necrosis followed by fibrosis in rats), haemolymphopoietic system (bone morrow hypocelularity, 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, pituitary hypertrophy, and testicular tubular atrophy, increased mesangial cells in kidney, haemorrhage 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
Carcinogenicity studies with sunitinib malate have not been performed.

Reproductive and Developmental toxicity.
No effects on male or female fertility were observed in reproductive toxicity studies . 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. Effects on male fertility in rat were observed in the form of tubular atrophy in the testes, reduction of spermatozoa in epididimes and colloid depletion in prostate and seminal vesicles at plasma exposure levels 18-fold higher than is observed in clinic.

In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions increased postimplantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5-fold higher than is observed in clinic. In rabbits, reductions in gravid uterine weights and number of live foetuses were due to increases in the number of resorptions , increases in post-implantation loss and complete litter loss in 4 of 6 pregnant females at plasma exposure levels 3-fold higher than is observed in clinic.

Sunitinib treatment in rats during organogenesis resulted in developmental effects at ≥5 mg/kg/day consisting of increased incidence of foetal skeletal malformations, predominantly characterized as retarded ossification of thoracic/lumbar vertebrae and occurred at plasma exposure levels 6-fold higher than is observed in clinic. 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-fold higher than is observed in clinic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
- Mannitol
- Croscarmellose Sodium
- Povidone
- Magnesium Stearate

Capsule Shell
- Gelatin
- Red Iron Oxide (E172)
- Titanium dioxide (E171)

Printing ink.
- Shellac
- Propylene glycol
- Sodium hydroxide
- Povidone
- Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polypropylene (HDPE) bottles with a polypropylene closure, containing 30 capsules .

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Ltd
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation:
Due-date for next renewal:

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

SUTENT 25 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains sunitinib malate, equivalent to 25.0 mg of sunitinib
Excipient(s): 39.663 mg of mannitol.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules
Gelatin capsules with caramel cap and orange body, printed with white ink “Pfizer” on the cap and “STN 25 mg” on the body and containing yellow to orange granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.
SUTENT is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy.
Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC. (see section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the treatment of renal cell carcinoma or GIST.

The recommended dose of SUTENT is one 50-mg dose orally, taken daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks.

Dose modifications in 12.5-mg steps may be applied based on individual safety and tolerability.Daily dose should not exceed 87.5 mg nor be decreased below 37.5 mg.

Co-administration of potent CYP3A4 inducers, such as rifampin, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of SUTENT may need to be increased in 12.5 mg increments (up to 87.5mg per day), based on careful monitoring of tolerability.
Co-administration of SUTENT with potent CYP3A4 inhibitors, such as ketoconazole should be avoided. (see sections 4.4 and 4.5). If this is not possible the doses of SUTENT may need to be reduced to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability
Selection of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP3A4 should be considered.

Paediatric use**:** The safety and efficacy of SUTENT in paediatric patients have not been established. SUTENT should not be used in paediatric population until further data become available.

Elderly patients use: Approximately 25% of the subjects in clinical studies of SUTENT were 65 or over. No significant differences in safety or effectiveness were observed between younger and older patients.

Hepatic Insufficiency: No clinical studies have been performed in patients with impaired hepatic function (see section 5.2).

Renal Insufficiency: No clinical studies have been performed in patients with impaired renal function.(see section 5.2)

SUTENT 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.

4.3 Contraindications

Hypersensitivity to sunitinib or to any of the excipients.

4.4 Special warnings and precautions for use

Co-administration of potent CYP3A4 inducers such as rifampin, may **decrease** sunitinib plasma concentrations. Combination with inducers should therefore be avoided. If this is not possible, the dosage of SUTENT may need to be increased (see Section 4.2 and 4.5)

Co-administration of strong CYP3A4 inhibitor such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. If this is not possible, the dosage of SUTENT may need to be reduced (see sections 4.2 and 4.5).

*Skin and tissue*s
Skin discolouration, possibly due to active substance colour (yellow) is a common treatment-related adverse event occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with SUTENT. 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.
Mouth pain/irritation was reported in approximately 14% of patients. Dysgeusia (taste disturbance) was reported in approximately 28% of patients.
The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.

Gastrointestinal events
Nausea, diarrhoea, stomatitis, dyspepsia and vomiting were the most commonly reported treatment-related gastrointestinal events.
Supportive care for gastrointestinal adverse events requiring treatment may include medication with an anti-emetic or anti-diarrhoeal medication.

Haemorrhage
Treatment-related tumour haemorrhage occurred in approximately 2 % of patients with GIST. These events may occur suddenly, and in the case of pulmonary tumours, may present as severe and life-threatening haemoptysis or pulmonary haemorrhage. Fatal pulmonary haemorrhage 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.Routine assessment of this event should include complete blood counts and physical examination.
Epistaxis was the most common treatment-related haemorrhagic adverse event, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. None of these events was serious.

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

Hypertension
Treatment-related hypertension was reported in approximately 16% of patients with solid tumours. SUTENT dosing was reduced or temporarily delayed in approximately 2.7 % of this patient population. None of these patients were discontinued from treatment with SUTENT. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of this patient population. 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.

Haematological
Decreased absolute neutrophil counts of grade 3 and 4 severity were reported in 13.1% and 0.9% patients, respectively. Decreased platelet counts of grade 3 and 4 severity were reported in 4% and 0.5% patients respectively. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.
Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

Cardiovascular
Decreases in left ventricular ejection fraction (LVEF) of ≥ 20% and below the lower limit of normal occurred in approximately 2% of SUTENT-treated GIST patients and of 4% MRCC patients and 2% of placebo-treated patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued.
Treatment-related adverse events of ‘cardiac failure’, ‘cardiac failure congestive’ or ‘left ventricular failure’ were reported in 0.7% of patients with solid tumours and 15 of patients treated with placebo. All patients had GIST. The relationship, if any, between receptor tyrosinase kinase (RTK) inhibition and cardiac function remains unclear.
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 congestive heart failure (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 the patient is receiving SUTENT. 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 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.

QT Interval prolongation
QT interval prolongation was investigated in a trial in 24 patients, aged 20-87 years, with advanced malignancies. At approximately twice therapeutic concentrations, SUTENT has been shown to prolong the QTcF interval (Frederica’s Correction) . There were no patients with greater than grade 2 (CTCAE v3.0) QT/QTc interval prolongation and no patient presented with a cardiac arrhythmia. The clinical relevance of the effects observed is unclear and will depend on individual patient risk factors and

susceptibilities present. SUTENT 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 potent CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of SUTENT reduced (see Section 4.5).

Venous Thromboembolic Events
Four patients (2%) on the two MRCC studies had venous thromboembolic events reported; two patients with pulmonary embolism (both grade 4) and two patients with deep venous thrombosis (DVT) (both grade 3). Dose interruption occurred in one of these cases. Seven patients (3%) on SUTENT and none on placebo in the pivotal GIST study experienced venous thromboembolic events; five of the seven were grade 3 DVTs, and two were grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Pulmonary Embolism
Treatment-related pulmonary embolism was reported in approximately 1.1% patients with solid tumours who received SUTENT. None of these events resulted in a patient discontinuing treatment with SUTENT; 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.

Hypothyroidism
Hypothyroidism was reported as an adverse event in 7 patients (4%) across the two MRCC studies. Additionally, TSH elevations were reported in 4 patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Treatment-emergent acquired hypothyroidism was noted in 8 GIST patients (4%) on SUTENT versus 1 (1%) on placebo. Patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Pancreatic Function
Increases in serum lipase and amylase activities were observed in patients with various solid tumours who received SUTENT. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours. Pancreatitis was observed in 0.4% of patients with solid tumours. If symptoms of pancreatitis are present, patients should have proper medical follow-up.

Seizures
In clinical studies of SUTENT, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, 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.

4.5 Interaction with other medicinal products and other forms of interaction

*Drugs that may **increase** sunitinib plasma concentrations.*
Concomitant administration of sunitinib malate with the potent CYP3A4 inhibitor, ketoconazole, resulted in a 49% and 51% increase of the complex [sunitinib +primary metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib malate in healthy volunteers.
Administration of SUTENT with potent inhibitors of the CYP3A4 family (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations
Combination 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 SUTENT may need to be reduced to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability (see section 4.2).

*Drugs that may **decrease** sunitinib plasma concentrations:*
Concomitant use of SUTENT with the CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction of the complex [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers.
Administration of SUTENT with potent inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or *Hypericum perforatum* known also as St. John's Wort) may decrease sunitinib concentrations. Combination 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 SUTENT may need to be increased in 12.5 mg increments (up to 87,5 mg per day) based on careful monitoring of tolerability. (see section 4.2).
To maintain sunitinib target concentrations, selection of co-medications with less enzyme induction potential, should be considered. If this is not possible, dose-adjustments of SUTENT may be necessary (see section 4.2)

Haemorrhage has been observed rarely in patients treated with SUTENT (see section 4.4). Patients receiving concomitant treatment with anti-coagulants (e.g. warfarin; acenocumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR), and physical examination

4.6 Pregnancy and lactation

Pregnancy
There are no studies in pregnant women using SUTENT. Studies in animals have shown reproductive toxicity including foetal malformations (see section 5.3). SUTENT should not be used during pregnancy or in any woman not employing adequate contraception unless the potential benefit justifies the potential risk to the foetus. 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 foetus.
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Based on non-clinical findings, male and female fertility may be compromised by treatment with SUTENT (see section 5.3)

Lactation
Sunitinib and/or its metabolites are excreted in rat milk. 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, women should not breast feed while taking SUTENT.

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 SUTENT.

4.8 Undesirable effects

The most important treatment-related serious adverse events associated with SUTENT treatment of patients with solid tumours were pulmonary embolism (1%), thrombocytopoenia (1%), tumour haemorrhage (0.9%), febrile neutropoenia (0.4%), and hypertension (0.4%). The most common treatment-related adverse events (experienced by at least 20% of the patients) of any grade included: fatigue; gastrointestinal disorders, such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting; skin discoloration; dysgeusia and anorexia. Fatigue, hypertension and neutropoenia were the most common treatment-related adverse events of grade 3 maximum severity and increased lipase was the most frequently occurring treatment-related adverse event of grade 4 maximum severity in patients with solid tumours.

Treatment-related adverse reactions that were reported in >5% of solid tumour patients are listed below, by system organ class, frequency and grade of severity. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Frequencies are defined as: very common (≥ 1/10), common (>1/100, to < 1/10), uncommon (≥1/1,000, <1/100), rare (>1/10,000, to ≤1/1,000), very rare (< 1/10,000).

Adverse Reactions reported in GIST studies

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Blood and the lymphatic system disorders	Very common	Anaemia	33 (12.8%)	13 (5.1%)	1 (0.4%)
	Common	Neutropoenia	24 (9.3%)	15 (5.8%)	1 (0.4%)
	Common	Thrombocytopoenia	23 (8.9%)	6 (2.3%)	1 (0.4%)
Endocrine disorders	Common	Hypothyroidism	15 (5.8%)	0 (0.0%)	1 (0.4%)
Metabolism and nutrition disorders	Common	Anorexia	44 (7.1%)	1 (0.4%)	0 (0.0%)
Nervous system disorders	Very common	Dysgeusia	48 (18.7%)	0 (0.0%)	0 (0.0%)
	Very common	Headache	27 (10.5%)	2 (0.8%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	43 (16.7%)	18 (7.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	17 (6.6%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	Common	Chromaturia	13 (5.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Diarrhoea	90 (35.0%)	13 (5.1%)	0 (0.0%)
	Very common	Nausea	69 (26.8%)	2 (0.8%)	0 (0.0%)
	Very common	Stomatitis	49 (19.1%)	2 (0.8%)	0 (0.0%)
	Very common	Vomiting	46 (17.9%)	1 (0.4%)	0 (0.0%)
	Very common	Dyspepsia	32 (12.5%)	2 (0.8%)	0 (0.0%)
	Common	Glossodynia	17 (6.6%)	0 (0.0%)	0 (0.0%)
	Common	Constipation	13 (5.1%)	1 (0.4%)	0 (0.0%)
	Very common	Abdominal pain*	30 (11.7%)	5 (1.9%)	1 (0.4%)
	Common	Oral pain	16 (6.2%)	0 (0.0%)	0 (0.0%)
	Common	Flatulence	15 (5.8%)	0 (0.0%)	0 (0.0%)
	Common	Dry mouth	15 (5.8%)	0 (0.0%)	0 (0.0%)
	Common	Gastro-oesophageal reflux disease	15 (5.8%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Very common	Skin discolouration	65 (25.3%)	0 (0.0%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	55 (21.4%)	14 (5.4%)	0 (0.0%)
	Very common	Rash***	39 (15.2%)	2 (0.8%)	0 (0.0%)
	Common	Hair colour changes	22 (8.6%)	0 (0.0%)	0 (0.0%)
	Common	Dry skin	15 (5.8%)	0 (0.0%)	0 (0.0%)
Muscoloskeletal, connective tissue and bone disorders	Common	Pain in extremity	21 (8.2%)	1 (0.4%)	0 (0.0%)
	Common	Arthralgia	15 (5.8%)	2 (0.8%)	0 (0.0%)
	Common	Myalgia	13 (5.1%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions	Very common	Fatigue/Asthenia	135 (52.5%)	25 (9.7%)	0 (0.0%)
	Very common	Mucosal inflammation	30 (11.7%)	0 (0.0%)	0 (0.0%)

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
	Common	Oedema**	21 (8.2%)	1 (0.4%)	0 (0.0%)
Investigations	Common	Haemoglobin decreased	16 (6.2%)	2 (0.8%)	0 (0.0%)
	Common	Blood creatinine phosphokinase increased	14 (5.4%)	0 (0.0%)	0 (0.0%)
	Common	Ejection fraction decreased	13 (5.1%)	1 (0.4%)	0 (0.0%)
	Common	Lipase increased	13 (5.1%)	5 (1.9%)	4 (1.6%)
	Common	Platelet count decreased	13 (5.1%)	2 (0.8%)	1 (0.4%)
		Any adverse event	222 (86.4%)	88 (34.2%)	24 (9.3%)

*The following terms have been combined: *abdominal pain*, *abdominal pain upper*, and *abdominal pain lower*.
**The following terms have been combined: oedema and oedema peripheral.
***The following terms have been combined: rash, rash erythematous, rash macular and rash scaly

Adverse <u>Reactions</u> reported in MRCC studies

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Blood and lymphatic system disorders	Very common	Neutropoenia	17 (10.1%)	8 (4.7%)	1 (0.6%)
	Common	Anaemia	16 (9.5%)	6 (3.6%)	0 (0.0%)
	Common	Thrombocytopoenia	15 (8.9%)	5 (3.0%)	2 (1.2%)
	Common	Leucopoenia	14 (8.3%)	7 (4.1%)	0 (0.0%)
Eye disorders	Common	Lacrimation increased	9 (5.3%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	Very common	Anorexia	47 (27.8%)	1 (0.6%)	0 (0.0%)
	Common	Dehydration	12 (7.1%)	4 (2.4%)	0 (0.0%)
	Common	Decreased appetite	11 (6.5%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	Very common	Dysgeusia	71 (42%)	0 (0.0%)	0 (0.0%)
	Very common	Headache	25 (14.8%)	1 (0.6%)	0 (0.0%)
	Common	Dizziness	13 (7.7%)	2 (1.2%)	0 (0.0%)
	Common	Paraesthesia	9 (5.3%)	0 (0.0%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	28 (16.6%)	7 (4.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	16 (9.5%)	0 (0.0%)	0 (0.0%)
	Common	Dyspnoea	9 (5.3%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Diarrhoea	83 (49.1%)	5 (3.0%)	0 (0.0%)
	Very common	Nausea	84 (49.7%)	2 (1.2%)	0 (0.0%)
	Very common	Stomatitis	70 (41.4%)	6 (3.6%)	0 (0.0%)
	Very common	Dyspepsia	69 (40.8%)	1 (0.6%)	0 (0.0%)
	Very common	Vomiting	52 (30.8%)	2 (1.2%)	0 (0.0%)
	Very common	Constipation	34 (20.1%)	0 (0.0%)	0 (0.0%)
	Very common	Glossodynia	25 (14.8%)	0 (0.0%)	0 (0.0%)

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
	Very common	Abdominal pain*	17 (10.1%)	2 (1.2%)	0 (0.0%)
	Common	Flatulence	16 (9.5%)	0 (0.0%)	0 (0.0%)
	Common	Abdominal distension	9 (5.3%)	0 (0.0%)	0 (0.0%)
	Common	Dry mouth	9 (5.3%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Very common	Skin discolouration	54 (32.0%)	0 (0.0%)	0 (0.0%)
	Very common	Rash**	46 (27.2%)	0 (0.0%)	0 (0.0%)
	Very common	Hair colour changes	24 (14.2%)	0 (0.0%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	21 (12.4%)	6 (3.6%)	0 (0.0%)
	Common	Alopecia	13 (7.7%)	0 (0.0%)	0 (0.0%)
	Common	Dermatitis exfoliative	10 (5.9%)	2 (1.2%)	0 (0.0%)
	Common	Periorbital oedema	9 (5.3%)	0 (0.0%)	0 (0.0%)
	Very common	Dry skin	22 (13.0%)	0 (0.0%)	0 (0.0%)
	Very common	Erythema	20 (11.8%)	0 (0.0%)	0 (0.0%)
Muscoloskeletal, connective tissue and bone disorders	Very common	Pain in extremity	21 (12.4)	1 (0.6%)	0 (0.0%)
	Common	Myalgia	15 (8.9%)	1 (0.6%)	0 (0.0%)
General disorders and administration site conditions	Very common	Fatigue/Asthenia	108 (63.9%)	19 (11.2%)	0 (0.0%)
	Very common	Mucosal inflammation	30 (17.8%)	1 (0.6%)	0 (0.0%)
Injury, poisoning, and procedural complications	Very common	Blister	7 (11.1%)	2 (3.2%)	0 (0.0%)
Investigations	Very common	Lipase increased	17 (10.1%)	12 (7.1%)	3 (1.8%)
	Common	Ejection fraction abnormal	16 (9.5%)	1 (0.6%)	0 (0.0%)
	Common	Blood amylase increased	9 (5.3%)	6 (3.6%)	0 (0.0%)
	Common	Weight decreased	11 (6.5%)	0 (0.0%)	0 (0.0%)
	Common	WBC decreased	10 (5.9%)	3 (1.8%)	0 (0.0%)
	Common	Platelet count decreased	9 (5.3%)	3 (1.8%)	2 (1.2%)
		Any adverse event	166 (98.2%)	77 (45.6%)	14 (8.3%)

*The following terms have been combined: *abdominal pain*, *abdominal pain upper*, and *abdominal pain lower*.
**The following terms have been combined: rash, rash erythematous, rash follicular, rash generalized, rash papular and rash pruritic

4.9 Overdose

There is no experience of acute overdosage with SUTENT. There is no specific antidote for overdosage with SUTENT and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed drug may be achieved by emesis or gastric lavage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent -Protein-tyrosine kinase inhibitor
ATC Code :LO1XE04.

Sunitinib malate inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib- was identified as a~~n~~ 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 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

CLINICAL STUDIES
The clinical safety and efficacy of SUTENT has been studied in the treatment of patients with malignant gastrointestinal stromal tumour (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) and the treatment of patients with metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy.

Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC.

Gastrointestinal Stromal Tumours
An initial open-label, dose-escalation study was conducted in patients with GIST after failure of imatinib (Median maximum daily dose 800 mg) due to resistance or intolerance. Ninety-seven patients were enrolled at various doses and schedules; 55 patients received 50 mg at the recommended treatment schedule 4 weeks on /2 weeks off ("schedule 4/2").
In this study the median Time To Progression (TTP) was 34.0 weeks (95% CI = 22.0 – 46.0 weeks).

A phase 3, randomized, double-blind, placebo-controlled study of SUTENT was conducted in patients 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 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 (207 patients received SUTENT and 105 patients received placebo). The primary efficacy endpoint of the study was TTP, defined as the time from randomization to first documentation of objective tumour progression.
The median TTP on SUTENT was 28.9 weeks (95% CI = 21.3-34.1 weeks) and was statistically significantly longer than the TTP of 5.1 weeks (95% CI = 4.4-10.1 weeks) on placebo. The difference in overall survival was statistically in favour of SUTENT [hazard ratio: 0.491 95%(C.I. 0.290- 0.831)]; the risk of death was 2 times higher in patients in the placebo arm compared to the SUTENT arm. The percentages of deaths were 14% for SUTENT vs 25% for placebo. Median overall survival had not yet been reached in either treatment arm at the time of analysis.

Cytokine-Refractory Metastatic Renal Cell Carcinoma (MRCC)
A phase 2 study of SUTENT was conducted in patients who were refractory to prior cytokine therapy with interleukin-2 or interferon-α. Sixty-three patients received a starting dose of 50 mg of SUTENT orally, once daily for 4 consecutive weeks followed by a 2-week rest period, to comprise a complete cycle of 6 weeks (schedule 4/2). The primary efficacy endpoint was objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumours (RECIST).
In this study the objective response rate was 36.5% (95% C.I. 24.7% - 49.6%) and the median time to progression (TTP) was 37.7 weeks (95% C.I 24.0 - 46.4 weeks).

A confirmatory, open-label, single-arm, multi-centre study evaluating the efficacy and safety of SUTENT was conducted in patients with MRCC who were refractory to prior cytokine therapy. One hundred and six patients received at least one 50 mg dose of SUTENT on Schedule 4/2.

The primary efficacy endpoint of this study was Objective Response Rate (ORR). Secondary endpoints included TTP, duration of response (DR) and overall survival (OS).
In this study the ORR was 38% (95% C.I. 26.8% – 47.5 %). The median DR and OS had not yet been reached.

This medicinal product has been authorised under a "conditional approval" scheme. This means that further evidence on this medicinal product is awaited, in particular about the effect of SUTENT in terms of progression-free survival in patients with MRCC. A study is being conducted to investigate this. The European Medicines Agency (EMEA) will review new information on the product every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and 266 patients with solid tumours.

Absorption
After oral administration of sunitinib, maximum concentrations (C_{max}) are generally observed from 6 – to 12 hours (T_{max}) post-dose.
Food has no effect on the bioavailability of sunitinib

Distribution
Binding of sunitinib and its primary active metabolite to human plasma protein in *in vitro* assays was 95% and 90%, respectively, with no apparent concentration dependence. According to the analysed dataset (10 studies in healthy volunteers and patients, single and multiple doses) the apparent volume of distribution (V/F) for sunitinib was large - 2230 l -, indicating distribution into the tissues.

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 inhibit metabolism, to any clinically relevant extent, of drugs that may be metabolized by these enzymes.
In-vitro studies indicate that SUTENT neither induces nor inhibits major CYP enzymes, including CYP3A4.

Biotransformation
Sunitinib is metabolized primarily by CYP3A4, the cytochrome P450 enzyme, which produces its primary active metabolite, which is then further metabolized by CYP3A4.
Concurrent administration of SUTENT with the potent CYP3A4 inducer, rifampin, resulted approximately in 56% and 78% reduction in sunitinib C_{max} and $AUC_{0-\infty}$, values respectively, after a single dose of SUTENT in healthy volunteers. Administration of SUTENT with other inducers of the CYP3A4 familiy /(e.g. dexamethasone, phenytoin, carbamazepine, phenobarbital or *Hypericum perforatum*, known also as St. John's Wort) may decrease sunitinib concentrations.

Elimination
Excretion is primarily via faeces (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 faeces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and faeces, but generally were not found in plasma. Total oral clearance (CL/F) was 34-62 l/hr.

Organ Function impairment
Hepatic insufficiency : No clinical studies have been performed in patients with impaired hepatic function
Studies excluded patients with ALT or AST >2.5 x ULN (Upper Limit of Normal) or, if due to underlying disease > 5.0 x ULN.
Renal insufficiency: No clinical studies have been performed in patients with impaired renal function
Studies excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses indicated that sunitinib apparent clearance (CL/F) was not affected by creatinine clearance within the range evaluated (42-347 ml/min).

Plasma Pharmacokinetics
Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40 - 60 hours, and 80 - 110 hours, respectively. In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its 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 is 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 tumour stasis/growth reduction *in vivo*. The primary active metabolite comprises 23 to 37% of the total exposure. No significant changes in the pharmacokinetics of sunitinib or the primary, active metabolite are observed with repeated daily administration or with repeated cycles in the dosing regimens tested. The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers.

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for weight, or ECOG score.
Available data indicate that females might have about a 30% lower apparent clearance (CL/F) of sunitinib than males: this difference however does not necessitate 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 diarrhoea in monkeys), adrenal gland (cortical congestion and/or haemorrhage in rats and monkeys, with necrosis followed by fibrosis in rats), haemolymphopoietic system (bone morrow hypocelularity, 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), 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, pituitary hypertrophy, and testicular tubular atrophy increased mesangial cells in kidney, haemorrhage 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
Carcinogenicity studies with sunitinib malate have not been performed.

Reproductive and Developmental toxicity
No effects on male or female fertility were observed in reproductive toxicity studies. 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. Effects on male fertility in rat were observed in the form of tubular atrophy in the testes, reduction of spermatozoa in epididimes, colloid depletion in prostate and seminal vesicles at plasma exposure levels 18-fold higher than is observed in clinic.

In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions increased postimplantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5-fold higher than is observed in clinic. In rabbits, reductions in gravid uterine weights and number of live foetuses were due to increases in the number of resorptions , increases in postimplantation loss, and complete litter loss in 4 of 6 pregnant females at plasma exposure levels 3-fold higher than is observed in clinic.

Sunitinib treatment in rats during organogenesis resulted in developmental effects at ≥5 mg/kg/day consisting of increased incidence of foetal skeletal malformations, predominantly characterized as retarded ossification of thoracic/lumbar vertebrae and. occurred at plasma exposure levels 6-fold higher than is observed in clinic. 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-fold higher than is observed in clinic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
- Mannitol
- Croscarmellose Sodium
- Povidone
- Magnesium Stearate

Orange Capsule Shell
- Gelatin
- Red Iron Oxide (E172)
- Titanium dioxide (E171)

Caramel Capsule Shell
- Gelatin
- Titanium dioxide (E171)
- Yellow Iron Oxide (E172)
- Red Iron Oxide (E172)
- Black Iron Oxide (E172)

Printing ink.
Shellac,
Propylene glycol,
Sodium hydroxide,
Povidone
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

High-density polypropylene (HDPE) bottles with a polypropylene closure, containing 30 capsules

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Ltd
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation:
Due-date for next renewal:

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

SUTENT 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains sunitinib malate equivalent to 50 mg of sunitinib
Excipient(s): 79..326 mg of mannitol.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard Capsules
Gelatin capsule with caramel cap and caramel body, printed with white ink “Pfizer” on the cap and “STN 50 mg” on the body and containing yellow to orange granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.
SUTENT is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy .
Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC. (see section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the treatment of renal cell carcinoma or GIST.

The recommended dose of SUTENT is one 50-mg dose orally, taken daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks.

Dose modifications in 12.5-mg steps may be applied based on individual safety and tolerability. Daily dose should not exceed 87.5 mg nor be decreased below 37.5 mg.

Co-administration of potent CYP3A4 inducers, such as rifampin, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of SUTENT may need to be increased in 12.5 mg increments (up to 87.5 mg per day) based on careful monitoring of tolerability.
Co-administration of potent CYP3A4 inhibitors, such as ketoconazole, should be avoided. (see sections 4.4 and 4.5). If this is not possible the doses of SUTENT may need to be decreased to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability
Selection of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP3A4 should be considered.

Paediatric use**:** The safety and efficacy of SUTENT in paediatric patients have not been established. SUTENT should not be used in paediatric population until further data become available

Elderly patients use: Approximately 25% of the subjects in clinical studies of SUTENT were 65 or over. No significant differences in safety or effectiveness were observed between younger and older patients.

Hepatic Insufficiency: No clinical studies have been performed in patients with impaired hepatic function.(see section 5.2).

Renal Insufficiency: No clinical studies have been performed in patients with impaired renal function. (see section 5.2).

SUTENT 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.

4.3 Contraindications

Hypersensitivity to sunitinib malate or to any of the excipients.

4.4 Special warnings and precautions for use

Co-administration of potent CYP3A4 inducers such as rifampin, may **decrease** sunitinib plasma concentrations. Combination with inducers should therefore be avoided. If this is not possible, the dosage of SUTENT may need to be increased (see sections 4.2 and 4.5)

Co-administration of strong CYP3A4 inhibitor such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. If this is not possible, the dosage of SUTENT may need to be reduced (see sections 4.2 and 4.5).

*Skin and tissue*s
Skin discolouration, possibly due to the active substance colour (yellow) is a common treatment-related adverse event occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with SUTENT. 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.
Mouth pain/irritation was reported in approximately 14% of patients. Dysgeusia (taste disturbance) was reported in approximately 28% of patients.
The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.

Gastrointestinal events
Nausea, diarrhoea, stomatitis, dyspepsia and vomiting were the most commonly reported treatment-related gastrointestinal events.
Supportive care for gastrointestinal adverse events requiring treatment may include medication with an anti-emetic or anti-diarrhoeal medication.

Haemorrhage
Treatment-related tumour haemorrhage occurred in approximately 2 % of patients with GIST. These events may occur suddenly, and in the case of pulmonary tumours, may present as severe and life-threatening haemoptysis or pulmonary haemorrhage. Fatal pulmonary haemorrhage 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. Routine assessment of this event should include complete blood counts and physical examination.
Epistaxis was the most common treatment-related haemorrhagic adverse event, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. None of these events was serious.

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

Hypertension
Treatment-related hypertension was reported in approximately 16% of patients with solid tumours. SUTENT dosing was reduced or temporarily delayed in approximately 2.7% of this patient population. None of these patients were discontinued from treatment with SUTENT. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of this patient population. 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.

Haematological
Decreased absolute neutrophil counts of grade 3 and 4 severity were reported in 13.1% and 0.9% patients, respectively. Decreased platelet counts of grade 3 and 4 severity were reported in 4% and 0.5% patients respectively. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation.
Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

Cardiovascular
Decreases in left ventricular ejection fraction (LVEF) of ≥ 20% and below the lower limit of normal occurred in approximately 2% of SUTENT-treated GIST patients and of 4% MRCC patients and 2% of placebo-treated patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued.
Treatment-related adverse events of ‘cardiac failure’, ‘cardiac failure congestive’ or ‘left ventricular failure’ were reported in 0.7% of patients with solid tumours and 1% of patients treated with placebo. All patients had GIST. The relationship, if any, between receptor tyrosine kinase (RTK) inhibition and cardiac function remains unclear.
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 congestive heart failure (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 the patient is receiving SUTENT. 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 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.

QT Interval prolongation
QT interval prolongation was investigated in a trial in 24 patients, aged 20-87 years, with advanced malignancies. At approximately twice therapeutic concentrations, SUTENT has been shown to prolong the QTcF interval (Frederica’s Correction). There were no patients with greater than grade 2 (CTCAE v3.0) QT/QTc interval prolongation and no patient presented with a cardiac arrhythmia. The clinical relevance of the effects observed is unclear and will depend on individual patient risk factors and

susceptibilities present. SUTENT 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 potent CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of SUTENT reduced (see Section 4.5).

Venous Thromboembolic Events
Four patients (2%) on the two MRCC studies had venous thromboembolic events reported; two patients with pulmonary embolism (both grade 4) and two patients with deep venous thrombosis (DVT) (both grade 3). Dose interruption occurred in one of these cases. Seven patients (3%) on SUTENT and none on placebo in the pivotal GIST study experienced venous thromboembolic events; five of the seven were grade 3 DVTs, and two were grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Pulmonary Embolism
Treatment-related pulmonary embolism was reported in approximately 1.1 % patients with solid tumours who received SUTENT. None of these events resulted in a patient discontinuing treatment with SUTENT; 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.

Hypothyroidism
Hypothyroidism was reported as an adverse event in 7 patients (4%) across the two MRCC studies. Additionally, TSH elevations were reported in 4 patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Treatment-emergent acquired hypothyroidism was noted in 8 GIST patients (4%) on SUTENT versus 1 (1%) on placebo. Patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Pancreatic Function
Increases in serum lipase and amylase activities were observed in patients with various solid tumours who received SUTENT. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours. Pancreatitis was observed in 0.4% of patients with solid tumours. If symptoms of pancreatitis are present, patients should have proper medical follow-up.

Seizures
In clinical studies of SUTENT, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, 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.

4.5 Interaction with other medicinal products and other forms of interaction

*Drugs that may **increase** sunitinib plasma concentrations.*
Concomitant administration of sunitinib malate with the potent CYP3A4 inhibitor, ketoconazole, resulted in a 49% and 51% increase of the complex [sunitinib +primary metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib malate in healthy volunteers.
Administration of SUTENT with potent inhibitors of the CYP3A4 family (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations
Combination 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 SUTENT may need to be reduced to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability (see section 4.2)

*Drugs that may **decrease** sunitinib plasma concentrations:*
Concomitant use of SUTENT with the CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction of the complex [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers.
Administration of SUTENT with potent inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin,phenobarbital or *Hypericum perforatum* known also as St. John's Wort) may decrease sunitinib concentrations. Combination 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 SUTENT may need to be increased in 12.5 mg increments (up to 87,5 mg per day) based on careful monitoring of tolerability. (see section 4.2).
To maintain sunitinib target concentrations, selection of co-medications with less enzyme induction potential, should be considered. If this is not possible, dose-adjustments of SUTENT may be necessary (see section 4.2)

Haemorrhage has been observed rarely in patients treated with SUTENT (se section 4.4. Patients receiving concomitant treatment with anti-coagulants (e.g. warfarin; acenocumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR), and physical examination

4.6 Pregnancy and lactation

Pregnancy
There are no studies in pregnant women using SUTENT. Studies in animals have shown reproductive toxicity including foetal malformations (see section 5.3). SUTENT should not be used during pregnancy or in any woman not employing adequate contraception unless the potential benefit justifies the potential risk to the foetus. 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 foetus.
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Based on non-clinical findings, male and female fertility may be compromised by treatment with SUTENT (see section 5.3)

Lactation
Sunitinib and/or its metabolites are excreted in rat milk. 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, women should not breast feed while taking SUTENT.

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 SUTENT.

4.8 Undesirable effects

The most important treatment-related serious adverse events associated with SUTENT treatment of patients with solid tumours were pulmonary embolism (1%), thrombocytopoenia (1%), tumour haemorrhage (0.9%), febrile neutropoenia (0.4%), and hypertension (0.4%). The most common treatment-related adverse events (experienced by at least 20% of the patients) of any grade included: fatigue; gastrointestinal disorders, such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting; skin discolouration; dysgeusia and anorexia. Fatigue, hypertension and neutropoenia were the most common treatment-related adverse events of grade 3 maximum severity and increased lipase was the most frequently occurring treatment-related adverse event of Grade 4 maximum severity in patients with solid tumours.

Treatment-related adverse reactions that were reported in >5% of solid tumour patients are listed below, by system organ class, frequency and grade of severity. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Frequencies are defined as: very common (≥ 1/10), common (≥1/100,< 1/1,000), uncommon (≥1/1,000, <1//100), rare (≥1/10,000, <1/1,000), very rare (< 1/10,000).

Adverse Reactions reported in GIST studies

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Blood and the lymphatic system disorders	Very common	Anaemia	33 (12.8%)	13 (5.1%)	1 (0.4%)
	Common	Neutropoenia	24 (9.3%)	15 (5.8%)	1 (0.4%)
	Common	Thrombocytopoenia	23 (8.9%)	6 (2.3%)	1 (0.4%)
Endocrine disorders	Common	Hypothyroidism	15 (5.8%)	0 (0.0%)	1 (0.4%)
Metabolism and nutrition disorders	Common	Anorexia	44 (7.1%)	1 (0.4%)	0 (0.0%)
Nervous system disorders	Very common	Dysgeusia	48 (18.7%)	0 (0.0%)	0 (0.0%)
	Very common	Headache	27 (10.5%)	2 (0.8%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	43 (16.7%)	18 (7.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	17 (6.6%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	Common	Chromaturia	13 (5.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Diarrhoea	90 (35.0%)	13 (5.1%)	0 (0.0%)
	Very common	Nausea	69 (26.8%)	2 (0.8%)	0 (0.0%)
	Very common	Stomatitis	49 (19.1%)	2 (0.8%)	0 (0.0%)
	Very common	Vomiting	46 (17.9%)	1 (0.4%)	0 (0.0%)
	Very common	Dyspepsia	32 (12.5%)	2 (0.8%)	0 (0.0%)
	Common	Glossodynia	17 (6.6%)	0 (0.0%)	0 (0.0%)
	Common	Constipation	13 (5.1%)	1 (0.4%)	0 (0.0%)
	Very common	Abdominal pain*	30 (11.7%)	5 (1.9%)	1 (0.4%)
	Common	Oral pain	16 (6.2%)	0 (0.0%)	0 (0.0%)
	Common	Flatulence	15 (5.8%)	0 (0.0%)	0 (0.0%)
	Common	Dry mouth	15 (5.8%)	0 (0.0%)	0 (0.0%)
	Common	Gastro-oesophageal reflux disease	15 (5.8%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Very common	Skin discolouration	65 (25.3%)	0 (0.0%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	55 (21.4%)	14 (5.4%)	0 (0.0%)
	Very common	Rash***	39 (15.2%)	2 (0.8%)	0 (0.0%)
	Common	Hair colour changes	22 (8.6%)	0 (0.0%)	0 (0.0%)
	Common	Dry skin	15 (5.8%)	0 (0.0%)	0 (0.0%)
Muscoloskeletal, connective tissue and bone disorders	Common	Pain in extremity	21 (8.2%)	1 (0.4%)	0 (0.0%)
	Common	Arthralgia	15 (5.8%)	2 (0.8%)	0 (0.0%)
	Common	Myalgia	13 (5.1%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions	Very common	Fatigue/Asthenia	135 (52.5%)	25 (9.7%)	0 (0.0%)
	Very common	Mucosal Inflammation	30 (11.7%)	0 (0.0%)	0 (0.0%)
	Common	Oedema**	21 (8.2%)	1 (0.4%)	0 (0.0%)

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Investigations	Common	Haemoglobin decreased	16 (6.2%)	2 (0.8%)	0 (0.0%)
	Common	Blood creatinine phosphokinase increased	14 (5.4%)	0 (0.0%)	0 (0.0%)
	Common	Ejection fraction decreased	13 (5.1%)	1 (0.4%)	0 (0.0%)
	Common	Lipase increased	13 (5.1%)	5 (1.9%)	4 (1.6%)
	Common	Platelet count decreased	13 (5.1%)	2 (0.8%)	1 (0.4%)
		Any adverse event	222 (86.4%)	88 (34.2%)	24 (9.3%)

*The following terms have been combined: *abdominal pain*, *abdominal pain upper*, and *abdominal pain lower*.
**The following terms have been combined: oedema and oedema peripheral.
***The following terms have been combined: rash, rash erythematous, rash macular and rash scaly

Adverse <u>Reactions</u> reported in MRCC studies

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Blood and lymphatic system disorders	Very common	Neutropoenia	17 (10.1%)	8 (4.7%)	1 (0.6%)
	Common	Anaemia	16 (9.5%)	6 (3.6%)	0 (0.0%)
	Common	Thrombocytopoenia	15 (8.9%)	5 (3.0%)	2 (1.2%)
	Common	Leucopoenia	14 (8.3%)	7 (4.1%)	0 (0.0%)
Eye disorders	Common	Lacrimation increased	9 (5.3%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	Very common	Anorexia	47 (27.8%)	1 (0.6%)	0 (0.0%)
	Common	Dehydration	12 (7.1%)	4 (2.4%)	0 (0.0%)
	Common	Decreased appetite	11 (6.5%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	Very common	Dysgeusia	71 (42%)	0 (0.0%)	0 (0.0%)
	Very common	Headache	25 (14.8%)	1 (0.6%)	0 (0.0%)
	Common	Dizziness	13 (7.7%)	2 (1.2%)	0 (0.0%)
	Common	Paraesthesia	9 (5.3%)	0 (0.0%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	28 (16.6%)	7 (4.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	16 (9.5%)	0 (0.0%)	0 (0.0%)
	Common	Dyspnoea	9 (5.3%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Diarrhoea	83 (49.1%)	5 (3.0%)	0 (0.0%)
	Very common	Nausea	84 (49.7%)	2 (1.2%)	0 (0.0%)
	Very common	Stomatitis	70 (41.4%)	6 (3.6%)	0 (0.0%)
	Very common	Dyspepsia	69 (40.8%)	1 (0.6%)	0 (0.0%)
	Very common	Vomiting	52 (30.8%)	2 (1.2%)	0 (0.0%)
	Very common	Constipation	34 (20.1%)	0 (0.0%)	0 (0.0%)
	Very common	Glossodynia	25 (14.8%)	0 (0.0%)	0 (0.0%)
	Very common	Abdominal pain*	17 (10.1%)	2 (1.2%)	0 (0.0%)
	Common	Flatulence	16 (9.5%)	0 (0.0%)	0 (0.0%)
	Common	Abdominal distension	9 (5.3%)	0 (0.0%)	0 (0.0%)

System Organ Class	***Frequency***	***Adverse Reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
	Common	Dry mouth	9 (5.3%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Very common	Skin discolouration	54 (32.0%)	0 (0.0%)	0 (0.0%)
	Very common	Rash**	46 (27.2%)	0 (0.0%)	0 (0.0%)
	Very common	Hair colour changes	24 (14.2%)	0 (0.0%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	21 (12.4%)	6 (3.6%)	0 (0.0%)
	Common	Alopecia	13 (7.7%)	0 (0.0%)	0 (0.0%)
	Common	Dermatitis exfoliative	10 (5.9%)	2 (1.2%)	0 (0.0%)
	Common	Periorbital oedema	9 (5.3%)	0 (0.0%)	0 (0.0%)
	Very common	Dry skin	22 (13.0%)	0 (0.0%)	0 (0.0%)
	Very common	Erythema	20 (11.8%)	0 (0.0%)	0 (0.0%)
Muscoloskeletal, connective tissue and bone disorders	Very common	Pain in extremity	21 (12.4)	1 (0.6%)	0 (0.0%)
	Common	Myalgia	15 (8.9%)	1 (0.6%)	0 (0.0%)
General disorders and administration site conditions	Very common	Fatigue/Asthenia	108 (63.9%)	19 (11.2%)	0 (0.0%)
	Very common	Mucosal inflammation	30 (17.8%)	1 (0.6%)	0 (0.0%)
Injury, poisoning, and procedural complications	Very common	Blister	7 (11.1%)	2 (3.2%)	0 (0.0%)
Investigations	Very common	Lipase increased	17 (10.1%)	12 (7.1%)	3 (1.8%)
	Common	Ejection fraction abnormal	16 (9.5%)	1 (0.6%)	0 (0.0%)
	Common	Blood amylase increased	9 (5.3%)	6 (3.6%)	0 (0.0%)
	Common	Weight decreased	11 (6.5%)	0 (0.0%)	0 (0.0%)
	Common	WBC decreased	10 (5.9%)	3 (1.8%)	0 (0.0%)
	Common	Platelet count decreased	9 (5.3%)	3 (1.8%)	2 (1.2%)
		Any adverse event	166 (98.2%)	77 (45.6%)	14 (8.3%)

*The following terms have been combined: *abdominal pain*, *abdominal pain upper*, and *abdominal pain lower*.

**The following terms have been combined: rash, rash erythematous, rash follicular, rash generalized, rash popular and rash pruritic

4.9 Overdose

There is no experience of acute overdosage with SUTENT. There is no specific antidote for overdosage with SUTENT and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed drug may be achieved by emesis or gastric lavage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent - Protein-tyrosine kinase inhibitor
ATC Code :LO1XE04

Sunitinib malate inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was identified as a~~n~~ 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 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

CLINICAL STUDIES
The clinical safety and efficacy of SUTENT has been studied in the treatment of patients with malignant gastrointestinal stromal tumour (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) and the treatment of patients with metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy.
Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC.

Gastrointestinal Stromal Tumours
An initial open-label, dose-escalation study was conducted in patients with GIST after failure of imatinib (Median maximum daily dose 800 mg) due to resistance or intolerance. Ninety-seven patients were enrolled at various doses and schedules; 55 patients received 50 mg at the recommended treatment schedule 4 weeks on /2 weeks off ("schedule 4/2").
In this study the median Time To Progression (TTP) was 34.0 weeks (95% CI = 22.0 – 46.0 weeks).

A phase 3, randomized, double-blind, placebo-controlled study of SUTENT was conducted in patients 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 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 (207 patients received SUTENT and 105 patients received placebo). The primary efficacy endpoint of the study was TTP, defined as the time from randomization to first documentation of objective tumour progression.
The median TTP on SUTENT was 28.9 weeks (95% CI = 21.3-34.1 weeks) and was statistically significantly longer than the TTP of 5.1 weeks (95% CI = 4.4-10.1 weeks) on placebo. The difference in overall survival was statistically in favour of SUTENT [hazard ratio: 0.491 95%(C.I. 0.290- 0.831); the risk of death was 2 times higher in patients in the placebo arm compared to the SUTENT arm. The percentages of deaths were 14% for SUTENT vs 25% for placebo. Median overall survival had not yet been reached in either treatment arm at the time of analysis.

Cytokine-Refractory Metastatic Renal Cell Carcinoma (MRCC)
A phase 2 study of SUTENT was conducted in patients who were refractory to prior cytokine therapy with interleukin-2 or interferon-α. Sixty-three patients received a starting dose of 50 mg of SUTENT orally, once daily for 4 consecutive weeks followed by a 2-week rest period, to comprise a complete cycle of 6 weeks (schedule 4/2). The primary efficacy endpoint was objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumours (RECIST).
In this study the objective response rate was 36.5% (95% C.I. 24.7% - 49.6%) and the median time to progression (TTP) was 37.7 weeks (95% C.I 24.0 - 46.4 weeks).

A confirmatory, open-label, single-arm, multi-centre study evaluating the efficacy and safety of SUTENT was conducted in patients with MRCC who were refractory to prior cytokine therapy. One hundred and six patients received at least one 50 mg dose of SUTENT on Schedule 4/2.

The primary efficacy endpoint of this study was Objective Response Rate (ORR). Secondary endpoints included TTP, duration of response (DR) and overall survival (OS).

In this study the ORR was 38% (95% C.I. 26.8% – 47.5 %). The median DR and OS had not yet been reached.

This medicinal product has been authorised under a "conditional approval" scheme. This means that further evidence on this medicinal product is awaited, in particular about the effect of SUTENT in terms of progression-free survival in patients with MRCC. A study is being conducted to investigate this. The European Medicines Agency (EMEA) will review new information on the product every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and 266 patients with solid tumours.

Absorption
After oral administration of sunitinib, maximum concentrations (C_{max}) are generally observed from 6 – to 12 hours (T_{max}) post-dose.
Food has no effect on the bioavailability of sunitinib

Distribution
Binding of sunitinib and its primary active metabolite to human plasma protein in *in vitro* assays was 95% and 90%, respectively, with no apparent concentration dependence. According to the analysed dataset (10 studies in healthy volunteers and patients, single and multiple doses) the apparent volume of distribution (V/F) for sunitinib was large - 2230 l - indicating distribution into the tissues.

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 inhibit metabolism, to any clinically relevant extent, of drugs that may be metabolized by these enzymes.
In-vitro studies indicate that SUTENT neither induces nor inhibits major CYP enzymes, including CYP3A4.

Biotransformation
Sunitinib is metabolized primarily by CYP3A4, the cytochrome P450 enzyme, which produces its primary active metabolite, which is then further metabolized by CYP3A4.
Concurrent administration of SUTENT with the potent CYP3A4 inducer, rifampin, resulted approximately in a 56% and 78% reduction in sunitinib C_{max} and $AUC_{0-\infty}$, values respectively, after a single dose of SUTENT in healthy volunteers. Administration of SUTENT with other inducers of the CYP3A4 family /(e.g. dexamethasone, phenytoin, carbamazepine, phenobarbital or *Hypericum perforatum*, known also as St. John's Wort) may decrease sunitinib concentrations.

Elimination
Excretion is primarily via faeces (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 faeces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and faeces, but generally were not found in plasma. Total oral clearance (CL/F) was 34-62 L/hr.

Organ Function impairment
Hepatic insufficiency : No clinical studies have been performed in patients with impaired hepatic function
Studies excluded patients with ALT or AST >2.5 x ULN (Upper Limit of Normal) or, if due to underlying disease > 5.0 x ULN.
Renal insufficiency: No clinical studies have been performed in patients with impaired renal function

Studies excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses indicated that sunitinib apparent clearance (CL/F) was not affected by creatinine clearance within the range evaluated (42-347 ml/min).

Plasma Pharmacokinetics

Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40 - 60 hours, and 80 - 110 hours, respectively. In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its 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 is 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 tumour stasis/growth reduction *in vivo*. The primary active metabolite comprises 23 to 37% of the total exposure. No significant changes in the pharmacokinetics of sunitinib or the primary, active metabolite are observed with repeated daily administration or with repeated cycles in the dosing regimens tested. The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers.

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for weight, or ECOG score.
Available data indicate that females might hav about 30% lower apparent clearance (CL/F) of sunitinib than males: this difference however does not necessitate 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 diarrhoea in monkeys), adrenal gland (cortical congestion and/or haemorrhage in rats and monkeys, with necrosis followed by fibrosis in rats), haemolymphopoietic system (bone morrow hypocelularity, 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, pituitary hypertrophy, and testicular tubular atrophy, increased mesangial cells in kidney, haemorrhage 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

Carcinogenicity studies with sunitinib malate have not been performed.

Reproductive and Developmental toxicity

No effects on male or female fertility were observed in reproductive toxicity studies . 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. Effects on male fertility in rat were observed in the form of tubular atrophy in the testes, reduction of spermatozoa in

epididimes and colloid depletion in prostate and seminal vesicles at plasma exposure levels 18-fold higher than is observed in clinic.

In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions increased postimplantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5-fold higher than is observed in clinic. In rabbits, reductions in gravid uterine weights and number of live foetuses were due to increases in the number of resorptions , increases in postimplantation loss, and complete litter loss in 4 of 6 pregnant females at plasma exposure levels 3-fold higher than is observed in clinic.

Sunitinib treatment in rats during organogenesis resulted in developmental effects at ≥5 mg/kg/day consisting of increased incidence of foetal skeletal malformations, predominantly characterized as retarded ossification of thoracic/lumbar vertebrae and occurred at plasma exposure levels 6-fold higher than is observed in clinic. 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-fold higher than is observed in clinic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
- Mannitol
- Croscarmellose Sodium
- Povidone (K-25)
- Magnesium Stearate

Capsule Shell
- Gelatin
- Titanium dioxide (E171)
- Yellow Iron Oxide (E172)
- Red Iron Oxide (E172)
- Black Iron Oxide (E172)

Printing ink.
- Shellac,
- Propylene glycol,
- Sodium hydroxide,
- Povidone
- Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

High-density polypropylene (HDPE) bottles with a polypropylene closure, containing 30 capsules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Ltd
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation:
Due-date for next renewal:

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORIZATION HOLDER RESPONSIBLE OF BATCH RELEASE
B. CONDITIONS OF THE MARKETING AUTHORIZATION
C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

PFIZER Italia S.r.l
Via del Commercio
Zona Industriale
IT-63046 Marino del Tronto (Ascoli Piceno)
Italy

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Risk Management Plan

The Marketing Authorisation Holder commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan, as per the CHMP Guideline on Risk Management Systems for medicinal products for human use, should be submitted at the same time as the PSURs, within 60 days of an important (Pharmacovigilance or Risk minimisation) milestone being reached or when the results of a study becoming available or at the request of the Competent authority.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame. The results of which shall be taken into account in the risk benefit balance during the assessment of the application for a renewal.

Clinical aspects:
The Marketing Authorisation Holder commits to provide results of an ongoing study in cytokine-naive patients with metastatic renal cell carcinoma by September 2006.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

{Outer Carton - 12.5 mg capsules}

1. NAME OF THE MEDICINAL PRODUCT

SUTENT 12.5 mg hard capsules
Sunitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains sunitinib malate, equivalent to 12.5 mg of sunitinib

3. LIST OF EXCIPIENTS

Ingredients of the capsules include mannitol and propylene glycol

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by a doctor

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

<Batch> number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUTENT 12.5 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS {HDPE Bottle – 12.5 mg capsules)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SUTENT 12.5 mg hard capsules
sunitinib
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

<EXP

4. BATCH NUMBER

<Batch> < {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 capsules

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
(Outer Carton – 25 mg capsules)

1. NAME OF THE MEDICINAL PRODUCT

SUTENT 25 mg hard capsules
Sunitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains sunitinib malate, equivalent to 25.0 mg of sunitinib

3. LIST OF EXCIPIENTS

Ingredients of the capsules include mannitol and propylene glycol

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by a doctor

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

<Batch> {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUTENT 25 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
{HDPE Bottle – 25 mg capsules}

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SUTENT 25 mg hard capsules
Sunitnib Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

<EXP >

4. BATCH NUMBER

<Batch> {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 capsules

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
{Outer Carton – 50 mg capsules}

1. NAME OF THE MEDICINAL PRODUCT

SUTENT 50 mg hard capsules
Sunitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains sunitinib malate, equivalent to 50.0 mg of sunitinib.

3. LIST OF EXCIPIENTS

Ingredients of the capsules include mannitol and propylene glycol.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by a doctor

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

<Batch> {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

SUTENT 50 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{HDPE Bottle – 50 mg capsules}

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SUTENT 50 mg hard capsules,
Sunitinib
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

<EXP >

4. BATCH NUMBER

<Batch> {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 capsules

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

SUTENT 12.5 mg hard capsules

Sunitinib

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT SUTENT IS AND WHAT IT IS USED FOR

SUTENT is a medicinal product used to treat cancer by preventing the activity of a special group of proteins which are known to be involved in the growth and spread of cancer cells.

SUTENT will only be prescribed to you by a doctor with experience in medicines to treat renal cell cancer or gastrointestinal stromal tumours.

SUTENT is a medicinal product used in the treatment of renal cell carcinoma, a form of kidney cancer that involves cancerous changes in the cells of the renal tubule.

SUTENT is also used in the treatment of malignant gastrointestinal stromal tumour (GIST). GIST is a cancer of the stomach and bowels. It arises from uncontrolled cell growth of the supporting tissues of these organs. SUTENT inhibits the growth of these cells.

If you have any questions about how SUTENT works or why this medicine has been prescribed for you, ask your doctor.

2. BEFORE YOU TAKE SUTENT

Follow all your doctor's instructions carefully, even if they differ from the general information contained in this leaflet

Do not take SUTENT:
If you are allergic to sunitinib or any of the other ingredients of SUTENT.

Take special care with SUTENT:

- If you have or had liver or kidney problems

- If you have high blood pressure
- If you are pregnant or think you may be (see details below)
- If you are breast-feeding (see detail below)

If any of those apply to you, tell you doctor before you take SUTENT

Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, including herbal medicines (, any medicines that could increase SUTENT concentration like ketoconazole, ritonavir, itraconazole, erythromycin, clarithromycin; or any medicines that could decrease SUTENT concentration like dexamethasone, pheytoin, carbamazepine rifampin, phenobarbital or *Hypericum perforatum* known also as St. John's Wort).

.

Taking SUTENT with food and drink
SUTENT can be taken with or without food; however do not take SUTENT with grapefruit juice.

Pregnancy and breast-feeding
If you are pregnant or think you may be, tell your doctor.
SUTENT is not to be used during pregnancy unless clearly necessary. Your doctor will discuss with you the potential risk of taking SUTENT during pregnancy.
Women who might get pregnant are advised to use effective contraception during treatment with SUTENT.
If you are breast-feeding, tell your doctor. Do not breast-feed during treatment with SUTENT.

Driving and using machines:
If you experience dizziness or you feel unusually tired, take special care when driving or using machines.

3. HOW TO TAKE SUTENT

Your doctor will prescribe a dose that is right for you. It is recommended that SUTENT be taken for 28 days (4 weeks), followed by 14 days (2 weeks) of rest (no medicine) given as a 6-weeks cycle.
Your doctor will determine how many cycles of treatment you will need.

If you take more SUTENT than you should
If you have accidentally taken too many capsules, talk to your doctor straight away. You may require medical attention.

If you forget to take SUTENT
Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, SUTENT can cause side effects, although not everybody gets them.

Very commonly reported side effects, likely to affect more than 10 in 100 people:

- mouth pain/irritation, mouth soreness, taste disturbances, upset stomach, nausea, vomiting, diarrhoea, constipation, abdominal pain, loss of appetite.
- skin discoloration, hair colour change, rash on the palms of the hands and soles of the feet, blisters, dryness of the skin
- tiredness, high blood pressure, migraine
- reduction in the number of: red blood cells and /or white blood cells

Other possible side effects, likely to affect between 1 and 10 in 100 people

- decreased activity of the thyroid gland, reduced heart blood flow
- nose bleeding, abnormally coloured urine, excessive tears flow
- joint pain, muscular pain, excessive fluids in tissues including the eye area
- abnormal sensation of the skin,, shortness of breath
- hair loss, weight loss

If any of the side effect gets serious or if you notice any side effect not listed in this leaflet, please tell your doctor.

5. HOW TO STORE SUTENT

- Keep out of reach and sight of children
- This medicinal product does not require any special storage conditions
- Do not use after the expiry date (EXP) which is stated on the outer pack and label
- Do not use any pack that is damaged or shows signs of tampering

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What SUTENT contains

- The active substance is sunitinib (as malate salt)
- The other ingredients are mannitol, croscarmellose sodium, povidone and magnesium stearate. The capsule shell is composed of gelatin, red iron oxide (E172) and titanium dioxide (E 171). The imprinting ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide

What SUTENT looks like and content of the pack

SUTENT is supplied as hard gelatin capsules with orange cap and orange body, printed with white ink "Pfizer" on the cap, "STN 12,5 mg" on the body. It is available in bottles of 30 capsules.

Marketing Authorisation Holder
Pfizer Limited
Ramsgate Road
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United Kingdom

Manufacturer
Pfizer Italia S.r.l.
Via del Commercio – Zona Industriale -
63046 Marino del Tronto (Ascoli Piceno)
Italy

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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United Kingdom
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Lietuva
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+ 370 52 51 4000

This leaflet was last approved in {date}

This medicine has been given "conditional approval". This means that there is more evidence to come about this medicine, in particular in the treatment of kidney cancer. SUTENT has shown to shrink the tumour. However, more information is awaited on the duration of this effect. The European Medicines Agency (EMEA) will review new information on the medicine every year and this leaflet will be updated as necessary

Detailed information on this medicines is available on the European Medicine Agency (EMEA) website: http://emea.eu.int . There are also links to other websites about rare diseases and treatments.

PACKAGE LEAFLET: INFORMATION FOR THE USER

SUTENT 25 mg hard capsules

Sunitinib

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you .Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT SUTENT IS AND WHAT IT IS USED FOR

SUTENT is a medicinal product used to treat cancer by preventing the activity of a special group of proteins which are known to be involved in the growth and spread of cancer cells.

SUTENT will only be prescribed to you by a doctor with experience in medicines to treat renal cell cancer or gastrointestinal stromal tumours.

SUTENT is a medicinal product used in the treatment of renal cell carcinoma, a form of kidney cancer that involves cancerous changes in the cells of the renal tubule.

SUTENT is also used in the treatment of malignant gastrointestinal stromal tumour (GIST). GIST is a cancer of the stomach and bowels. It arises from uncontrolled cell growth of the supporting tissues of these organs. SUTENT inhibits the growth of these cells.

If you have any questions about how SUTENT works or why this medicine has been prescribed for you, ask your doctor.

2. BEFORE YOU TAKE SUTENT

Follow all your doctor's instructions carefully, even if they differ from the general information contained in this leaflet.

Do not take SUTENT:
If you are allergic to sunitinib or any of the other ingredients of SUTENT

Take special care with SUTENT:

- If you have or had liver or kidney problems
- If you have high blood pressure
- If you are pregnant or think you may be (see details below)
- If you are breast-feeding (see detail below)
- If any of those apply to you, tell you doctor before you take SUTENT

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, including herbal medicines (, any medicines that could increase SUTENT concentration like ketoconazole, ritonavir, itraconazole, erythromycin, clarithromycin; or any medicines that could decrease SUTENT concentration like dexamethasone, pheytoin, carbamazepine rifampin, phenobarbital or *Hypericum perforatum* known also as St. John's Wort).

Taking SUTENT with food and drink
SUTENT can be taken with or without food; however do not take SUTENT with grapefruit juice.

Pregnancy and breast-feeding
If you are pregnant or think you may be, tell your doctor.
SUTENT is not to be used during pregnancy unless clearly necessary. Your doctor will discuss with you the potential risk of taking SUTENT during pregnancy.
Women who might get pregnant are advised to use effective contraception during treatment with SUTENT.
If you are breast-feeding, tell your doctor. Do not breast-feed during treatment with SUTENT.

Driving and using machines
If you experience dizziness or you feel unusually tired, take special care when driving or using machines.

3. HOW TO TAKE SUTENT

Your doctor will prescribe a dose that is right for you. It is recommended that SUTENT be taken for 28 days (4 weeks), followed by 14 days (2 weeks) of rest (no medicine) given as a 6-weeks cycle.
Your doctor will determine how many cycles of treatment you will need.

If you take more SUTENT than you should
If you have accidentally taken too many capsules, talk to your doctor straight away. You may require medical attention.

If you forget to take SUTENT
Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, SUTENT can cause side effects, although not everybody gets them.

Very commonly reported effects likely to affect more than 10 in 100 people

- mouth pain/irritation, mouth soreness, taste disturbances, upset stomach, nausea, vomiting, diarrhoea, constipation, abdominal pain, loss of appetite
- skin discolouration, hair colour change, rash on the palms of the hands and soles of the feet, blisters, dryness of the skin
- tiredness, high blood pressure, migraine
- reduction in the number of red blood cells and/or white blood cells

Other possible side effects likely to affect between 1 and 10 in 100 people

- decreased activity of the thyroid gland, reduced heart blood flow
- nose bleeding, abnormally coloured urine, excessive tears flow
- joint pain, muscular pain, excessive fluids in tissues including the eye area
- abnormal sensation of the skin, shortness of breath
- hair loss, weight loss

If any of the side effect gets serious or if you notice any side effect not listed in this leaflet, please tell your doctor.

5. HOW TO STORE SUTENT

- Keep out of reach and sight of children
- This medicinal product does not require any special storage conditions
- Do not use after the expiry date (EXP), which is stated on the outer pack and label
- Do not use any pack that is damaged or shows signs of tampering

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What SUTENT contains

- The active substance is sunitinib (as malate salt)
- The other ingredients are mannitol, croscarmellose sodium, povidone and magnesium stearate. The capsule shell is composed of gelatin, yellow iron oxide (e 172), red Iron oxide (E172), black iron oxide (E 172) and titanium dioxide (E 171). The imprinting ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

What SUTENT looks like and content of the pack

SUTENT is supplied as hard gelatin capsules with caramel cap and orange body, printed with white ink "Pfizer" on the cap, "STN 25 mg" on the body. It is available in bottles of 30 capsules.

Marketing Authorisation Holder
Pfizer Limited
Ramsgate Road
Sandwich, Kent CT13 9NJ
United Kingdom

Manufacturer
Pfizer Italia S.r.l.
Via del Commercio – Zona Industriale -
63046 Marino del Tronto (Ascoli Piceno)
Italy

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

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PACKAGE LEAFLET: INFORMATION FOR THE USER

SUTENT 50 mg hard capsules

Sunitinib

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If you experience dizziness or you feel unusually tired, take special care when driving or using machines.

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If you have accidentally taken too many capsules, talk to your doctor straight away. You may require medical attention

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What SUTENT looks like and content of the pack

SUTENT is supplied as hard gelatin capsules with caramel cap and caramel body, printed with white ink “Pfizer” on the cap, “STN 50 mg” on the body. It is available in bottles of 30 capsules

Marketing Authorisation Holder
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Ramsgate Road
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Manufacturer
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This leaflet was last approved on {date}

This medicine has been given "conditional approval". This means that there is more evidence to come about this medicine, in particular in the treatment of kidney cancer. SUTENT has shown to shrink the tumour. However, more information is awaited on the duration of this effect. The European Medicines Agency (EMEA) will review new information on the medicine every year and this leaflet will be updated as necessary

Detailed information on this medicines is available on the European Medicine Agency (EMEA) website: http://emea.eu.int . There are also links to other websites about rare diseases and treatments.