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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

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

Gastrointestinal stromal tumour (GIST)
SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance.

Metastatic renal cell carcinoma (MRCC)
SUTENT is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.

Pancreatic neuroendocrine tumours (pNET)
SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.
Experience with SUTENT as first-line treatment is limited (see section 5.1).

4.2 Posology and method of administration

Therapy with sunitinib should be initiated by a physician experienced in the administration of anti-cancer agents.

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

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

Dose adjustments
Safety and tolerability
For GIST and MRCC, dose modifications in 12.5 mg steps may be applied based on individual safety and tolerability. Daily dose should not exceed 75 mg nor be decreased below 25 mg.

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

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

CYP3A4 inhibitors/inducers
Co-administration of sunitinib with potent CYP3A4 inducers, such as rifampicin, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of sunitinib may need to be increased in 12.5 mg steps (up to 87.5 mg per day for GIST and MRCC or 62.5 mg per day for pNET) based on careful monitoring of tolerability.

Co-administration of sunitinib with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of sunitinib may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability.
Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered.

Special populations
Paediatric population
The safety and efficacy of sunitinib in patients below 18 years of age have not been established.
No data are available.
There is no relevant use of sunitinib in children from birth to less than 6 years in the indication of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib treatment due to resistance or intolerance. There is no relevant use of sunitinib in the paediatric population in the indications treatment of advanced/metastatic renal cell carcinoma (MRCC) and treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression.
Use of sunitinib in the paediatric population is not recommended.

Elderly patients (≥ 65 years old)
Approximately one-third of the patients in clinical studies who received sunitinib were 65 years of age or over. No significant differences in safety or effectiveness were observed between younger and older patients.

Hepatic impairment
No starting dose adjustment is recommended when administering sunitinib to patients with mild or moderate (Child-Pugh class A and B) hepatic impairment. Sunitinib has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment and therefore its use in patients with severe hepatic impairment cannot be recommended (see section 5.2).

Renal impairment
No starting dose adjustment is required when administering sunitinib to patients with renal impairment (mild-severe) or with end-stage renal disease (ESRD) on haemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability (see section 5.2).

Method of administration
SUTENT is for oral administration. It 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 the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Co-administration with potent CYP3A4 inducers should be avoided because it may decrease sunitinib plasma concentration (see sections 4.2 and 4.5).

Co-administration with potent CYP3A4 inhibitors should be avoided because it may increase the plasma concentration of sunitinib (see sections 4.2 and 4.5).

Skin and tissue disorders

Skin discolouration, possibly due to the active substance colour (yellow), is a very common adverse reaction occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with sunitinib. Other possible dermatologic effects may include dryness, thickness or cracking of the skin, blisters, or occasional rash on the palms of the hands and soles of the feet.

The above reactions were not cumulative, were typically reversible and generally did not result in treatment discontinuation.Cases of pyoderma gangrenosum, generally reversible after drug discontinuation, have been reported. Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM) and cases suggestive of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). If signs or symptoms of SJS, TEN, or EM (e.g. progressive skin rash often with blisters or mucosal lesions) are present, sunitinib treatment should be discontinued. If the diagnosis of SJS or TEN is confirmed, treatment must not be re-started. In some cases of suspected EM, patients tolerated the reintroduction of sunitinib therapy at a lower dose after resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines.

Haemorrhage and tumour bleeding

Haemorrhagic events, some of which were fatal, reported through post-marketing experience have included gastro-intestinal, respiratory, urinary tract and brain haemorrhages.

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

Epistaxis was the most common haemorrhagic adverse reaction, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. Some of the epistaxis events were severe, but very rarely fatal.

Events of tumour haemorrhage, sometimes associated with tumour necrosis, have been reported; some of these haemorrhagic events were fatal.

In clinical trials, 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. Cases of pulmonary haemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib for MRCC, GIST and lung cancer. SUTENT is not approved for use in patients with lung cancer.

Patients receiving concomitant treatment with anticoagulants (e.g. warfarin, acenocoumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR) and physical examination.

Gastrointestinal disorders

Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia and stomatitis/oral pain were the most commonly reported gastrointestinal adverse reactions; oesophagitis events have been also reported (see section 4.8).

Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with anti-emetic, anti-diarrhoeal or antacid properties.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred in patients with intra-abdominal malignancies treated with sunitinib. Fatal gastrointestinal bleeding occurred in 0.98% of patients receiving placebo in the GIST phase 3 study.

Hypertension
Hypertension was reported in approximately 22.7% of patients with solid tumours. The dose of sunitinib was reduced or its administration temporarily suspended in approximately 2.7% of the patients who experienced hypertension. In none of these patients sunitinib was permanently discontinued. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of patients with solid tumours. Hypertension was reported in approximately 33.9% of patients receiving sunitinib for treatment-naive MRCC compared to 3.6% of patients receiving IFN-α. Severe hypertension occurred in 12% of treatment-naïve patients on sunitinib and <1% of patients on IFN-α. Hypertension was reported in 26.5% of patients receiving sunitinib in a Phase 3 pNET study, compared to 4.9% of patients receiving placebo. Severe hypertension occurred in 10% of pNET patients on sunitinib and 3% of patients on placebo. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

Haematological disorders
Decreased absolute neutrophil counts of grade 3 and 4 severity respectively were reported in 10% and 1.7% of patients on the phase 3 GIST study, in 16% and 1.6% of patients on the phase 3 MRCC study, and in 13% and 2.4% of patients on the phase 3 pNET study. Decreased platelet counts of grade 3 and 4 severity respectively were reported in 3.7% and 0.4% of patients on the phase 3 GIST study, in 8.2% and 1.1% of patients on the phase 3 MRCC study, and in 3.7% and 1.2% of patients on the phase 3 pNET study. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. None of these events in the phase 3 studies were fatal, but rare fatal haematological events, including haemorrhage associated with thrombocytopenia and neutropenic infections, have been reported through post-marketing experience.
Anaemia has been observed to occur early as well as late during treatment with sunitinib; Grade 3 and 4 cases have been reported.
Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with sunitinib.

Cardiac disorders
Cardiovascular events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported in patients treated with sunitinib. These data suggest that sunitinib increases the risk of cardiomyopathy. No specific additional risk factors for sunitinib-induced cardiomyopathy apart from the drug-specific effect have been identified in the treated patients.
In clinical trials, decreases in left ventricular ejection fraction (LVEF) of ≥ 20% and below the lower limit of normal occurred in approximately 2% of sunitinib-treated GIST patients, 4% of cytokine-refractory MRCC patients, and 2% of placebo-treated GIST patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued. In the treatment-naïve MRCC study, 27% patients on sunitinib and 15% of patients on IFN-α had an LVEF value below the lower limit of normal. Two patients (<1%) who received sunitinib were diagnosed with congestive heart failure (CHF).
In GIST patients ‘cardiac failure’, ‘cardiac failure congestive’ or ‘left ventricular failure’ were reported in 1.2% of patients treated with sunitinib and 1% of patients treated with placebo. In the pivotal phase 3 GIST study (n=312), treatment-related fatal cardiac reactions occurred in 1% of patients on each arm of the study (i.e. sunitinib and placebo arms). In a phase 2 study in cytokine-refractory MRCC patients, 0.9% of patients experienced treatment-related fatal myocardial infarction and in the phase 3 study in treatment-naïve MRCC patients, 0.6% of patients on the IFN-α arm and 0% patients on the sunitinib arm experienced fatal cardiac events. In the phase 3 pNET study, one (1%) patient who received sunitinib had treatment-related fatal cardiac failure. 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 sunitinib administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from sunitinib clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction.

Close monitoring for clinical signs and symptoms of CHF should be performed, especially in patients with cardiac risk factors and/or history of coronary artery disease.
Physicians are advised to weigh this risk against the potential benefits of sunitinib. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.
In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. The administration of sunitinib should be interrupted and/or the dose reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

QT interval prolongation
Data from non-clinical (*in vitro* and *in vivo*) studies, at doses higher than the recommended human dose, indicated that sunitinib has the potential to inhibit the cardiac action potential repolarisation process (e.g. prolongation of QT interval).
Increases in the QTc interval to over 500 msec occurred in 0.5%, and changes from baseline in excess of 60 msec occurred in 1.1% of the 450 solid tumour patients; both of these parameters are recognized as potentially significant changes. At approximately twice therapeutic concentrations, sunitinib has been shown to prolong the QTcF Interval (Frederica's Correction).
QTc interval prolongation was investigated in a trial in 24 patients, ages 20-87 years, with advanced malignancies. The results of this study demonstrated that sunitinib had an effect on QTc interval (defined as a mean placebo-adjusted change of > 10 msec with a 90% CI upper limit > 15 msec) at therapeutic concentration (day 3) using the within-day baseline correction method, and at greater than therapeutic concentration (Day 9) using both baseline correction methods. No patients had a QTc interval >500 msec. Although an effect on QTcF interval was observed on Day 3 at 24 hours post-dose (i.e. at therapeutic plasma concentration expected after the recommended starting dose of 50 mg) with the within-day baseline correction method, the clinical significance of this finding is unclear.
Using comprehensive serial ECG assessments at times corresponding to either therapeutic or greater than therapeutic exposures, none of the patients in the evaluable or ITT populations were observed to develop QTc interval prolongation considered as "severe" (i.e. equal to or greater than Grade 3 by CTCAE version 3.0).
At therapeutic plasma concentrations, the maximum QTcF interval (Frederica's correction) mean change from baseline was 9.6 msec (90% CI 15.1msec). At approximately twice therapeutic concentrations, the maximum QTcF interval change from baseline was 15.4 msec (90% CI 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF interval change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 (CTCAE version 3.0).
QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. Torsade de pointes has been observed in <0.1% of sunitinib-exposed patients. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant administration of sunitinib with potent CYP3A4 inhibitors should be limited because of the possible increase in sunitinib plasma concentrations (see section 4.2 and 4.5).

Venous thromboembolic events
Treatment-related venous thromboembolic events were reported in approximately 1.0% of patients with solid tumours who received sunitinib on clinical trials, including GIST and MRCC.
Seven patients (3%) on sunitinib and none on placebo in a phase 3 GIST study experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT) and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.
Thirteen patients (3%) receiving sunitinib in the phase 3 treatment-naïve MRCC study and four patients (2%) on the two cytokine-refractory MRCC studies had venous thromboembolic events reported. Nine of these patients had pulmonary embolisms, one was Grade 2 and eight were Grade 4. Eight of these patients had DVT, one with Grade 1, two with Grade 2, four with Grade 3 and one with

Grade 4. One patient with pulmonary embolism in the cytokine-refractory MRCC study experienced dose interruption.
In treatment-naïve MRCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolisms, all with Grade 4.
Venous thromboembolic events were reported for 1 (1.2%) subject in the sunitinib arm and 5 (6.1%) subjects in the placebo arm in the phase 3 pNET study. Two of these subjects on placebo had DVT, one with Grade 2 and one with Grade 3.
No cases with fatal outcome were reported in GIST, MRCC and pNET registrational studies. Cases with fatal outcome have been observed in post-marketing setting (see respiratory events and section 4.8).

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

Respiratory events
Patients who presented with pulmonary embolism within the previous 12 months were excluded from sunitinib clinical studies.
In patients who received sunitinib in phase 3 registrational studies, pulmonary events (i.e. dyspnoea, pleural effusion, pulmonary embolism or pulmonary oedema) were reported in approximately 17.8% of patients with GIST, in approximately 26.7% of patients with MRCC and in 12% of patients with pNET.
Approximately 22.2% of patients with solid tumours, including GIST and MRCC, who received sunitinib in clinical trials experienced pulmonary events.
Cases of pulmonary embolism were observed in approximately 3.1% of patients with GIST and in approximately 1.2% of patients with MRCC, who received sunitinib in phase 3 studies (see section 4.4 - Venous thromboembolic events). No pulmonary embolism was reported for patients with pNET who received sunitinib in the phase 3 study. Rare cases with fatal outcome have been observed in post-marketing setting (see section 4.8).

Thyroid dysfunction
Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. During sunitinib treatment, routine monitoring of thyroid function should be performed every 3 months. In addition, patients should be observed closely for signs and symptoms of thyroid dysfunction during treatment, and patients who develop any signs and/or symptoms suggestive of thyroid dysfunction should have laboratory testing of thyroid function performed as clinically indicated. Patients who develop thyroid dysfunction should be treated as per standard medical practice.
Hypothyroidism has been observed to occur early as well as late during treatment with sunitinib. Hypothyroidism was reported as an adverse reaction in 7 patients (4%) receiving sunitinib across the two cytokine-refractory MRCC studies; in 61 patients (16%) on sunitinib and three patients (<1%) in the IFN-α arm in the treatment-naïve MRCC study.
Additionally, TSH elevations were reported in 4 cytokine-refractory MRCC patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Acquired hypothyroidism was noted in 8 GIST patients (4%) on sunitinib *versus* 1 (1%) on placebo. In the phase 3 pNET study hypothyroidism was reported in 6 patients (7.2%) receiving sunitinib and in one patient (1.2%) on placebo.
Thyroid function was monitored prospectively in two studies in patients with breast cancer; SUTENT is not approved for use in breast cancer. In one study, hypothyroidism was reported in 15 (13.6%) subjects on sunitinib and 3 (2.9%) subjects on standard of care. Blood TSH increase was reported in 1 (0.9%) subject on sunitinib and no subjects on standard of care. Hyperthyroidism was reported in no

sunitinib-treated subjects and 1 (1.0%) subject receiving standard of care. In the other study hypothyroidism was reported in a total of 31 (13%) sunitinib subjects and 2 (0.8%) capecitabine subjects. Blood TSH increase was reported in 12 (5.0%) sunitinib subjects and no capecitabine subjects. Hyperthyroidism was reported in 4 (1.7%) sunitinib subjects and no capecitabine subjects. Blood TSH decrease was reported in 3 (1.3%) sunitinib subjects and no capecitabine subjects. T4 increase was reported in 2 (0.8%) sunitinib subjects and 1 (0.4%) capecitabine subject. T3 increase was reported in 1 (0.8%) sunitinib subject and no capecitabine subjects. All thyroid-related events reported were Grade 1-2.
Cases of hyperthyroidism, some followed by hypothyroidism, and cases of thyroiditis have been uncommonly reported in clinical trials and through post-marketing experience.

Pancreatitis
Increases in serum lipase and amylase activities were observed in patients with various solid tumours who received sunitinib. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours.
Pancreatitis has been observed uncommonly (<1%) in patients receiving sunitinib for GIST or MRCC.
Cases of serious pancreatic events, some with fatal outcome, have been reported.
If symptoms of pancreatitis are present, patients should have sunitinib discontinued and be provided with appropriate supportive care.
No treatment-related pancreatitis was reported in the phase 3 pNET study.

Hepatotoxicity
Hepatotoxicity has been observed in patients treated with sunitinib. Cases of hepatic failure, some with a fatal outcome, were observed in <1% of solid tumor patients treated with sunitinib. Monitor liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) before initiation of treatment, during each cycle of treatment, and as clinically indicated. If signs or symptoms of hepatic failure are present, sunitinib should be discontinued and appropriate supportive care should be provided.

Hepatobiliary disorders
Sunitinib treatment may be associated with cholecystitis, including acalculous cholecystitis and emphysematous cholecystitis. In clinical registrational studies the incidence of cholecystitis was 0.5%. Post-marketing cases of cholecystitis have been reported.

Renal function
Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.
Risk factors associated with renal impairment/failure in patients receiving sunitinib included, in addition to underlying renal cell carcinoma, older age, diabetes mellitus, underlying renal impairment, cardiac failure, hypertension, sepsis, dehydration/hypovolemia, and rhabdomyolysis.
The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. Discontinue sunitinib in patients with nephrotic syndrome.

Fistula
If fistula formation occurs, sunitinib treatment should be interrupted. Limited information is available on the continued use of sunitinib in patients with fistulae.

Impaired wound healing
Cases of impaired wound healing have been reported during sunitinib therapy.
No formal clinical studies of the effect of sunitinib on wound healing have been conducted.
Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume

sunitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Osteonecrosis of the Jaw (ONJ)
Cases of ONJ have been reported in patients treated with SUTENT. The majority of cases occurred in patients who had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when SUTENT and intravenous bisphosphonates are used either simultaneously or sequentially.
Invasive dental procedures are also an identified risk factor. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 4.8).

Hypersensitivity/angioedema
If angioedema due to hypersensitivity occurs, sunitinib treatment should be interrupted and standard medical care provided.

Nervous system disorders
Taste disturbance
Dysgeusia was reported in approximately 28% of patients receiving sunitinib in clinical trials.

Seizures
In clinical studies of sunitinib and from post-marketing experience, seizures have been observed in subjects with or without radiological evidence of brain metastases. In addition, there have been few reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning and visual loss, including cortical blindness, should be controlled with medical management including control of hypertension. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Tumour Lysis Syndrome (TLS)
Cases of TLS, some fatal, have been rarely observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib. Risk factors for TLS include high tumour burden, preexisting chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated as clinically indicated, and prophylactic hydration should be considered.

Infections
Serious infections, with or without neutropenia, including some with a fatal outcome, have been reported. The infections observed most commonly with sunitinib treatment are infections typically seen in cancer patients, e.g. respiratory, urinary tract, skin infections and sepsis.
Rare cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported. Sunitinib therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

*Medicinal products that may **increase** sunitinib plasma concentrations*
In healthy volunteers, concomitant administration of a single dose of sunitinib with the potent CYP3A4 inhibitor ketoconazole resulted in an increase of the combined [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values of 49% and 51%, respectively.
Administration of sunitinib with potent CYP3A4 inhibitors (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations.

Combination with CYP3A4 inhibitors should therefore be avoided, or the selection of an alternate concomitant medicinal product with no or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dose of SUTENT may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability (see section 4.2).

*Medicinal products that may **decrease** sunitinib plasma concentrations*
In healthy volunteers, concomitant administration of a single dose of sunitinib with the CYP3A4 inducer rifampicin resulted in a reduction of the combined [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values of 23% and 46%, respectively.
Administration of sunitinib with potent CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort*/Hypericum perforatum*) may decrease sunitinib concentrations. Combination with CYP3A4 inducers should therefore be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered. 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 for GIST and MRCC or 62.5 mg per day for pNET), based on careful monitoring of tolerability (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no studies in pregnant women using sunitinib. Studies in animals have shown reproductive toxicity including foetal malformations (see section 5.3). SUTENT should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the foetus. If SUTENT is used during pregnancy or if the patient becomes pregnant while on treatment with SUTENT, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with SUTENT.

Breastfeeding
Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite is excreted in human milk. Because active substances are commonly excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should not breast-feed while taking SUTENT.

Fertility
Based on nonclinical findings, male and female fertility may be compromised by treatment with sunitinib (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most serious adverse reactions associated with sunitinib, some fatal, are renal failure, heart failure, pulmonary embolism, gastrointestinal perforation, and haemorrhages (e.g. respiratory tract, gastrointestinal, tumour, urinary tract, and brain haemorrhages). The most common adverse reactions of any grade (experienced by at least 20% of the patients in RCC, GIST, and pNET registrational trials) included decreased appetite, taste disturbance, hypertension, fatigue, gastrointestinal disorders (i.e. diarrhoea, nausea, stomatitis, dyspepsia and vomiting), skin discolouration, and palmar-plantar erythrodysaesthesia syndrome. These symptoms may diminish as treatment continues. Hypothyroidism may develop during treatment. Haematological disorders (e.g neutropoenia, thrombocyopoenia, and anaemia) are amongst the most common adverse drug reactions.

Fatal events other than those listed in section 4.4 above or in section 4.8 below that were considered possibly related to sunitinib included multi-system organ failure, disseminated intravascular coagulation, peritoneal haemorrhage, rhabdomyolysis, cerebrovascular accident, dehydration, adrenal insufficiency, renal failure, respiratory failure, pleural effusion, pneumothorax, shock, and sudden death.

Tabulated list of adverse reactions

Adverse reactions that were reported in GIST, MRCC, and pNET patients in the phase 2/3 studies are listed below, by system organ class, frequency and grade of severity (NCI-CTCAE). 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), not known (cannot be estimated from the available data).

Table 1 - Adverse reactions reported in clinical trials

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Infections and infestations	Very common	Viral infections[a]	125 (11.4%)	0 (0.0%)	0 (0.0%)
	Common	Respiratory infections[b]	67 (6.1%)	16 (1.5%)	0 (0.0%)
	Common	Abscess[c]	40 (3.7%)	11 (1.0%)	2 (0.2%)
	Common	Fungal infections[d]	16 (1.5%)	1 (0.1%)	1 (0.1%)
	Common	Urinary tract infection	82 (7.5%)	15 (1.4%)	0 (0.0%)
	Common	Skin infections[e]	19 (1.7%)	1 (0.1%)	1 (0.1%)
	Uncommon	Sepsis[f]	6 (0.5%)	2 (0.2%)	3 (0.3%)
	Uncommon	Bacterial infections[g]	10 (0.9%)	2 (0.2%)	3 (0.3%)
Blood and lymphatic system disorders	Very common	Neutropoenia	200 (18.3%)	93 (8.5%)	18 (1.6%)
	Very common	Thrombocytopoenia	181 (16.6%)	62 (5.7%)	13 (1.2%)
	Very common	Anaemia	240 (22.0%)	68 (6.2%)	17 (1.6%)
	Common	Leukopoenia	95 (8.7%)	36 (3.3%)	3 (0.3%)
	Common	Lymphopoenia	38 (3.5%)	18 (1.6%)	2 (0.2%)
	Uncommon	Pancytopenia	3 (0.3%)	2 (0.2%)	0 (0.0%)
Immune system disorders	Uncommon	Hypersensitivity	10 (0.9%)	0 (0.0%)	0 (0.0%)
Endocrine disorders	Very common	Hypothyroidism	157 (14.4%)	13 (1.2%)	2 (0.2%)
	Uncommon	Hyperthyroidism	6 (0.5%)	2 (0.2%)	0 (0.0%)
Metabolism and nutrition disorders	Very common	Decreased appetite[h]	476 (43.5%)	28 (2.6%)	1 (0.1%)
	Common	Dehydration	97 (8.9%)	27 (2.5%)	3 (0.3%)
	Uncommon	Tumour lysis syndrome	2 (0.2%)	1 (0.1%)	0 (0.0%)
Psychiatric disorders	Very common	Insomnia	179 (16.4%)	5 (0.5%)	0 (0.0%)
	Common	Depression	103 (9.4%)	1 (0.1%)	2 (0.2%)
Nervous system disorders	Very common	Dizziness	149 (13.6%)	7 (0.6%)	0 (0.0%)
	Very common	Headache	290 (26.5%)	18 (1.6%)	0 (0.0%)
	Very common	Taste disturbance[i]	392 (35.9%)	2 (0.2%)	0 (0.0%)
	Common	Neuropathy peripheral	95 (8.7%)	5 (0.5%)	0 (0.0%)
	Common	Paraesthesia	93 (8.5%)	2 (0.2%)	0 (0.0%)
	Common	Hypoaesthesia	68 (6.2%)	1 (0.1%)	0 (0.0%)
	Common	Hyperaesthesia	34 (3.1%)	1 (0.1%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Uncommon	Cerebrovascular accident[j]	1 (0.1%)	0 (0.0%)	1 (0.1%)
	Uncommon	Posterior reversible encephalopathy syndrome	2 (0.2%)	0 (0.0%)	1 (0.1%)
	Uncommon	Transient ischaemic attack	3 (0.3%)	0 (0.0%)	2 (0.2%)
Eye disorders	Common	Periorbital oedema	63 (5.8%)	1 (0.1%)	0 (0.0%)
	Common	Eyelid oedema	35 (3.2%)	1 (0.1%)	0 (0.0%)
	Common	Lacrimation increased	57 (5.2%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	Uncommon	Cardiac failure congestive	4 (0.4%)	3 (0.3%)	0 (0.0%)
	Uncommon	Cardiac failure	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Cardiomyopathy	4 (0.4%)	1 (0.1%)	0 (0.0%)
	Uncommon	Pericardial effusion	9 (0.8%)	2 (0.2%)	1 (0.1%)
	Uncommon	Left ventricular failure	1 (0.1%)	0 (0.0%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	334 (30.6%)	120 (11.0%)	0 (0.0%)
	Common	Deep vein thrombosis	19 (1.7%)	11 (1.0%)	0 (0.0%)
	Common	Hot flush	41 (3.8%)	0 (0.0%)	0 (0.0%)
	Common	Flushing	31 (2.8%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea	261 (23.9%)	46 (4.2%)	3 (0.3%)
	Very common	Epistaxis	195 (17.8%)	8 (0.7%)	0 (0.0%)
	Very common	Oropharyngeal pain[k]	111 (10.2%)	2 (0.2%)	0 (0.0%)
	Very common	Cough	225 (20.6%)	6 (0.5%)	0 (0.0%)
	Common	Pulmonary embolism	21 (1.9%)	2 (0.2%)	18 (1.6%)
	Common	Pleural effusion	45 (4.1%)	13 (1.2%)	3 (0.3%)
	Common	Haemoptysis	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Common	Dyspnoea exertional	56 (5.1%)	4 (0.4%)	0 (0.0%)
	Common	Nasal congestion	40 (3.7%)	0 (0.0%)	0 (0.0%)
	Common	Nasal dryness	24 (2.2%)	0 (0.0%)	0 (0.0%)
	Uncommon	Pulmonary haemorrhage	5 (0.5%)	0 (0.0%)	0 (0.0%)
	Uncommon	Respiratory failure	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Stomatitis[l]	321 (29.4%)	24 (2.2%)	0 (0.0%)
	Very common	Abdominal pain[m]	484 (44.3%)	96 (8.8%)	7 (0.6%)
	Very common	Vomiting	423 (38.7%)	40 (3.7%)	0 (0.0%)
	Very common	Diarrhoea	664 (60.8%)	82 (7.5%)	0 (0.0%)
	Very common	Dyspepsia	338 (30.9%)	14 (1.3%)	0 (0.0%)
	Very common	Glossodynia	109 (10.0%)	0 (0.0%)	0 (0.0%)
	Very common	Oral pain	120 (11.0%)	5 (0.5%)	0 (0.0%)
	Very common	Nausea	583 (53.3%)	45 (4.1%)	0 (0.0%)
	Very common	Constipation	312 (28.5%)	12 (1.1%)	1 (0.1%)
	Very common	Flatulence	155 (14.2%)	0 (0.0%)	0 (0.0%)
	Very common	Dry mouth	115 (10.5%)	0 (0.0%)	0 (0.0%)
	Very common	Gastro-oesophageal reflux disease	125 (11.4%)	4 (0.4%)	0 (0.0%)
	Common	Dysphagia	56 (5.1%)	5 (0.5%)	1 (0.1%)
	Common	Oesophagitis	18 (1.6%)	6 (0.5%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Common	Abdominal discomfort	82 (7.5%)	2 (0.2%)	0 (0.0%)
	Common	Rectal haemorrhage	53 (4.8%)	4 (0.4%)	0 (0.0%)
	Common	Gingival bleeding	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Common	Mouth ulceration	21 (1.9%)	0 (0.0%)	1 (0.1%)
	Common	Proctalgia	39 (3.6%)	3 (0.3%)	0 (0.0%)
	Common	Cheilitis	28 (2. 6%)	1 (0.1%)	1 (0.1%)
	Common	Haemorrhoids	81 (7.4%)	0 (0.0%)	0 (0.0%)
	Common	Oral discomfort	19 (1.7%)	0 (0.0%)	0 (0.0%)
	Common	Eructation	22 (2.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Intestinal perforation	2 (0.2%)	2 (0.2%)	0 (0.0%)
	Uncommon	Pancreatitis	9 (0.8%)	3 (0.3%)	0 (0.0%)
	Uncommon	Anal fistula	8 (0.7%)	2 (0.2%)	1 (0.1%)
Hepatobiliary disorders	Uncommon	Hepatic failure	4 (0.4%)	1 (0.1%)	1 (0.1%)
	Uncommon	Hepatitis	1 (0.1%)	1 (0.1%)	0 (0.0%)
	Uncommon	Cholecystitis	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Hepatic function abnormal	4 (0.4%)	1 (0.1%)	1 (0.1%)
Skin and subcutaneous tissue disorders	Very common	Pigmentation disorder[n]	326 (29.8%)	1 (0.1%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	300 (27.4%)	86 (7.9%)	0 (0.0%)
	Very common	Rash[o]	329 (30.1%)	10 (0.9%)	1 (0.1%)
	Very common	Erythema	109 (10.0%)	2 (0.2%)	0 (0.0%)
	Very common	Alopecia	116 (10.6%)	0 (0.0%)	0 (0.0%)
	Very common	Hair colour changes	200 (18.3%)	1 (0.1%)	0 (0.0%)
	Very common	Dry skin	185 (16.9%)	1 (0.1%)	0 (0.0%)
	Common	Skin exfoliation	74 (6.8%)	5 (0.5%)	0 (0.0%)
	Common	Skin Reaction[p]	29 (2.7%)	3 (0.3%)	0 (0.0%)
	Common	Eczema	19 (1.7%)	1 (0.1%)	0 (0.0%)
	Common	Blister	50 (4.6%)	4 (0.4%)	0 (0.0%)
	Common	Acne	31 (2.8%)	0 (0.0%)	0 (0.0%)
	Common	Pruritus	98 (9.0%)	1 (0.1%)	0 (0.0%)
	Common	Skin hyperpigmentation	17 (1.6%)	0 (0.0%)	0 (0.0%)
	Common	Skin lesion	52 (4.8%)	2 (0.2%)	0 (0.0%)
	Common	Hyperkeratosis	38 (3.5%)	7 (0.6%)	0 (0.0%)
	Common	Dermatitis	35 (3.2%)	6 (0.5%)	0 (0.0%)
	Common	Nail disorder[q]	44 (4.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Stevens-Johnson syndrome	1 (0.1%)	1 (0.1%)	0 (0.0%)
	Uncommon	Toxic epidermal necrolysis	1 (0.1%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity	249 (22.8%)	20 (1.8%)	3 (0.3%)
	Very common	Myalgia	128 (11.7%)	7 (0.6%)	0 (0.0%)
	Very common	Arthralgia	253 (23.1%)	19 (1.7%)	1 (0.1%)
	Very common	Musculoskeletal pain	118 (10.8%)	13 (1.2%)	1 (0.1%)
	Very common	Muscle spasms	110 (10.1%)	5 (0.5%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Very common	Back pain	257 (23.5%)	32 (2.9%)	2 (0.2%)
	Common	Muscular weakness	56 (5.1%)	6 (0.5%)	1 (0.1%)
	Uncommon	Osteonecrosis of the jaw	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Fistula	4 (0.4%)	1 (0.1%)	1 (0.1%)
	Uncommon	Myopathy	1 (0.1%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	Common	Renal failure	21 (1.9%)	7 (0.6%)	1 (0.1%)
	Common	Renal failure acute	12 (1.1%)	5 (0.5%)	1 (0.1%)
	Common	Chromaturia	44 (4.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Nephrotic syndrome	2 (0.2%)	1 (0.1%)	1 (0.1%)
	Uncommon	Proteinuria	9 (0.8%)	6 (0.5%)	0 (0.0%)
General disorders and administration site conditions	Very common	Chest Pain	119 (10.9%)	14 (1.3%)	1 (0.1%)
	Very common	Mucosal inflammation	233 (21.3%)	17 (1.6%)	1 (0.1%)
	Very common	Fatigue[r]	834 (76.3%)	204 (18.7%)	13 (1.2%)
	Very common	Oedema [s]	313 (28.6%)	14 (1.3%)	1 (0.1%)
	Very common	Pyrexia	236 (21.6%)	13 (1.2%)	1 (0.1%)
	Very common	Chills	112 (10.2%)	5 (0.5%)	0 (0.0%)
	Common	Pain	95 (8.7%)	12 (1.1%)	1 (0.1%)
	Common	Influenza like illness	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Impaired healing	3 (0.3%)	0 (0.0%)	0 (0.0%)
Investigations	Very common	Ejection fraction decreased[t]	130 (11.9%)	24 (2.2%)	0 (0.0%)
	Very common	Weight decreased	169 (15.5%)	9 (0.8%)	0 (0.0%)
	Common	White blood cell count decreased	86 (7.9%)	36 (3.3%)	0 (0.0 %)
	Common	Lipase increased	81 (7.4%)	36 (3.3%)	21 (1.9%)
	Common	Platelet count decreased	83 (7.6%)	21 (1.9%)	3 (0.3%)
	Common	Haemoglobin decreased	66 (6.0%)	20 (1.8%)	0 (0.0%)
	Common	Blood creatinine phosphokinase increased	44 (4.0%)	9 (0.8%)	4 (0.4%)
	Common	Amylase increased[u]	49 (4.5%)	25 (2.3%)	2 (0.2%)
	Common	Aspartate aminotransferase increased	50 (4.6%)	13 (1.2%)	1 (0.1%)
	Common	Alanine aminotransferase increased	42 (3.8%)	12 (1.1%)	2 (0.2%)
	Common	Blood creatinine increased	75 (6.9%)	9 (0.8%)	1 (0.1%)
	Common	Blood pressure increased	25 (2.3%)	3 (0.3%)	0 (0.0%)
	Common	Blood uric acid increased	21 (1.9%)	1 (0.1%)	12 (1.1%)
	Uncommon	Blood thyroid stimulating hormone increased	9 (0.8%)	0 (0.0%)	0 (0.0%)
	Uncommon	Electrocardiogram QT prolonged	7 (0.6%)	0 (0.0%)	1 (0.1%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
		Any adverse event	1087 (99.5%)	553 (50.6%)	210 (19.2%)

The following terms have been combined:

[a] Nasopharyngitis and oral herpes
[b] Bronchitis, lower respiratory tract infection, pneumonia and respiratory tract infection
[c] Abscess, abscess limb, anal abscess, gingival abscess, liver abscess, pancreatic abscess, perineal abscess, perirectal abscess, rectal abscess, subcutaneous abscess and tooth abscess
[d] Oesophageal candidiasis and oral candidiasis
[e] Cellulitis and skin infection
[f] Sepsis and sepsis shock
[g] Abdominal abscess, abdominal sepsis, diverticulitis and osteomyelitis
[h] Decreased appetite and anorexia
[i] Dysgeusia, ageusia and taste disturbance
[j] Cerebrovascular accident and cerebral infarction
[k] Oropharyngeal and laryngeal pain
[l] Stomatitis and aphtous stomatitis
[m] Abdominal distension and abdominal pain
[n] Yellow skin, skin discolouration and pigmentation disorder
[o] Dermatitis psoriasiform, exfoliative rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic
[p] Skin reaction and skin disorder
[q] Nail disorder and discolouration
[r] Fatigue and asthenia
[s] Face oedema, oedema and oedema peripheral
[t] Ejection fraction decreased/abnormal
[u] Amylase and amylase increased

Table 2 - Adverse reactions identified through post-marketing experience

The following adverse reactions have been identified during post-approval use of SUTENT. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programmes, clinical pharmacology studies and exploratory studies in unapproved indications.

Infections and infestations	
Uncommon*	Necrotising Fasciitis
Blood and lymphatic system disorders	
Uncommon*	Thrombotic microangiopathy
Immune system disorders	
Uncommon*	Angioedema
Endocrine disorders	
Uncommon*	Thyroiditis
Cardiac disorders	
Uncommon *	Torsade de pointes
Skin and subcutaneous tissue disorders	
Uncommon*	Pyoderma gangrenosum
Uncommon*	Erythema multiforme
Musculoskeletal and connective tissue disorders	
Uncommon*	Rhabdomyolysis

* Frequency of the adverse reaction calculated with the 3/X methodology described in the Guideline on Summary of Product Characteristics.

Description of selected adverse reactions
Infection and infestations: Cases of serious infection (with or without neutropoenia), including cases with fatal outcome, have been reported. Cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported (see also section 4.4).

Blood and lymphatic system disorders: Cases of thrombotic microangiopathy have been reported. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Immune system disorders: Hypersensitivity reactions, including angioedema, have been reported.

Nervous system disorders: There have been few reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS) (See also section 4.4).

Endocrine disorders: Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience (see also section 4.4).

Metabolism and nutrition disorders: Cases of TLS, some fatal, have been reported in patients treated with sunitinib.

Cardiac disorders: Cardiac events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported through post-marketing experience (see also section 4.4).

Respiratory, thoracic and mediastinal disorders: Cases of pulmonary embolism and cases of pulmonary haemorrhage, in some cases with fatal outcome, have been reported.

Gastrointestinal disorders: Cases of oesophagitis, in some cases with fatal outcome, have been reported.

Hepatobiliary disorders: Hepatic dysfunction has been reported and may include Liver Function Test abnormalities, hepatitis or liver failure. Cases of cholecystitis, in some cases with fatal outcome, have been reported (see also section 4.4).

Skin and subcutaneous tissue disorders: Cases of pyoderma gangrenosum, generally reversible after drug discontinuation, have been reported (see also section 4.4).

Musculoskeletal and connective tissue disorders: Cases of myopathy and/or rhabdomyolysis, some with acute renal failure, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.
Cases of fistula formation, sometimes associated with tumour necrosis and regression, in some cases with fatal outcomes, have been reported.
Cases of impaired wound healing have been reported during sunitinib therapy.
Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with SUTENT, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4).

Renal and urinary disorders: Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported (see also section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote for overdose with sunitinib and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed active substance may be achieved by emesis or gastric lavage. A few cases of overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of sunitinib, or without adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors; ATC code: L01XE04

Mechanism of action
Sunitinib inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, neoangiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (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 efficacy and safety
The clinical safety and efficacy of sunitinib has been studied in the treatment of patients with 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), the treatment of patients with MRCC and the treatment of patients with unresectable pNET.
Efficacy is based on time to tumour progression and an increase in survival in GIST, on progression free survival and objective response rates for treatment-naïve and cytokine-refractory MRCC respectively, and on progression free survival for pNET.

Gastrointestinal stromal tumours (GIST)
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 Tumour Progression (TTP) was 34.0 weeks (95% CI = 22.0 – 46.0 weeks).
A phase 3, randomized, double-blind, placebo-controlled study of sunitinib 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 sunitinib or placebo, orally once daily on Schedule 4/2 until disease progression or withdrawal from the study for another reason (207 patients received sunitinib 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. At the time of the pre-specified interim analysis, the median TTP on sunitinib was 28.9 weeks (95% CI = 21.3-34.1 weeks) as assessed by the Investigator and 27.3 weeks (95% CI = 16.0-32.1 weeks) as assessed by the Independent Review and was statistically significantly longer than the TTP on placebo of 5.1 weeks (95% CI = 4.4-10.1 weeks) as assessed by the Investigator and 6.4 weeks (95% CI = 4.4-10.0 weeks) as assessed by the Independent Review. The difference in overall survival was statistically in favour of

sunitinib [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 sunitinib arm.
After the interim analysis of efficacy and safety, at recommendation of the Independent DSMB, the study was unblinded and patients on the placebo arm were offered open-label sunitinib treatment.
A total of 255 patients received sunitinib in the open-label treatment phase of the study, including 99 patients who were initially treated with placebo.
The analyses of primary and secondary endpoints in the open-label phase of the study reaffirmed the results obtained at the time of the interim analysis, as shown in the table below:

Table 3 - Summary of Efficacy Endpoints (ITT population)

	Double-Blind Treatment [a]				
	Median (95% CI)		Hazard Ratio		Placebo Cross-Over Group
Endpoint	**SUTENT**	**Placebo**	**(95% CI)**	**p**	**Treatment[b]**
Primary: TTP (weeks)					
Interim	27.3 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.329 (0.233 to 0.466)	<0.001	-
Final	26.6 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.339 (0.244 to 0.472)	<0.001	10.4 (4.3 to 22.0)
Secondary					
PFS (weeks) [c]					
Interim	24.1 (11.1 to 28.3)	6.0 (4.4 to 9.9)	0.333 (0.238 to 0.467)	<0.001	-
Final	22.9 (10.9 to 28.0)	6.0 (4.4 to 9.7)	0.347 (0.253 to 0.475)	<0.001	-
ORR (%)[d]					
Interim	6.8 (3.7 to 11.1)	0 (-)	NA	0.006	-
Final	6.6 (3.8 to 10.5)	0 (-)	NA	0.004	10.1 (5.0 to 17.8)
OS (weeks)[e]					
Interim	-	-	0.491 (0.290 to 0.831)	0.007	-
Final	72.7 (61.3 to 83.0)	64.9 (45.7 to 96.0)	0.876 (0.679 to 1.129)	0.306	-

a Results of double-blind treatment are from the ITT population and using central radiologist measurement, as appropriate.
b Efficacy results for the 99 subjects who crossed over from placebo to SUTENT after unblinding. Baseline was reset at cross-over and efficacy analyses were based on investigators assessment
c The interim PFS numbers have been updated based on a recalculation of the original data
d Results for ORR are given as percent of subjects with confirmed response with the 95% CI.
e Median not achieved because the data were not yet mature.

Median overall survival (OS) in the ITT population was 72.7 weeks and 64.9 weeks (HR 0.876, 95% CI 0.679 – 1.129, p=0.306), in the sunitinib and placebo arms respectively. In this analysis, the placebo arm included those patients randomized to placebo who subsequently received open-label sunitinib treatment.

Treatment-naïve metastatic renal cell carcinoma (MRCC)
A phase 3, randomized, multi-centre international study evaluating the efficacy and safety of sunitinib compared with IFN-α in treatment-naïve MRCC patients was conducted. Seven hundred and fifty patients were randomized 1:1 to the treatment arms; they received treatment with either sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily oral administration followed by 2 weeks of rest (schedule 4/2), or IFN-α, administered as a subcutaneous injection of 3 million units (MU) the

first week, 6 MU the second week, and 9 MU the third week and thereafter, on 3 non-consecutive days each week.

The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for sunitinib treatment and 4.1 months (range: 0.1 – 45.6) for IFN- α treatment. Treatment-related serious adverse events (TRSAEs) were reported in 23.7% of patients receiving sunitinib and in 6.9% of patients receiving IFN-α. However, the discontinuation rates due to adverse events were 20% for sunitinib and 23% for IFN-α. Dose interruptions occurred in 202 patients (54%) on sunitinib and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on sunitinib and 98 patients (27%) on IFN-α. Patients were treated until disease progression or withdrawal from the study. The primary efficacy endpoint was progression free survival (PFS). A planned interim analysis showed a statistically significant advantage for sunitinib over IFN-α, in this study, the median PFS for the sunitinib-treated group was 47.3 weeks, compared with 22.0 weeks for the IFN-α-treated group; the hazard ratio was 0.415 (95% CI: 0.320-0.539, p-value <0.001). Other endpoints included objective response rate (ORR), overall survival (OS) and safety. Core radiology assessment was discontinued after the primary endpoint had been met. At the final analysis, the ORR as determined by the investigators' assessment was 46% (95% CI: 41 - 51) for the sunitinib arm and 12.0% (95% CI: 9 - 16) for the IFN-α arm (p<0.001).

Sunitinib treatment was associated with longer survival compared to IFN-α. The median OS was 114.6 weeks for the sunitinib arm (95% CI: 100.1 - 142.9 weeks) and 94.9 weeks for the IFN-α arm (95% CI: 77.7 - 117.0 weeks) with a hazard ratio of 0.821 (95% CI: 0.673 - 1.001; p=0.0510 by unstratified log-rank).

The overall PFS and OS, observed in the ITT population, as determined by the core radiology laboratory assessment, are summarized in the table below:

Summary of Efficacy Endpoints (ITT population)

Summary of Progression-Free Survival	**Sunitinib (N=375)**	**IFN-α (N=375)**
Subject did not progress or die [n (%)]	161 (42.9)	176 (46.9)
Subject observed to have progressed or died [n (%)]	214 (57.1)	199 (53.1)
PFS (weeks)		
Quartile (95% CI)		
25%	22.7 (18.0 to 34.0)	10.0 (7.3 to 10.3)
50%	48.3 (46.4 to 58.3)	22.1 (17.1 to 24.0)
75%	84.3 (72.9 to 95.1)	58.1 (45.6 to 82.1)
Unstratified Analysis		
Hazard Ratio (sunitinib vs IFN-α)	0.5268	
95% CI for Hazard Ratio	(0.4316 to 0.6430)	
p-value[a]	<0.0001	

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

Summary of Overall Survival	Sunitinib (N = 375)	IFN-α (N = 375)
Subject not known to have died [n (%)]	185 (49.3)	175 (46.7)
Subject observed to have died [n (%)]	190 (50.7)	200 (53.3)
OS (weeks)		
Quartile (95% CI)		
25%	56.6 (48.7 to 68.4)	41.7 (32.6 to 51.6)
50%	114.6 (100.1 to 142.9)	94.9 (77.7 to 117.0)
75%	NA (NA to NA)	NA (NA to NA)
Unstratified Analysis		
Hazard Ratio (sunitinib vs IFN-α)	0.8209	
95% CI for Hazard Ratio	(0.6730 to 1.0013)	
p-value [a]	0.0510	

[a] From a 2-sided log-rank test.
NA: Not Available (Not Reached)

Cytokine-refractory metastatic renal cell carcinoma (MRCC)
A phase 2 study of sunitinib was conducted in patients who were refractory to prior cytokine therapy with interleukin-2 or IFN-α. Sixty-three patients received a starting dose of 50 mg sunitinib 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 sunitinib 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 sunitinib 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 35.8% (95% C.I. 26.8% – 47.5 %). The median DR and OS had not yet been reached.

Pancreatic neuroendocrine tumours (pNET)
A supportive phase 2, open-label, multi-center study evaluated the efficacy and safety of single-agent sunitinib 50 mg daily on Schedule 4/2 [4 weeks on treatment, 2-week rest period] in patients with unresectable pNET. In a pancreatic islet cell tumour cohort of 66 patients, the primary endpoint of response rate was 17%.
A pivotal phase 3, multi-centre, international, randomized, double-blind placebo-controlled study of single-agent sunitinib was conducted in patients with unresectable pNET.
Patients were required to have documented progression, based on RECIST, within the prior 12 months and were randomized (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled rest period (n=86) or placebo (n=85).
The primary objective was to compare Progression-Free Survival (PFS) in patients receiving sunitinib *versus* patients receiving placebo. Other endpoints included Overall Survival (OS), Objective Response Rate (ORR), Patient-reported Outcomes (PRO) and safety.
Demographics were comparable between the sunitinib and placebo groups. Additionally, 49% of sunitinib patients had non-functioning tumours *versus* 52% of placebo patients and 92% patients in both arms had liver metastases.
Use of somatostatin analogs was allowed in the study.
A total of 66% of sunitinib patients received prior systemic therapy compared with 72% of placebo patients. In addition, 24% of sunitinib patients had received somatostatin analogs compared with 22% of placebo patients.
A clinically significant advantage in investigator-assessed PFS for sunitinib over placebo was observed. The median PFS was 11.4 months for the sunitinib arm compared to 5.5 months for the placebo arm [hazard ratio: 0.418 (95% CI 0.263, 0.662), p-value =0.0001]; similar results were observed when derived tumour response assessments based upon application of RECIST to

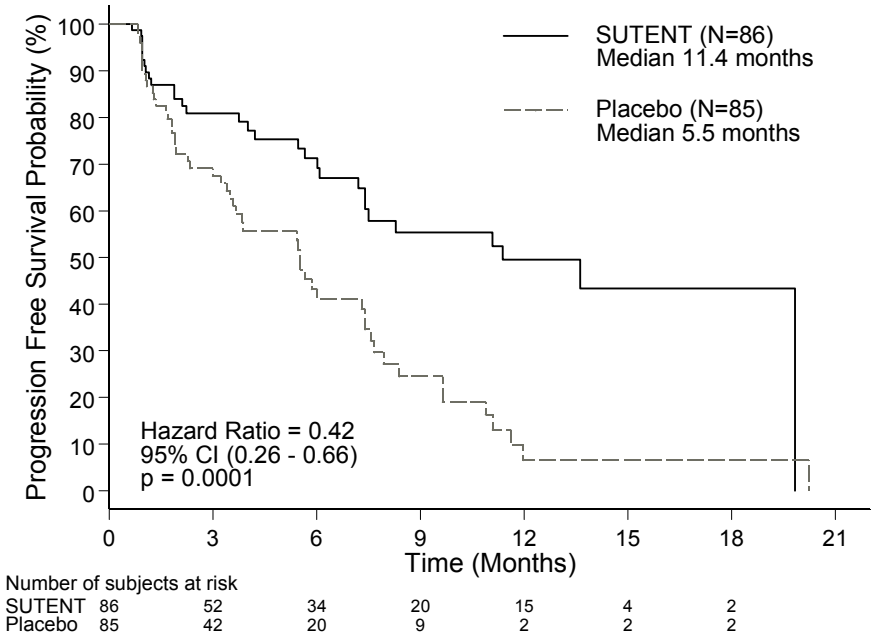
investigator tumour measurements were used to determine disease progression, as shown in Table 4. A hazard ratio favouring sunitinib was observed in all subgroups of baseline characteristics evaluated, including an analysis by number of prior systemic therapies. A total of 29 patients in the sunitinib arm and 24 in the placebo arm had received no prior systemic treatment; among these patients, the hazard ratio for PFS was 0.365 (95% CI 0.156, 0.857), p=0.0156. Similarly, among 57 patients in the sunitinib arm (including 28 with 1 prior systemic therapy and 29 with 2 or more prior systemic therapies) and 61 patients in the placebo arm (including 25 with 1 prior systemic therapy and 36 with 2 or more prior systemic therapies) who had received prior systemic therapy, the hazard ratio for PFS was 0.456 (95% CI 0.264, 0.787), p=0.0036.
A sensitivity analysis of PFS was conducted where progression was based upon investigator-reported tumour measurements and where all subjects censored for reasons other than study termination were treated as PFS events. This analysis provided a conservative estimate of the treatment effect of sunitinib and supported the primary analysis, demonstrating a hazard ratio of 0.507 (95% CI 0.350, 0.733) and p=0.000193. The pivotal study in pancreatic NET was terminated prematurely at the recommendation of an independent Drug Monitoring Committee, and the primary endpoint was based upon investigator assessment, both of which may have affected the estimates of the treatment effect. In order to rule out bias in the investigator-based assessment of PFS, a blinded independent central review of scans was performed and supported the investigator assessment, as shown in Table 4.

Table 4 - pNET Efficacy Results from the Phase 3 Study

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

CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached
[a]2-sided unstratified log-rank test
[b]Fisher's Exact test

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



OS data were not mature at the time of the analysis. There were 9 deaths in the sunitinib arm and 21 deaths in the placebo arm. A statistically significant difference in ORR favouring sunitinib over placebo was observed.
Upon disease progression, patients were unblinded and placebo patients could have been offered access to open-label sunitinib in a separate extension study. As a result of the early study closure, remaining patients were unblinded and offered access to open-label sunitinib in an extension study. A total of 59 patients from the placebo arm received sunitinib in an extension study.
Results from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC-30) showed that the overall global health-related quality of life and the five functioning domains (physical, role, cognitive, emotional and social) were maintained for patients on sunitinib treatment as compared to placebo with limited adverse symptomatic effects.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of the studies with SUTENT in one or more subsets of the paediatric population in gastrointestinal stromal tumours (GIST) (see section 4.2 for information on the paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with SUTENT in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of the studies with SUTENT in all subsets of the paediatric population for treatment of gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of sunitinib has been evaluated in 135 healthy volunteers and 266 patients with solid tumours. The pharmacokinetics were similar in all solid tumours populations tested and in healthy volunteers.
In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and Cmax 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 schedules tested.

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

Distribution
In vitro, binding of sunitinib and its primary active metabolite to human plasma protein was 95% and 90%, respectively, with no apparent concentration dependence. The apparent volume of distribution (V_d) for sunitinib was large, 2230 l, indicating distribution into the tissues.

Metabolic interactions
The calculated *in vitro* Ki values for all cytochrome (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 induce metabolism, to any clinically relevant extent, of other actives substances that may be metabolised by these enzymes.

Biotransformation
Sunitinib is metabolised primarily by CYP3A4, the cytochrome P450 isoform which produces its primary active metabolite, desethyl sunitinib, which is then further metabolized by the same isoenzyme.
Co-administration of sunitinib with potent CYP3A4 inducers or inhibitors should be avoided because the plasma levels of sunitinib may be altered (see sections 4.4 and 4.5).

Elimination
Excretion is primarily via faeces (61%), with renal elimination of unchanged active substance and metabolites accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major 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/h. 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.

Special populations
Hepatic impairment: Sunitinib and its primary metabolite are mainly metabolized by the liver. Systemic exposures after a single dose of sunitinib were similar in subjects with mild or moderate (Child-Pugh class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh class C) hepatic impairment.
Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN (upper limit of normal) or, if due to liver metastasis, > 5.0 x ULN.

Renal impairment: Population pharmacokinetic analyses indicated that sunitinib apparent clearance (CL/F) was not affected by creatinine clearance within the range evaluated (42 - 347 ml/min). Systemic exposures after a single dose of sunitinib were similar in subjects with severe renal impairment (CLcr<30 ml/min) compared to subjects with normal renal function (CLcr>80 ml/min). Although sunitinib and its primary metabolite were not eliminated through hemodialysis in subjects with ESRD, the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function.

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

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

5.3 Preclinical safety data

In rat and monkey repeated-dose toxicity studies up to 9-months duration, the primary target organ effects were identified in the gastrointestinal tract (emesis and 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 hypocellularity, and lymphoid depletion of thymus, spleen, and lymph node), exocrine pancreas (acinar cell degranulation with single cell necrosis), salivary gland (acinar hypertrophy), bone joint (growth plate thickening), uterus (atrophy) and ovaries (decreased follicular development). All findings occurred at clinically relevant sunitinib plasma exposure levels. Additional effects, observed in other studies included QTc interval prolongation, LVEF reduction, pituitary hypertrophy, and testicular tubular atrophy, increased mesangial cells in kidney, haemorrhage in gastro-intestinal 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 genotoxic potential.

Carcinogenicity
In a 1-month, oral gavage dose-range finding study (0, 10, 25, 75, or 200 mg/kg/day) with continuous daily dosing in rasH2 transgenic mice, carcinoma and hyperplasia of Brunner's glands of the duodenum were observed at the highest dose (200 mg/kg/day) tested.
A 6-month, oral gavage carcinogenicity study (0, 8, 25, 75 [reduced to 50] mg/kg/day), with daily dosing was conducted in rasH2 transgenic mice. Gastroduodenal carcinomas, an increased incidence of background haemangiosarcomas, and/or gastric mucosal hyperplasia were observed at doses of ≥25 mg/kg/day following 1- or 6-months duration (≥7.3 times the AUC in patients administered the recommended daily dose [RDD]).
In a 2-year rat carcinogenicity study (0, 0.33, 1, or 3 mg/kg/day), administration of sunitinib in 28-day cycles followed by 7-day dose-free periods resulted in increases in the incidence of pheochromocytomas and hyperplasia in the adrenal medulla of male rats given 3 mg/kg/day following >1 year of dosing (≥7.8 times the AUC in patients administered the RDD). Brunner's glands carcinoma occurred in the duodenum at ≥1 mg/kg/day in females and at 3 mg/kg/day in males, and mucous cell hyperplasia was evident in the glandular stomach at 3 mg/kg/day in males, which occurred at ≥0.9, 7.8 and 7.8 times the AUC in patients administered the RDD, respectively. The

relevance to humans of the neoplastic findings observed in the mouse (rasH2 transgenic) and rat carcinogenicity studies with sunitinib treatment is unclear.

Reproductive and developmental toxicity
No effects on 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 epididymides and colloid depletion in prostate and seminal vesicles at plasma exposure levels 18-fold higher than observed in clinic.
In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions, increased post-implantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5-fold higher than 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 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 5.5-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 observed in clinic.
Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre-and postnatal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at ≥ 1 mg/kg/day but no maternal reproductive toxicity was observed up to 3 mg/kg/day (estimate exposure ≥ 2.3 times the AUC in patients administered the RDD). Reduced offspring body weights were observed during the pre-weaning and post-weaning periods at 3 mg/kg/day. No development toxicity was observed at 1 mg/kg/day (approximate exposure ≥0.9 times the AUC in patients administered the RDD).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Mannitol (E421)
Croscarmellose sodium
Povidone (K-25)
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

3 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 polyethylene (HDPE) bottle with a polypropylene closure containing 30 hard capsules.

Poly(chlorotrifluoroethylene)/PVC transparent perforated unit dose blister with aluminium foil coated with heat seal lacquer containing 28 x 1 hard capsules.

Not all pack sizes may be marketed.

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)

EU/1/06/347/001
EU/1/06/347/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 2006
Date of latest renewal: 9 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

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

Gastrointestinal stromal tumour (GIST)
SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance.

Metastatic renal cell carcinoma (MRCC)
SUTENT is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.

Pancreatic neuroendocrine tumours (pNET)
SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.
Experience with SUTENT as first-line treatment is limited (see section 5.1).

4.2 Posology and method of administration

Therapy with sunitinib should be initiated by a physician experienced in the administration of anti-cancer agents.

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

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

Dose adjustments
Safety and tolerability
For GIST and MRCC, dose modifications in 12.5 mg steps may be applied based on individual safety and tolerability. Daily dose should not exceed 75 mg nor be decreased below 25 mg.

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

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

CYP3A4 inhibitors/inducers
Co-administration of sunitinib with potent CYP3A4 inducers, such as rifampicin, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of sunitinib may need to be increased in 12.5 mg steps (up to 87.5 mg per day for GIST and MRCC or 62.5 mg per day for pNET) based on careful monitoring of tolerability.

Co-administration of sunitinib with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of sunitinib may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability.
Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered.

Special populations
Paediatric population
The safety and efficacy of sunitinib in patients below 18 years of age have not been established.
No data are available.
There is no relevant use of sunitinib in children from birth to less than 6 years in the indication of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib treatment due to resistance or intolerance. There is no relevant use of sunitinib in the paediatric population in the indications treatment of advanced/metastatic renal cell carcinoma (MRCC) and treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression.
Use of sunitinib in the paediatric population is not recommended.

Elderly patients (≥ 65 years old)
Approximately one-third of the patients in clinical studies who received sunitinib were 65 years of age or over. No significant differences in safety or effectiveness were observed between younger and older patients.

Hepatic impairment
No starting dose adjustment is recommended when administering sunitinib to patients with mild or moderate (Child-Pugh class A and B) hepatic impairment. Sunitinib has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment and therefore its use in patients with severe hepatic impairment cannot be recommended (see section 5.2).

Renal impairment
No starting dose adjustment is required when administering sunitinib to patients with renal impairment (mild-severe) or with end-stage renal disease (ESRD) on haemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability (see section 5.2).

Method of administration
SUTENT is for oral administration. It 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 the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Co-administration with potent CYP3A4 inducers should be avoided because it may decrease sunitinib plasma concentration (see sections 4.2 and 4.5).

Co-administration with potent CYP3A4 inhibitors should be avoided because it may increase the plasma concentration of sunitinib (see sections 4.2 and 4.5).

Skin and tissue disorders

Skin discolouration, possibly due to the active substance colour (yellow), is a very common adverse reaction occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with sunitinib. Other possible dermatologic effects may include dryness, thickness or cracking of the skin, blisters, or occasional rash on the palms of the hands and soles of the feet.

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

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

Haemorrhage and tumour bleeding

Haemorrhagic events, some of which were fatal, reported through post-marketing experience have included gastro-intestinal, respiratory, urinary tract and brain haemorrhages.

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

Epistaxis was the most common haemorrhagic adverse reaction, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. Some of the epistaxis events were severe, but very rarely fatal.

Events of tumour haemorrhage, sometimes associated with tumour necrosis, have been reported; some of these haemorrhagic events were fatal.

In clinical trials, 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. Cases of pulmonary haemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib for MRCC, GIST and lung cancer. SUTENT is not approved for use in patients with lung cancer.

Patients receiving concomitant treatment with anticoagulants (e.g. warfarin, acenocoumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR) and physical examination.

Gastrointestinal disorders

Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia and stomatitis/oral pain were the most commonly reported gastrointestinal adverse reactions; oesophagitis events have been also reported (see section 4.8).

Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with anti-emetic, anti-diarrhoeal or antacid properties.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred in patients with intra-abdominal malignancies treated with sunitinib. Fatal gastrointestinal bleeding occurred in 0.98% of patients receiving placebo in the GIST phase 3 study.

Hypertension

Hypertension was reported in approximately 22.7% of patients with solid tumours. The dose of sunitinib was reduced or its administration temporarily suspended in approximately 2.7% of the patients who experienced hypertension. In none of these patients sunitinib was permanently discontinued. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of patients with solid tumours. Hypertension was reported in approximately 33.9% of patients receiving sunitinib for treatment-naïve MRCC, compared to 3.6% of patients receiving IFN-α. Severe hypertension occurred in 12% of treatment-naïve patients on sunitinib and <1% of patients on IFN-α. Hypertension was reported in 26.5% of patients receiving sunitinib in a phase 3 pNET study, compared to 4.9% of patients receiving placebo. Severe hypertension occurred in 10% of pNET patients on sunitinib and 3% of patients on placebo. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

Haematological disorders

Decreased absolute neutrophil counts of grade 3 and 4 severity respectively were reported in 10% and 1.7% of patients on the phase 3 GIST study, in 16% and 1.6% of patients on the phase 3 MRCC study, and in 13% and 2.4% of patients on the phase 3 pNET study. Decreased platelet counts of grade 3 and 4 severity respectively were reported in 3.7% and 0.4% of patients on the phase 3 GIST study, in 8.2% and 1.1% of patients on the phase 3 MRCC study, and in 3.7% and 1.2% of patients on the phase 3 pNET study. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. None of these events in the phase 3 studies were fatal, but rare fatal haematological events, including haemorrhage associated with thrombocytopenia and neutropenic infections, have been reported through post-marketing experience.

Anaemia has been observed to occur early as well as late during treatment with sunitinib; Grade 3 and 4 cases have been reported.

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

Cardiac disorders

Cardiovascular events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported in patients treated with sunitinib. These data suggest that sunitinib increases the risk of cardiomyopathy. No specific additional risk factors for sunitinib-induced cardiomyopathy apart from the drug-specific effect have been identified in the treated patients.

In clinical trials, decreases in left ventricular ejection fraction (LVEF) of ≥ 20% and below the lower limit of normal occurred in approximately 2% of sunitinib-treated GIST patients, 4% of cytokine-refractory MRCC patients, and 2% of placebo-treated GIST patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued. In the treatment-naïve MRCC study, 27% patients on sunitinib and 15% of patients on IFN-α had an LVEF value below the lower limit of normal. Two patients (<1%) who received sunitinib were diagnosed with congestive heart failure (CHF).

In GIST patients ‘cardiac failure’, ‘cardiac failure congestive’ or ‘left ventricular failure’ were reported in 1.2% of patients treated with sunitinib and 1% of patients treated with placebo. In the pivotal phase 3 GIST study (n=312), treatment-related fatal cardiac reactions occurred in 1% of patients on each arm of the study (i.e. sunitinib and placebo arms). In a phase 2 study in cytokine-refractory MRCC patients, 0.9% of patients experienced treatment-related fatal myocardial infarction and in the phase 3 study in treatment-naïve MRCC patients, 0.6% of patients on the IFN-α arm and 0% patients on the sunitinib arm experienced fatal cardiac events. In the phase 3 pNET study, one (1%) patient who received sunitinib had treatment-related fatal cardiac failure. 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 sunitinib administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from sunitinib clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction.

Close monitoring for clinical signs and symptoms of CHF should be performed, especially in patients with cardiac risk factors and/or history of coronary artery disease.
Physicians are advised to weigh this risk against the potential benefits of sunitinib. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.
In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. The administration of sunitinib should be interrupted and/or the dose reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

QT interval prolongation
Data from non-clinical (*in vitro* and *in vivo*) studies, at doses higher than the recommended human dose, indicated that sunitinib has the potential to inhibit the cardiac action potential repolarisation process (e.g. prolongation of QT interval).
Increases in the QTc interval to over 500 msec occurred in 0.5%, and changes from baseline in excess of 60 msec occurred in 1.1% of the 450 solid tumour patients; both of these parameters are recognized as potentially significant changes. At approximately twice therapeutic concentrations, sunitinib has been shown to prolong the QTcF Interval (Frederica's Correction).
QTc interval prolongation was investigated in a trial in 24 patients, ages 20-87 years, with advanced malignancies. The results of this study demonstrated that sunitinib had an effect on QTc interval (defined as a mean placebo-adjusted change of > 10 msec with a 90% CI upper limit > 15 msec) at therapeutic concentration (day 3) using the within-day baseline correction method, and at greater than therapeutic concentration (Day 9) using both baseline correction methods. No patients had a QTc interval >500 msec. Although an effect on QTcF interval was observed on Day 3 at 24 hours post-dose (i.e. at therapeutic plasma concentration expected after the recommended starting dose of 50 mg) with the within-day baseline correction method, the clinical significance of this finding is unclear.
Using comprehensive serial ECG assessments at times corresponding to either therapeutic or greater than therapeutic exposures, none of the patients in the evaluable or ITT populations were observed to develop QTc interval prolongation considered as "severe" (i.e. equal to or greater than Grade 3 by CTCAE version 3.0).
At therapeutic plasma concentrations, the maximum QTcF interval (Frederica's correction) mean change from baseline was 9.6 msec (90% CI 15.1msec). At approximately twice therapeutic concentrations, the maximum QTcF interval change from baseline was 15.4 msec (90% CI 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF interval change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 (CTCAE version 3.0).
QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. Torsade de pointes has been observed in <0.1% of sunitinib-exposed patients. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant administration of sunitinib with potent CYP3A4 inhibitors should be limited because of the possible increase in sunitinib plasma concentrations (see section 4.2 and 4.5).

Venous thromboembolic events
Treatment-related venous thromboembolic events were reported in approximately 1.0% of patients with solid tumours who received sunitinib on clinical trials, including GIST and MRCC.
Seven patients (3%) on sunitinib and none on placebo in a phase 3 GIST study experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT) and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.
Thirteen patients (3%) receiving sunitinib in the phase 3 treatment-naïve MRCC study and four patients (2%) on the two cytokine-refractory MRCC studies had venous thromboembolic events reported. Nine of these patients had pulmonary embolisms, one was Grade 2 and eight were Grade 4. Eight of these patients had DVT, one with Grade 1, two with Grade 2, four with Grade 3 and one with

Grade 4. One patient with pulmonary embolism in the cytokine-refractory MRCC study experienced dose interruption.
In treatment-naïve MRCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolisms, all with Grade 4.
Venous thromboembolic events were reported for 1 (1.2%) subject in the sunitinib arm and 5 (6.1%) subjects in the placebo arm in the phase 3 pNET study. Two of these subjects on placebo had DVT, one with Grade 2 and one with Grade 3.

No cases with fatal outcome were reported in GIST, MRCC and pNET registrational studies. Cases with fatal outcome have been observed in post-marketing setting (see respiratory events and section 4.8).

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

Respiratory events
Patients who presented with pulmonary embolism within the previous 12 months were excluded from sunitinib clinical studies.
In patients who received sunitinib in phase 3 registrational studies, pulmonary events (i.e. dyspnoea, pleural effusion, pulmonary embolism or pulmonary oedema) were reported in approximately 17.8% of patients with GIST, in approximately 26.7% of patients with MRCC and in 12% of patients with pNET.
Approximately 22.2% of patients with solid tumours, including GIST and MRCC, who received sunitinib in clinical trials experienced pulmonary events.
Cases of pulmonary embolism were observed in approximately 3.1% of patients with GIST and in approximately 1.2% of patients with MRCC, who received sunitinib in phase 3 studies (see section 4.4 - Venous thromboembolic events). No pulmonary embolism was reported for patients with pNET who received sunitinib in the phase 3 study. Rare cases with fatal outcome have been observed in post-marketing setting (see section 4.8).

Thyroid dysfunction
Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. During sunitinib treatment, routine monitoring of thyroid function should be performed every 3 months. In addition, patients should be observed closely for signs and symptoms of thyroid dysfunction during treatment, and patients who develop any signs and/or symptoms suggestive of thyroid dysfunction should have laboratory testing of thyroid function performed as clinically indicated. Patients who develop thyroid dysfunction should be treated as per standard medical practice.
Hypothyroidism has been observed to occur early as well as late during treatment with sunitinib. Hypothyroidism was reported as an adverse reaction in 7 patients (4%) receiving sunitinib across the two cytokine-refractory MRCC studies; in 61 patients (16%) on sunitinib and three patients (<1%) in the IFN-α arm in the treatment-naïve MRCC study.
Additionally, TSH elevations were reported in 4 cytokine-refractory MRCC patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Acquired hypothyroidism was noted in 8 GIST patients (4%) on sunitinib *versus* 1 (1%) on placebo. In the phase 3 pNET study hypothyroidism was reported in 6 patients (7.2%) receiving sunitinib and in one patient (1.2%) on placebo.
Thyroid function was monitored prospectively in two studies in patients with breast cancer; SUTENT is not approved for use in breast cancer. In one study, hypothyroidism was reported in 15 (13.6%) subjects on sunitinib and 3 (2.9%) subjects on standard of care. Blood TSH increase was reported in

1 (0.9%) subject on sunitinib and no subjects on standard of care. Hyperthyroidism was reported in no sunitinib-treated subjects and 1 (1.0%) subject receiving standard of care. In the other study hypothyroidism was reported in a total of 31 (13%) sunitinib subjects and 2 (0.8%) capecitabine subjects. Blood TSH increase was reported in 12 (5.0%) sunitinib subjects and no capecitabine subjects. Hyperthyroidism was reported in 4 (1.7%) sunitinib subjects and no capecitabine subjects. Blood TSH decrease was reported in 3 (1.3%) sunitinib subjects and no capecitabine subjects. T4 increase was reported in 2 (0.8%) sunitinib subjects and 1 (0.4%) capecitabine subject. T3 increase was reported in 1 (0.8%) sunitinib subject and no capecitabine subjects. All thyroid-related events reported were Grade 1-2.
Cases of hyperthyroidism, some followed by hypothyroidism, and cases of thyroiditis have been uncommonly reported in clinical trials and through post-marketing experience.

Pancreatitis
Increases in serum lipase and amylase activities were observed in patients with various solid tumours who received sunitinib. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours.
Pancreatitis has been observed uncommonly (<1%) in patients receiving sunitinib for GIST or MRCC. Cases of serious pancreatic events, some with fatal outcome, have been reported.
If symptoms of pancreatitis are present, patients should have sunitinib discontinued and be provided with appropriate supportive care.
No treatment-related pancreatitis was reported in the phase 3 pNET study.

Hepatotoxicity
Hepatotoxicity has been observed in patients treated with sunitinib. Cases of hepatic failure, some with a fatal outcome, were observed in <1% of solid tumor patients treated with sunitinib. Monitor liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) before initiation of treatment, during each cycle of treatment, and as clinically indicated. If signs or symptoms of hepatic failure are present, sunitinib should be discontinued and appropriate supportive care should be provided.

Hepatobiliary disorders
Sunitinib treatment may be associated with cholecystitis, including acalculous cholecystitis and emphysematous cholecystitis. In clinical registrational studies the incidence of cholecystitis was 0.5%. Post-marketing cases of cholecystitis have been reported.

Renal function
Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.
Risk factors associated with renal impairment/failure in patients receiving sunitinib included, in addition to underlying renal cell carcinoma, older age, diabetes mellitus, underlying renal impairment, cardiac failure, hypertension, sepsis, dehydration/hypovolemia, and rhabdomyolysis.
The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. Discontinue sunitinib in patients with nephrotic syndrome.

Fistula
If fistula formation occurs, sunitinib treatment should be interrupted. Limited information is available on the continued use of sunitinib in patients with fistulae.

Impaired wound healing
Cases of impaired wound healing have been reported during sunitinib therapy.
No formal clinical studies of the effect of sunitinib on wound healing have been conducted.
Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of

reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sunitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Osteonecrosis of the Jaw (ONJ)
Cases of ONJ have been reported in patients treated with SUTENT. The majority of cases occurred in patients who had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when SUTENT and intravenous bisphosphonates are used either simultaneously or sequentially.
Invasive dental procedures are also an identified risk factor. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 4.8).

Hypersensitivity/angioedema
If angioedema due to hypersensitivity occurs, sunitinib treatment should be interrupted and standard medical care provided.

Nervous system disorders
Taste disturbance
Dysgeusia was reported in approximately 28% of patients receiving sunitinib in clinical trials.

Seizures
In clinical studies of sunitinib and from post-marketing experience, seizures have been observed in subjects with or without radiological evidence of brain metastases. In addition, there have been few reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning and visual loss, including cortical blindness, should be controlled with medical management including control of hypertension. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Tumour Lysis Syndrome (TLS)
Cases of TLS, some fatal, have been rarely observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib. Risk factors for TLS include high tumour burden, preexisting chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated as clinically indicated, and prophylactic hydration should be considered.

Infections
Serious infections, with or without neutropenia, including some with a fatal outcome, have been reported. The infections observed most commonly with sunitinib treatment are infections typically seen in cancer patients, e.g. respiratory, urinary tract, skin infections and sepsis.
Rare cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported. Sunitinib therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

*Medicinal products that may **increase** sunitinib plasma concentrations*
In healthy volunteers, concomitant administration of a single dose of sunitinib with the potent CYP3A4 inhibitor ketoconazole resulted in an increase of the combined [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values of 49% and 51%, respectively.
Administration of sunitinib with potent CYP3A4 inhibitors (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations.

Combination with CYP3A4 inhibitors should therefore be avoided, or the selection of an alternate concomitant medicinal product with no or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dose of SUTENT may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability (see section 4.2).

*Medicinal products that may **decrease** sunitinib plasma concentrations*
In healthy volunteers, concomitant administration of a single dose of sunitinib with the CYP3A4 inducer rifampicin resulted in a reduction of the combined [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values of 23% and 46%, respectively.
Administration of sunitinib with potent CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort*/Hypericum perforatum*) may decrease sunitinib concentrations. Combination with CYP3A4 inducers should therefore be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered. 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 for GIST and MRCC or 62.5 mg per day for pNET), based on careful monitoring of tolerability (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no studies in pregnant women using sunitinib. Studies in animals have shown reproductive toxicity including foetal malformations (see section 5.3). SUTENT should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the foetus. If SUTENT is used during pregnancy or if the patient becomes pregnant while on treatment with SUTENT, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with SUTENT.

Breastfeeding
Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite is excreted in human milk. Because active substances are commonly excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should not breast-feed while taking SUTENT.

Fertility
Based on nonclinical findings, male and female fertility may be compromised by treatment with sunitinib (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most serious adverse reactions associated with sunitinib, some fatal, are renal failure, heart failure, pulmonary embolism, gastrointestinal perforation, and haemorrhages (e.g. respiratory tract, gastrointestinal, tumour, urinary tract, and brain haemorrhages). The most common adverse reactions of any grade (experienced by at least 20% of the patients in RCC, GIST, and pNET registrational trials) included decreased appetite, taste disturbance, hypertension, fatigue, gastrointestinal disorders (i.e. diarrhoea, nausea, stomatitis, dyspepsia and vomiting), skin discolouration, and palmar-plantar erythrodysaesthesia syndrome. These symptoms may diminish as treatment continues. Hypothyroidism may develop during treatment. Haematological disorders (e.g neutropoenia, thrombocyopoenia, and anaemia) are amongst the most common adverse drug reactions.

Fatal events other than those listed in section 4.4 above or in section 4.8 below that were considered possibly related to sunitinib included multi-system organ failure, disseminated intravascular coagulation, peritoneal haemorrhage, rhabdomyolysis, cerebrovascular accident, dehydration, adrenal insufficiency, renal failure, respiratory failure, pleural effusion, pneumothorax, shock, and sudden death.

Tabulated list of adverse reactions

Adverse reactions that were reported in GIST, MRCC, and pNET patients in the phase 2/3 studies are listed below, by system organ class, frequency and grade of severity (NCI-CTCAE). 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), not known (cannot be estimated from the available data).

Table 1 - Adverse reactions reported in clinical trials

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Infections and infestations	Very common	Viral infections[a]	125 (11.4%)	0 (0.0%)	0 (0.0%)
	Common	Respiratory infections[b]	67 (6.1%)	16 (1.5%)	0 (0.0%)
	Common	Abscess[c]	40 (3.7%)	11 (1.0%)	2 (0.2%)
	Common	Fungal infections[d]	16 (1.5%)	1 (0.1%)	1 (0.1%)
	Common	Urinary tract infection	82 (7.5%)	15 (1.4%)	0 (0.0%)
	Common	Skin infections[e]	19 (1.7%)	1 (0.1%)	1 (0.1%)
	Uncommon	Sepsis[f]	6 (0.5%)	2 (0.2%)	3 (0.3%)
	Uncommon	Bacterial infections[g]	10 (0.9%)	2 (0.2%)	3 (0.3%)
Blood and lymphatic system disorders	Very common	Neutropoenia	200 (18.3%)	93 (8.5%)	18 (1.6%)
	Very common	Thrombocytopoenia	181 (16.6%)	62 (5.7%)	13 (1.2%)
	Very common	Anaemia	240 (22.0%)	68 (6.2%)	17 (1.6%)
	Common	Leukopoenia	95 (8.7%)	36 (3.3%)	3 (0.3%)
	Common	Lymphopoenia	38 (3.5%)	18 (1.6%)	2 (0.2%)
	Uncommon	Pancytopenia	3 (0.3%)	2 (0.2%)	0 (0.0%)
Immune system disorders	Uncommon	Hypersensitivity	10 (0.9%)	0 (0.0%)	0 (0.0%)
Endocrine disorders	Very common	Hypothyroidism	157 (14.4%)	13 (1.2%)	2 (0.2%)
	Uncommon	Hyperthyroidism	6 (0.5%)	2 (0.2%)	0 (0.0%)
Metabolism and nutrition disorders	Very common	Decreased appetite[h]	476 (43.5%)	28 (2.6%)	1 (0.1%)
	Common	Dehydration	97 (8.9%)	27 (2.5%)	3 (0.3%)
	Uncommon	Tumour lysis syndrome	2 (0.2%)	1 (0.1%)	0 (0.0%)
Psychiatric disorders	Very common	Insomnia	179 (16.4%)	5 (0.5%)	0 (0.0%)
	Common	Depression	103 (9.4%)	1 (0.1%)	2 (0.2%)
Nervous system disorders	Very common	Dizziness	149 (13.6%)	7 (0.6%)	0 (0.0%)
	Very common	Headache	290 (26.5%)	18 (1.6%)	0 (0.0%)
	Very common	Taste disturbance[i]	392 (35.9%)	2 (0.2%)	0 (0.0%)
	Common	Neuropathy peripheral	95 (8.7%)	5 (0.5%)	0 (0.0%)
	Common	Paraesthesia	93 (8.5%)	2 (0.2%)	0 (0.0%)
	Common	Hypoaesthesia	68 (6.2%)	1 (0.1%)	0 (0.0%)
	Common	Hyperaesthesia	34 (3.1%)	1 (0.1%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Uncommon	Cerebrovascular accident[j]	1 (0.1%)	0 (0.0%)	1 (0.1%)
	Uncommon	Posterior reversible encephalopathy syndrome	2 (0.2%)	0 (0.0%)	1 (0.1%)
	Uncommon	Transient ischaemic attack	3 (0.3%)	0 (0.0%)	2 (0.2%)
Eye disorders	Common	Periorbital oedema	63 (5.8%)	1 (0.1%)	0 (0.0%)
	Common	Eyelid oedema	35 (3.2%)	1 (0.1%)	0 (0.0%)
	Common	Lacrimation increased	57 (5.2%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	Uncommon	Cardiac failure congestive	4 (0.4%)	3 (0.3%)	0 (0.0%)
	Uncommon	Cardiac failure	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Cardiomyopathy	4 (0.4%)	1 (0.1%)	0 (0.0%)
	Uncommon	Pericardial effusion	9 (0.8%)	2 (0.2%)	1 (0.1%)
	Uncommon	Left ventricular failure	1 (0.1%)	0 (0.0%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	334 (30.6%)	120 (11.0%)	0 (0.0%)
	Common	Deep vein thrombosis	19 (1.7%)	11 (1.0%)	0 (0.0%)
	Common	Hot flush	41 (3.8%)	0 (0.0%)	0 (0.0%)
	Common	Flushing	31 (2.8%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea	261 (23.9%)	46 (4.2%)	3 (0.3%)
	Very common	Epistaxis	195 (17.8%)	8 (0.7%)	0 (0.0%)
	Very common	Oropharyngeal pain[k]	111 (10.2%)	2 (0.2%)	0 (0.0%)
	Very common	Cough	225 (20.6%)	6 (0.5%)	0 (0.0%)
	Common	Pulmonary embolism	21 (1.9%)	2 (0.2%)	18 (1.6%)
	Common	Pleural effusion	45 (4.1%)	13 (1.2%)	3 (0.3%)
	Common	Haemoptysis	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Common	Dyspnoea exertional	56 (5.1%)	4 (0.4%)	0 (0.0%)
	Common	Nasal congestion	40 (3.7%)	0 (0.0%)	0 (0.0%)
	Common	Nasal dryness	24 (2.2%)	0 (0.0%)	0 (0.0%)
	Uncommon	Pulmonary haemorrhage	5 (0.5%)	0 (0.0%)	0 (0.0%)
	Uncommon	Respiratory failure	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Stomatitis[l]	321 (29.4%)	24 (2.2%)	0 (0.0%)
	Very common	Abdominal pain[m]	484 (44.3%)	96 (8.8%)	7 (0.6%)
	Very common	Vomiting	423 (38.7%)	40 (3.7%)	0 (0.0%)
	Very common	Diarrhoea	664 (60.8%)	82 (7.5%)	0 (0.0%)
	Very common	Dyspepsia	338 (30.9%)	14 (1.3%)	0 (0.0%)
	Very common	Glossodynia	109 (10.0%)	0 (0.0%)	0 (0.0%)
	Very common	Oral pain	120 (11.0%)	5 (0.5%)	0 (0.0%)
	Very common	Nausea	583 (53.3%)	45 (4.1%)	0 (0.0%)
	Very common	Constipation	312 (28.5%)	12 (1.1%)	1 (0.1%)
	Very common	Flatulence	155 (14.2%)	0 (0.0%)	0 (0.0%)
	Very common	Dry mouth	115 (10.5%)	0 (0.0%)	0 (0.0%)
	Very common	Gastro-oesophageal reflux disease	125 (11.4%)	4 (0.4%)	0 (0.0%)
	Common	Dysphagia	56 (5.1%)	5 (0.5%)	1 (0.1%)
	Common	Oesophagitis	18 (1.6%)	6 (0.5%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Common	Abdominal discomfort	82 (7.5%)	2 (0.2%)	0 (0.0%)
	Common	Rectal haemorrhage	53 (4.8%)	4 (0.4%)	0 (0.0%)
	Common	Gingival bleeding	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Common	Mouth ulceration	21 (1.9%)	0 (0.0%)	1 (0.1%)
	Common	Proctalgia	39 (3.6%)	3 (0.3%)	0 (0.0%)
	Common	Cheilitis	28 (2. 6%)	1 (0.1%)	1 (0.1%)
	Common	Haemorrhoids	81 (7.4%)	0 (0.0%)	0 (0.0%)
	Common	Oral discomfort	19 (1.7%)	0 (0.0%)	0 (0.0%)
	Common	Eructation	22 (2.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Intestinal perforation	2 (0.2%)	2 (0.2%)	0 (0.0%)
	Uncommon	Pancreatitis	9 (0.8%)	3 (0.3%)	0 (0.0%)
	Uncommon	Anal fistula	8 (0.7%)	2 (0.2%)	1 (0.1%)
Hepatobiliary disorders	Uncommon	Hepatic failure	4 (0.4%)	1 (0.1%)	1 (0.1%)
	Uncommon	Hepatitis	1 (0.1%)	1 (0.1%)	0 (0.0%)
	Uncommon	Cholecystitis	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Hepatic function abnormal	4 (0.4%)	1 (0.1%)	1 (0.1%)
Skin and subcutaneous tissue disorders	Very common	Pigmentation disorder[n]	326 (29.8%)	1 (0.1%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	300 (27.4%)	86 (7.9%)	0 (0.0%)
	Very common	Rash[o]	329 (30.1%)	10 (0.9%)	1 (0.1%)
	Very common	Erythema	109 (10.0%)	2 (0.2%)	0 (0.0%)
	Very common	Alopecia	116 (10.6%)	0 (0.0%)	0 (0.0%)
	Very common	Hair colour changes	200 (18.3%)	1 (0.1%)	0 (0.0%)
	Very common	Dry skin	185 (16.9%)	1 (0.1%)	0 (0.0%)
	Common	Skin exfoliation	74 (6.8%)	5 (0.5%)	0 (0.0%)
	Common	Skin Reaction[p]	29 (2.7%)	3 (0.3%)	0 (0.0%)
	Common	Eczema	19 (1.7%)	1 (0.1%)	0 (0.0%)
	Common	Blister	50 (4.6%)	4 (0.4%)	0 (0.0%)
	Common	Acne	31 (2.8%)	0 (0.0%)	0 (0.0%)
	Common	Pruritus	98 (9.0%)	1 (0.1%)	0 (0.0%)
	Common	Skin hyperpigmentation	17 (1.6%)	0 (0.0%)	0 (0.0%)
	Common	Skin lesion	52 (4.8%)	2 (0.2%)	0 (0.0%)
	Common	Hyperkeratosis	38 (3.5%)	7 (0.6%)	0 (0.0%)
	Common	Dermatitis	35 (3.2%)	6 (0.5%)	0 (0.0%)
	Common	Nail disorder[q]	44 (4.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Stevens-Johnson syndrome	1 (0.1%)	1 (0.1%)	0 (0.0%)
	Uncommon	Toxic epidermal necrolysis	1 (0.1%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity	249 (22.8%)	20 (1.8%)	3 (0.3%)
	Very common	Myalgia	128 (11.7%)	7 (0.6%)	0 (0.0%)
	Very common	Arthralgia	253 (23.1%)	19 (1.7%)	1 (0.1%)
	Very common	Musculoskeletal pain	118 (10.8%)	13 (1.2%)	1 (0.1%)
	Very common	Muscle spasms	110 (10.1%)	5 (0.5%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Very common	Back pain	257 (23.5%)	32 (2.9%)	2 (0.2%)
	Common	Muscular weakness	56 (5.1%)	6 (0.5%)	1 (0.1%)
	Uncommon	Osteonecrosis of the jaw	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Fistula	4 (0.4%)	1 (0.1%)	1 (0.1%)
	Uncommon	Myopathy	1 (0.1%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	Common	Renal failure	21 (1.9%)	7 (0.6%)	1 (0.1%)
	Common	Renal failure acute	12 (1.1%)	5 (0.5%)	1 (0.1%)
	Common	Chromaturia	44 (4.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Nephrotic syndrome	2 (0.2%)	1 (0.1%)	1 (0.1%)
	Uncommon	Proteinuria	9 (0.8%)	6 (0.5%)	0 (0.0%)
General disorders and administration site conditions	Very common	Chest Pain	119 (10.9%)	14 (1.3%)	1 (0.1%)
	Very common	Mucosal inflammation	233 (21.3%)	17 (1.6%)	1 (0.1%)
	Very common	Fatigue[r]	834 (76.3%)	204 (18.7%)	13 (1.2%)
	Very common	Oedema [s]	313 (28.6%)	14 (1.3%)	1 (0.1%)
	Very common	Pyrexia	236 (21.6%)	13 (1.2%)	1 (0.1%)
	Very common	Chills	112 (10.2%)	5 (0.5%)	0 (0.0%)
	Common	Pain	95 (8.7%)	12 (1.1%)	1 (0.1%)
	Common	Influenza like illness	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Impaired healing	3 (0.3%)	0 (0.0%)	0 (0.0%)
Investigations	Very common	Ejection fraction decreased[t]	130 (11.9%)	24 (2.2%)	0 (0.0%)
	Very common	Weight decreased	169 (15.5%)	9 (0.8%)	0 (0.0%)
	Common	White blood cell count decreased	86 (7.9%)	36 (3.3%)	0 (0.0 %)
	Common	Lipase increased	81 (7.4%)	36 (3.3%)	21 (1.9%)
	Common	Platelet count decreased	83 (7.6%)	21 (1.9%)	3 (0.3%)
	Common	Haemoglobin decreased	66 (6.0%)	20 (1.8%)	0 (0.0%)
	Common	Blood creatinine phosphokinase increased	44 (4.0%)	9 (0.8%)	4 (0.4%)
	Common	Amylase increased[u]	49 (4.5%)	25 (2.3%)	2 (0.2%)
	Common	Aspartate aminotransferase increased	50 (4.6%)	13 (1.2%)	1 (0.1%)
	Common	Alanine aminotransferase increased	42 (3.8%)	12 (1.1%)	2 (0.2%)
	Common	Blood creatinine increased	75 (6.9%)	9 (0.8%)	1 (0.1%)
	Common	Blood pressure increased	25 (2.3%)	3 (0.3%)	0 (0.0%)
	Common	Blood uric acid increased	21 (1.9%)	1 (0.1%)	12 (1.1%)
	Uncommon	Blood thyroid stimulating hormone increased	9 (0.8%)	0 (0.0%)	0 (0.0%)
	Uncommon	Electrocardiogram QT prolonged	7 (0.6%)	0 (0.0%)	1 (0.1%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
		Any adverse event	1087 (99.5%)	553 (50.6%)	210 (19.2%)

The following terms have been combined:

[a] Nasopharyngitis and oral herpes
[b] Bronchitis, lower respiratory tract infection, pneumonia and respiratory tract infection
[c] Abscess, abscess limb, anal abscess, gingival abscess, liver abscess, pancreatic abscess, perineal abscess, perirectal abscess, rectal abscess, subcutaneous abscess and tooth abscess
[d] Oesophageal candidiasis and oral candidiasis
[e] Cellulitis and skin infection
[f] Sepsis and sepsis shock
[g] Abdominal abscess, abdominal sepsis, diverticulitis and osteomyelitis
[h] Decreased appetite and anorexia
[i] Dysgeusia, ageusia and taste disturbance
[j] Cerebrovascular accident and cerebral infarction
[k] Oropharyngeal and laryngeal pain
[l] Stomatitis and aphtous stomatitis
[m] Abdominal distension and abdominal pain
[n] Yellow skin, skin discolouration and pigmentation disorder
[o] Dermatitis psoriasiform, exfoliative rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic
[p] Skin reaction and skin disorder
[q] Nail disorder and discolouration
[r] Fatigue and asthenia
[s] Face oedema, oedema and oedema peripheral
[t] Ejection fraction decreased/abnormal
[u] Amylase and amylase increased

Table 2 - Adverse reactions identified through post-marketing experience

The following adverse reactions have been identified during post-approval use of SUTENT. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programmes, clinical pharmacology studies and exploratory studies in unapproved indications.

Infections and infestations	
Uncommon*	Necrotising Fasciitis
Blood and lymphatic system disorders	
Uncommon*	Thrombotic microangiopathy
Immune system disorders	
Uncommon*	Angioedema
Endocrine disorders	
Uncommon*	Thyroiditis
Cardiac disorders	
Uncommon*	Torsade de pointes
Skin and subcutaneous tissue disorders	
Uncommon*	Pyoderma gangrenosum
Uncommon*	Erythema multiforme
Musculoskeletal and connective tissue disorders	
Uncommon*	Rhabdomyolysis

* Frequency of the adverse reaction calculated with the 3/X methodology described in the Guideline on Summary of Product Characteristics.

Description of selected adverse reactions
Infection and infestations: Cases of serious infection (with or without neutropoenia), including cases with fatal outcome, have been reported. Cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported (see also section 4.4).

Blood and lymphatic system disorders: Cases of thrombotic microangiopathy have been reported. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Immune system disorders: Hypersensitivity reactions, including angioedema, have been reported.

Nervous system disorders: There have been few reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS) (See also section 4.4).

Endocrine disorders: Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience (see also section 4.4).

Metabolism and nutrition disorders: Cases of TLS, some fatal, have been reported in patients treated with sunitinib.

Cardiac disorders: Cardiac events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported through post-marketing experience (see also section 4.4).

Respiratory, thoracic and mediastinal disorders: Cases of pulmonary embolism and cases of pulmonary haemorrhage, in some cases with fatal outcome, have been reported.

Gastrointestinal disorders: Cases of oesophagitis, in some cases with fatal outcome, have been reported.

Hepatobiliary disorders: Hepatic dysfunction has been reported and may include Liver Function Test abnormalities, hepatitis or liver failure. Cases of cholecystitis, in some cases with fatal outcome, have been reported (see also section 4.4).

Skin and subcutaneous tissue disorders: Cases of pyoderma gangrenosum, generally reversible after drug discontinuation, have been reported (see also section 4.4).

Musculoskeletal and connective tissue disorders: Cases of myopathy and/or rhabdomyolysis, some with acute renal failure, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.
Cases of fistula formation, sometimes associated with tumour necrosis and regression, in some cases with fatal outcomes, have been reported.
Cases of impaired wound healing have been reported during sunitinib therapy.
Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with SUTENT, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4).

Renal and urinary disorders: Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported. (see also section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote for overdose with sunitinib and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed active substance may be achieved by emesis or gastric lavage. A few cases of overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of sunitinib, or without adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors; ATC code: L01XE04

Mechanism of action
Sunitinib inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, neoangiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (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 efficacy and safety
The clinical safety and efficacy of sunitinib has been studied in the treatment of patients with 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), the treatment of patients with MRCC and the treatment of patients with unresectable pNET.
Efficacy is based on time to tumour progression and an increase in survival in GIST, on progression free survival and objective response rates for treatment-naïve and cytokine-refractory MRCC respectively, and on progression free survival for pNET.

Gastrointestinal stromal tumours (GIST)
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 Tumour Progression (TTP) was 34.0 weeks (95% CI = 22.0 – 46.0 weeks).
A phase 3, randomized, double-blind, placebo-controlled study of sunitinib 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 sunitinib or placebo, orally once daily on Schedule 4/2 until disease progression or withdrawal from the study for another reason (207 patients received sunitinib 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. At the time of the pre-specified interim analysis, the median TTP on sunitinib was 28.9 weeks (95% CI = 21.3-34.1 weeks) as assessed by the Investigator and 27.3 weeks (95% CI = 16.0-32.1 weeks) as assessed by the Independent Review and was statistically significantly longer than the TTP on placebo of 5.1 weeks (95% CI = 4.4-10.1 weeks) as assessed by the Investigator and 6.4 weeks (95% CI = 4.4-10.0 weeks) as assessed by the Independent Review. The difference in overall survival was statistically in favour of

sunitinib [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 sunitinib arm.
After the interim analysis of efficacy and safety, at recommendation of the Independent DSMB, the study was unblinded and patients on the placebo arm were offered open-label sunitinib treatment.
A total of 255 patients received sunitinib in the open-label treatment phase of the study, including 99 patients who were initially treated with placebo.
The analyses of primary and secondary endpoints in the open-label phase of the study reaffirmed the results obtained at the time of the interim analysis, as shown in the table below:

Table 3 - Summary of Efficacy Endpoints (ITT population)

	Double-Blind Treatment [a]				
	Median (95% CI)		Hazard Ratio		Placebo Cross-Over Group
Endpoint	**SUTENT**	**Placebo**	**(95% CI)**	**p**	**Treatment[b]**
Primary: TTP (weeks)					
Interim	27.3 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.329 (0.233 to 0.466)	<0.001	-
Final	26.6 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.339 (0.244 to 0.472)	<0.001	10.4 (4.3 to 22.0)
Secondary					
PFS (weeks) [c]					
Interim	24.1 (11.1 to 28.3)	6.0 (4.4 to 9.9)	0.333 (0.238 to 0.467)	<0.001	-
Final	22.9 (10.9 to 28.0)	6.0 (4.4 to 9.7)	0.347 (0.253 to 0.475)	<0.001	-
ORR (%)[d]					
Interim	6.8 (3.7 to 11.1)	0 (-)	NA	0.006	-
Final	6.6 (3.8 to 10.5)	0 (-)	NA	0.004	10.1 (5.0 to 17.8)
OS (weeks)[e]					
Interim	-	-	0.491 (0.290 to 0.831)	0.007	-
Final	72.7 (61.3 to 83.0)	64.9 (45.7 to 96.0)	0.876 (0.679 to 1.129)	0.306	-

a Results of double-blind treatment are from the ITT population and using central radiologist measurement, as appropriate.
b Efficacy results for the 99 subjects who crossed over from placebo to SUTENT after unblinding. Baseline was reset at cross-over and efficacy analyses were based on investigators assessment
c The interim PFS numbers have been updated based on a recalculation of the original data
d Results for ORR are given as percent of subjects with confirmed response with the 95% CI.
e Median not achieved because the data were not yet mature.

Median overall survival (OS) in the ITT population was 72.7 weeks and 64.9 weeks (HR 0.876, 95% CI 0.679 – 1.129, p=0.306), in the sunitinib and placebo arms respectively. In this analysis, the placebo arm included those patients randomized to placebo who subsequently received open-label sunitinib treatment.

Treatment-naïve metastatic renal cell carcinoma (MRCC)
A phase 3, randomized, multi-centre international study evaluating the efficacy and safety of sunitinib compared with IFN-α in treatment-naïve MRCC patients was conducted. Seven hundred and fifty patients were randomized 1:1 to the treatment arms; they received treatment with either sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily oral administration followed by 2 weeks of rest (schedule 4/2), or IFN-α, administered as a subcutaneous injection of 3 million units (MU) the

first week, 6 MU the second week, and 9 MU the third week and thereafter, on 3 non-consecutive days each week.
The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for sunitinib treatment and 4.1 months (range: 0.1 – 45.6) for IFN- α treatment. Treatment-related serious adverse events (TRSAEs) were reported in 23.7% of patients receiving sunitinib and in 6.9% of patients receiving IFN-α. ,. However, the discontinuation rates due to adverse events were 20% for sunitinib and 23% for IFN-α. Dose interruptions occurred in 202 patients (54%) on sunitinib and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on sunitinib and 98 patients (27%) on IFN-α.
Patients were treated until disease progression or withdrawal from the study. The primary efficacy endpoint was progression free survival (PFS). A planned interim analysis showed a statistically significant advantage for sunitinib over IFN-α, in this study, the median PFS for the sunitinib-treated group was 47.3 weeks, compared with 22.0 weeks for the IFN-α-treated group; the hazard ratio was 0.415 (95% CI: 0.320-0.539, p-value <0.001). Other endpoints included objective response rate (ORR), overall survival (OS) and safety. Core radiology assessment was discontinued after the primary endpoint had been met. At the final analysis, the ORR as determined by the investigators' assessment was 46% (95% CI: 41 - 51) for the sunitinib arm and 12.0% (95% CI: 9 - 16) for the IFN-α arm (p<0.001).
Sunitinib treatment was associated with longer survival compared to IFN-α. The median OS was 114.6 weeks for the sunitinib arm (95% CI: 100.1 - 142.9 weeks) and 94.9 weeks for the IFN-α arm (95% CI: 77.7 - 117.0 weeks) with a hazard ratio of 0.821 (95% CI: 0.673 - 1.001; p=0.0510 by unstratified log-rank).
The overall PFS and OS, observed in the ITT population, as determined by the core radiology laboratory assessment, are summarized in the table below:

Summary of Efficacy Endpoints (ITT population)

Summary of Progression-Free Survival	**Sunitinib (N=375)**	**IFN-α (N=375)**
Subject did not progress or die [n (%)]	161 (42.9)	176 (46.9)
Subject observed to have progressed or died [n (%)]	214 (57.1)	199 (53.1)
PFS (weeks)		
Quartile (95% CI)		
25%	22.7 (18.0 to 34.0)	10.0 (7.3 to 10.3)
50%	48.3 (46.4 to 58.3)	22.1 (17.1 to 24.0)
75%	84.3 (72.9 to 95.1)	58.1 (45.6 to 82.1)
Unstratified Analysis		
Hazard Ratio (sunitinib vs IFN-α)	0.5268	
95% CI for Hazard Ratio	(0.4316 to 0.6430)	
p-value[a]	<0.0001	

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

Summary of Overall Survival	**Sunitinib (N = 375)**	**IFN-α (N = 375)**
Subject not known to have died [n (%)]	185 (49.3)	175 (46.7)
Subject observed to have died [n (%)]	190 (50.7)	200 (53.3)
OS (weeks)		
Quartile (95% CI)		
25%	56.6 (48.7 to 68.4)	41.7 (32.6 to 51.6)
50%	114.6 (100.1 to 142.9)	94.9 (77.7 to 117.0)
75%	NA (NA to NA)	NA (NA to NA)
Unstratified Analysis		
Hazard Ratio (sunitinib vs IFN-α)	0.8209	
95% CI for Hazard Ratio	(0.6730 to 1.0013)	
p-value[a]	0.0510	

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

NA: Not Available (Not Reached)

Cytokine-refractory metastatic renal cell carcinoma (MRCC)
A phase 2 study of sunitinib was conducted in patients who were refractory to prior cytokine therapy with interleukin-2 or IFN-α. Sixty-three patients received a starting dose of 50 mg sunitinib 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 sunitinib 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 sunitinib 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 35.8% (95% C.I. 26.8% – 47.5 %). The median DR and OS had not yet been reached.

Pancreatic neuroendocrine tumours (pNET)
A supportive phase 2, open-label, multi-center study evaluated the efficacy and safety of single-agent sunitinib 50 mg daily on Schedule 4/2 [4 weeks on treatment, 2-week rest period] in patients with unresectable pNET. In a pancreatic islet cell tumour cohort of 66 patients, the primary endpoint of response rate was 17%.
A pivotal phase 3, multi-centre, international, randomized, double-blind placebo-controlled study of single-agent sunitinib was conducted in patients with unresectable pNET.
Patients were required to have documented progression, based on RECIST, within the prior 12 months and were randomized (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled rest period (n=86) or placebo (n=85).
The primary objective was to compare Progression-Free Survival (PFS) in patients receiving sunitinib *versus* patients receiving placebo. Other endpoints included Overall Survival (OS), Objective Response Rate (ORR), Patient-reported Outcomes (PRO) and safety.
Demographics were comparable between the sunitinib and placebo groups. Additionally, 49% of sunitinib patients had non-functioning tumours *versus* 52% of placebo patients and 92% patients in both arms had liver metastases.
Use of somatostatin analogs was allowed in the study.
A total of 66% of sunitinib patients received prior systemic therapy compared with 72% of placebo patients. In addition, 24% of sunitinib patients had received somatostatin analogs compared with 22% of placebo patients.
A clinically significant advantage in investigator-assessed PFS for sunitinib over placebo was observed. The median PFS was 11.4 months for the sunitinib arm compared to 5.5 months for the placebo arm [hazard ratio: 0.418 (95% CI 0.263, 0.662), p-value =0.0001]; similar results were observed when derived tumour response assessments based upon application of RECIST to investigator tumour measurements were used to determine disease progression, as shown in Table 4. A hazard ratio favouring sunitinib was observed in all subgroups of baseline characteristics evaluated, including an analysis by number of prior systemic therapies. A total of 29 patients in the sunitinib arm and 24 in the placebo arm had received no prior systemic treatment; among these patients, the hazard ratio for PFS was 0.365 (95% CI 0.156, 0.857), p=0.0156. Similarly, among 57 patients in the sunitinib arm (including 28 with 1 prior systemic therapy and 29 with 2 or more prior systemic therapies) and 61 patients in the placebo arm (including 25 with 1 prior systemic therapy and 36 with 2 or more prior systemic therapies) who had received prior systemic therapy, the hazard ratio for PFS was 0.456 (95% CI 0.264, 0.787), p=0.0036.
A sensitivity analysis of PFS was conducted where progression was based upon investigator-reported tumour measurements and where all subjects censored for reasons other than study termination were treated as PFS events. This analysis provided a conservative estimate of the treatment effect of sunitinib and supported the primary analysis, demonstrating a hazard ratio of 0.507 (95% CI 0.350, 0.733) and p=0.000193. The pivotal study in pancreatic NET was terminated prematurely at the

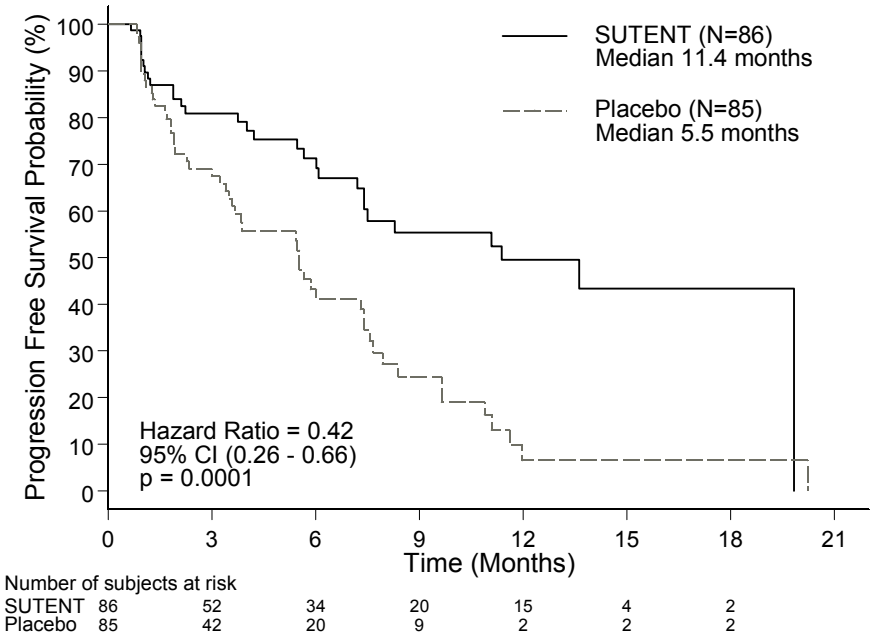
recommendation of an independent Drug Monitoring Committee, and the primary endpoint was based upon investigator assessment, both of which may have affected the estimates of the treatment effect. In order to rule out bias in the investigator-based assessment of PFS, a blinded independent central review of scans was performed and supported the investigator assessment, as shown in Table 4.

Table 4 - pNET Efficacy Results from the Phase 3 Study

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

CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached
[a]2-sided unstratified log-rank test
[b]Fisher's Exact test

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



OS data were not mature at the time of the analysis. There were 9 deaths in the sunitinib arm and 21 deaths in the placebo arm. A statistically significant difference in ORR favouring sunitinib over placebo was observed.
Upon disease progression, patients were unblinded and placebo patients could have been offered access to open-label sunitinib in a separate extension study. As a result of the early study closure, remaining patients were unblinded and offered access to open-label sunitinib in an extension study. A total of 59 patients from the placebo arm received sunitinib in an extension study.
Results from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC-30) showed that the overall global health-related quality of life and the five functioning domains (physical, role, cognitive, emotional and social) were maintained for patients on sunitinib treatment as compared to placebo with limited adverse symptomatic effects.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of the studies with SUTENT in one or more subsets of the paediatric population in gastrointestinal stromal tumours (GIST) (see section 4.2 for information on the paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with SUTENT in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of the studies with SUTENT in all subsets of the paediatric population for treatment of gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of sunitinib has been evaluated in 135 healthy volunteers and 266 patients with solid tumours. The pharmacokinetics were similar in all solid tumours populations tested and in healthy volunteers.
In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and Cmax 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 schedules tested.

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

Distribution
In vitro, binding of sunitinib and its primary active metabolite to human plasma protein was 95% and 90%, respectively, with no apparent concentration dependence. The apparent volume of distribution (V_d) for sunitinib was large, 2230 l, indicating distribution into the tissues.

Metabolic interactions
The calculated *in vitro* Ki values for all cytochrome (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 induce metabolism, to any clinically relevant extent, of other actives substances that may be metabolised by these enzymes.

Biotransformation
Sunitinib is metabolised primarily by CYP3A4, the cytochrome P450 isoform which produces its primary active metabolite, desethyl sunitinib, which is then further metabolized by the same isoenzyme.
Co-administration of sunitinib with potent CYP3A4 inducers or inhibitors should be avoided because the plasma levels of sunitinib may be altered (see sections 4.4 and 4.5).

Elimination
Excretion is primarily via faeces (61%), with renal elimination of unchanged active substance and metabolites accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major 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/h. 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.

Special populations
Hepatic impairment: Sunitinib and its primary metabolite are mainly metabolized by the liver. Systemic exposures after a single dose of sunitinib were similar in subjects with mild or moderate (Child-Pugh class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN (upper limit of normal) or, if due to liver metastasis, > 5.0 x ULN.

Renal impairment: Population pharmacokinetic analyses indicated that sunitinib apparent clearance (CL/F) was not affected by creatinine clearance within the range evaluated (42 - 347 ml/min). Systemic exposures after a single dose of sunitinib were similar in subjects with severe renal impairment (CLcr<30 ml/min) compared to subjects with normal renal function (CLcr>80 ml/min). Although sunitinib and its primary metabolite were not eliminated through hemodialysis in subjects with ESRD, the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function.

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

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

5.3 Preclinical safety data

In rat and monkey repeated-dose toxicity studies up to 9-months duration, the primary target organ effects were identified in the gastrointestinal tract (emesis and 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 hypocellularity, and lymphoid depletion of thymus, spleen, and lymph node), exocrine pancreas (acinar cell degranulation with single cell necrosis), salivary gland (acinar hypertrophy), bone joint (growth plate thickening), uterus (atrophy) and ovaries (decreased follicular development). All findings occurred at clinically relevant sunitinib plasma exposure levels. Additional effects, observed in other studies included QTc interval prolongation, LVEF reduction, pituitary hypertrophy, and testicular tubular atrophy, increased mesangial cells in

kidney, haemorrhage in gastro-intestinal 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 genotoxic potential.

Carcinogenicity

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

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

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

Reproductive and developmental toxicity

No effects on 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 epididymides and colloid depletion in prostate and seminal vesicles at plasma exposure levels 18-fold higher than observed in clinic.

In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions, increased post-implantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5-fold higher than 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 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 5.5-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 observed in clinic.

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

observed during the pre-weaning and post-weaning periods at 3 mg/kg/day. No development toxicity was observed at 1 mg/kg/day (approximate exposure ≥0.9 times the AUC in patients administered the RDD).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Mannitol (E421)
Croscarmellose Sodium
Povidone (K-25)
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

3 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 polyethylene (HDPE) bottle with a polypropylene closure containing 30 hard capsules.

Poly(chlorotrifluoroethylene)/PVC transparent perforated unit dose blister with aluminium foil coated with heat seal lacquer containing 28 x 1 hard capsules.

Not all pack sizes may be marketed.

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)

EU/1/06/347/002
EU/1/06/347/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 2006
Date of latest renewal: 9 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

SUTENT 37.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains sunitinib malate, equivalent to 37.5 mg of sunitinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Gelatin capsules with yellow cap and yellow body, printed with black ink “Pfizer” on the cap and “STN 37.5 mg” on the body and containing yellow to orange granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gastrointestinal stromal tumour (GIST)
SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance.

Metastatic renal cell carcinoma (MRCC)
SUTENT is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.

Pancreatic neuroendocrine tumours (pNET)
SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.
Experience with SUTENT as first-line treatment is limited (see section 5.1).

4.2 Posology and method of administration

Therapy with sunitinib should be initiated by a physician experienced in the administration of anti-cancer agents.

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

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

Dose adjustments
Safety and tolerability
For GIST and MRCC, dose modifications in 12.5 mg steps may be applied based on individual safety and tolerability. Daily dose should not exceed 75 mg nor be decreased below 25 mg.

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

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

CYP3A4 inhibitors/inducers
Co-administration of sunitinib with potent CYP3A4 inducers, such as rifampicin, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of sunitinib may need to be increased in 12.5 mg steps (up to 87.5 mg per day for GIST and MRCC or 62.5 mg per day for pNET) based on careful monitoring of tolerability.

Co-administration of sunitinib with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of sunitinib may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability.
Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered.

Special populations
Paediatric population
The safety and efficacy of sunitinib in patients below 18 years of age have not been established.
No data are available.
There is no relevant use of sunitinib in children from birth to less than 6 years in the indication of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib treatment due to resistance or intolerance. There is no relevant use of sunitinib in the paediatric population in the indications treatment of advanced/metastatic renal cell carcinoma (MRCC) and treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression.
Use of sunitinib in the paediatric population is not recommended.

Elderly patients (≥ 65 years old)
Approximately one-third of the patients in clinical studies who received sunitinib were 65 years of age or over. No significant differences in safety or effectiveness were observed between younger and older patients.

Hepatic impairment
No starting dose adjustment is recommended when administering sunitinib to patients with mild or moderate (Child-Pugh class A and B) hepatic impairment. Sunitinib has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment and therefore its use in patients with severe hepatic impairment cannot be recommended (see section 5.2).

Renal impairment
No starting dose adjustment is required when administering sunitinib to patients with renal impairment (mild-severe) or with end-stage renal disease (ESRD) on haemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability (see section 5.2).

Method of administration
SUTENT is for oral administration. It 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 the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Co-administration with potent CYP3A4 inducers should be avoided because it may decrease sunitinib plasma concentration (see sections 4.2 and 4.5).

Co-administration with potent CYP3A4 inhibitors because it may increase the plasma concentration of sunitinib (see sections 4.2 and 4.5).

Skin and tissue disorders
Skin discolouration, possibly due to the active substance colour (yellow), is a very common adverse reaction occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with sunitinib. Other possible dermatologic effects may include dryness, thickness or cracking of the skin, blisters, or occasional rash on the palms of the hands and soles of the feet.
The above reactions were not cumulative, were typically reversible and generally did not result in treatment discontinuation.
Cases of pyoderma gangrenosum, generally reversible after drug discontinuation, have been reported.
Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM) and cases suggestive of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). If signs or symptoms of SJS, TEN, or EM (e.g. progressive skin rash often with blisters or mucosal lesions) are present, sunitinib treatment should be discontinued. If the diagnosis of SJS or TEN is confirmed, treatment must not be re-started. In some cases of suspected EM, patients tolerated the reintroduction of sunitinib therapy at a lower dose after resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines.

Haemorrhage and tumour bleeding
Haemorrhagic events, some of which were fatal, reported through post-marketing experience have included gastro-intestinal, respiratory, urinary tract and brain haemorrhages.
Bleeding events occurred in 18% of patients receiving sunitinib in a phase 3 GIST Study compared to 17% of patients receiving placebo. In patients receiving sunitinib for treatment-naïve MRCC, 39% had bleeding events compared to 11% of patients receiving IFN-α. Seventeen (4.5%) patients on sunitinib *versus* 5 (1.7%) of patients on IFN-α experienced Grade 3 or greater bleeding events. Of patients receiving sunitinib for cytokine-refractory MRCC, 26% experienced bleeding. Bleeding events, excluding epistaxis, occurred in21.7% of patients receiving sunitinib in the phase 3 pNET study compared to 9.85% of patients receiving placebo. Routine assessment of this event should include complete blood counts and physical examination.
Epistaxis was the most common haemorrhagic adverse reaction, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. Some of the epistaxis events were severe, but very rarely fatal.
Events of tumour haemorrhage, sometimes associated with tumour necrosis, have been reported; some of these haemorrhagic events were fatal.
In clinical trials, 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. Cases of pulmonary haemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib for MRCC, GIST and lung cancer. SUTENT is not approved for use in patients with lung cancer.
Patients receiving concomitant treatment with anticoagulants (e.g. warfarin, acenocoumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR) and physical examination.

Gastrointestinal disorders
Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia and stomatitis/oral pain were the most commonly reported gastrointestinal adverse reactions; oesophagitis events have been also reported (see section 4.8).
Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with anti-emetic, anti-diarrhoeal or antacid properties.
Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred in patients with intra-abdominal malignancies treated with sunitinib. Fatal gastrointestinal bleeding occurred in 0.98% of patients receiving placebo in the GIST phase 3 study.

Hypertension

Hypertension was reported in approximately 22.7% of patients with solid tumours. The dose of sunitinib was reduced or its administration temporarily suspended in approximately 2.7% of the patients who experienced hypertension. In none of these patients sunitinib was permanently discontinued. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of patients with solid tumours. Hypertension was reported in approximately 33.9% of patients receiving sunitinib for treatment-naïve MRCC, compared to 3.6% of patients receiving IFN-α. Severe hypertension occurred in 12% of treatment-naïve patients on sunitinib and <1% of patients on IFN-α. Hypertension was reported in 26.5% of patients receiving sunitinib in a phase 3 pNET study, compared to 4.9% of patients receiving placebo. Severe hypertension occurred in 10% of pNET patients on sunitinib and 3% of patients on placebo. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

Haematological disorders

Decreased absolute neutrophil counts of grade 3 and 4 severity respectively were reported in 10% and 1.7% of patients on the phase 3 GIST study, in 16% and 1.6% of patients on the phase 3 MRCC study, and in 13% and 2.4% of patients on the phase 3 pNET study. Decreased platelet counts of grade 3 and 4 severity respectively were reported in 3.7% and 0.4% of patients on the phase 3 GIST study, in 8.2% and 1.1% of patients on the phase 3 MRCC study, and in 3.7% and 1.2% of patients on the phase 3 pNET study. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. None of these events in the phase 3 studies were fatal, but rare fatal haematological events, including haemorrhage associated with thrombocytopenia and neutropenic infections, have been reported through post-marketing experience.

Anaemia has been observed to occur early as well as late during treatment with sunitinib; Grade 3 and 4 cases have been reported.

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

Cardiac disorders

Cardiovascular events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported in patients treated with sunitinib. These data suggest that sunitinib increases the risk of cardiomyopathy. No specific additional risk factors for sunitinib-induced cardiomyopathy apart from the drug-specific effect have been identified in the treated patients.

In clinical trials, decreases in left ventricular ejection fraction (LVEF) of ≥ 20% and below the lower limit of normal occurred in approximately 2% of sunitinib-treated GIST patients, 4% of cytokine-refractory MRCC patients, and 2% of placebo-treated GIST patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued. In the treatment-naïve MRCC study, 27% patients on sunitinib and 15% of patients on IFN-α had an LVEF value below the lower limit of normal. Two patients (<1%) who received sunitinib were diagnosed with congestive heart failure (CHF).

In GIST patients ‘cardiac failure’, ‘cardiac failure congestive’ or ‘left ventricular failure’ were reported in 1.2% of patients treated with sunitinib and 1% of patients treated with placebo. In the pivotal phase 3 GIST study (n=312), treatment-related fatal cardiac reactions occurred in 1% of patients on each arm of the study (i.e. sunitinib and placebo arms). In a phase 2 study in cytokine-refractory MRCC patients, 0.9% of patients experienced treatment-related fatal myocardial infarction and in the phase 3 study in treatment-naïve MRCC patients, 0.6% of patients on the IFN-α arm and 0% patients on the sunitinib arm experienced fatal cardiac events. In the phase 3 pNET study, one (1%) patient who received sunitinib had treatment-related fatal cardiac failure. 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 sunitinib administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from sunitinib clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction.

Close monitoring for clinical signs and symptoms of CHF should be performed, especially in patients with cardiac risk factors and/or history of coronary artery disease.
Physicians are advised to weigh this risk against the potential benefits of sunitinib. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.
In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. The administration of sunitinib should be interrupted and/or the dose reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

QT interval prolongation
Data from non-clinical (*in vitro* and *in vivo*) studies, at doses higher than the recommended human dose, indicated that sunitinib has the potential to inhibit the cardiac action potential repolarisation process (e.g. prolongation of QT interval).
Increases in the QTc interval to over 500 msec occurred in 0.5%, and changes from baseline in excess of 60 msec occurred in 1.1% of the 450 solid tumour patients; both of these parameters are recognized as potentially significant changes. At approximately twice therapeutic concentrations, sunitinib has been shown to prolong the QTcF Interval (Frederica's Correction).
QTc interval prolongation was investigated in a trial in 24 patients, ages 20-87 years, with advanced malignancies. The results of this study demonstrated that sunitinib had an effect on QTc interval (defined as a mean placebo-adjusted change of > 10 msec with a 90% CI upper limit > 15 msec) at therapeutic concentration (day 3) using the within-day baseline correction method, and at greater than therapeutic concentration (Day 9) using both baseline correction methods. No patients had a QTc interval >500 msec. Although an effect on QTcF interval was observed on Day 3 at 24 hours post-dose (i.e. at therapeutic plasma concentration expected after the recommended starting dose of 50 mg) with the within-day baseline correction method, the clinical significance of this finding is unclear.
Using comprehensive serial ECG assessments at times corresponding to either therapeutic or greater than therapeutic exposures, none of the patients in the evaluable or ITT populations were observed to develop QTc interval prolongation considered as "severe" (i.e. equal to or greater than Grade 3 by CTCAE version 3.0).
At therapeutic plasma concentrations, the maximum QTcF interval (Frederica's correction) mean change from baseline was 9.6 msec (90% CI 15.1msec). At approximately twice therapeutic concentrations, the maximum QTcF interval change from baseline was 15.4 msec (90% CI 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF interval change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 (CTCAE version 3.0).
QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. Torsade de pointes has been observed in <0.1% of sunitinib-exposed patients. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant administration of sunitinib with potent CYP3A4 inhibitors should be limited because of the possible increase in sunitinib plasma concentrations (see section 4.2 and 4.5).

Venous thromboembolic events
Treatment-related venous thromboembolic events were reported in approximately 1.0% of patients with solid tumours who received sunitinib on clinical trials, including GIST and MRCC.
Seven patients (3%) on sunitinib and none on placebo in a phase 3 GIST study experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT) and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.
Thirteen patients (3%) receiving sunitinib in the phase 3 treatment-naïve MRCC study and four patients (2%) on the two cytokine-refractory MRCC studies had venous thromboembolic events reported. Nine of these patients had pulmonary embolisms, one was Grade 2 and eight were Grade 4. Eight of these patients had DVT, one with Grade 1, two with Grade 2, four with Grade 3 and one with

Grade 4. One patient with pulmonary embolism in the cytokine-refractory MRCC study experienced dose interruption.
In treatment-naïve MRCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolisms, all with Grade 4.
Venous thromboembolic events were reported for 1 (1.2%) subject in the sunitinib arm and 5 (6.1%) subjects in the placebo arm in the phase 3 pNET study. Two of these subjects on placebo had DVT, one with Grade 2 and one with Grade 3.
No cases with fatal outcome were reported in GIST, MRCC and pNET registrational studies. Cases with fatal outcome have been observed in post-marketing setting (see respiratory events and section 4.8).

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

Respiratory events
Patients who presented with pulmonary embolism within the previous 12 months were excluded from sunitinib clinical studies.
In patients who received sunitinib in phase 3 registrational studies, pulmonary events (i.e. dyspnoea, pleural effusion, pulmonary embolism or pulmonary oedema) were reported in approximately 17.8% of patients with GIST, in approximately 26.7% of patients with MRCC and in 12% of patients with pNET.
Approximately 22.2% of patients with solid tumours, including GIST and MRCC, who received sunitinib in clinical trials experienced pulmonary events.
Cases of pulmonary embolism were observed in approximately 3.1% of patients with GIST and in approximately 1.2% of patients with MRCC, who received sunitinib in phase 3 studies (see section 4.4 - Venous thromboembolic events). No pulmonary embolism was reported for patients with pNET who received sunitinib in the phase 3 study. Rare cases with fatal outcome have been observed in post-marketing setting (see section 4.8).

Thyroid dysfunction
Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. During sunitinib treatment, routine monitoring of thyroid function should be performed every 3 months. In addition, patients should be observed closely for signs and symptoms of thyroid dysfunction during treatment, and patients who develop any signs and/or symptoms suggestive of thyroid dysfunction should have laboratory testing of thyroid function performed as clinically indicated. Patients who develop thyroid dysfunction should be treated as per standard medical practice.
Hypothyroidism has been observed to occur early as well as late during treatment with sunitinib. Hypothyroidism was reported as an adverse reaction in 7 patients (4%) receiving sunitinib across the two cytokine-refractory MRCC studies; in 61 patients (16%) on sunitinib and three patients (<1%) in the IFN-α arm in the treatment-naïve MRCC study.
Additionally, TSH elevations were reported in 4 cytokine-refractory MRCC patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Acquired hypothyroidism was noted in 8 GIST patients (4%) on sunitinib *versus* 1 (1%) on placebo. In the phase 3 pNET study hypothyroidism was reported in 6 patients (7.2%) receiving sunitinib and in one patient (1.2%) on placebo.
Thyroid function was monitored prospectively in two studies in patients with breast cancer; SUTENT is not approved for use in breast cancer. In one study, hypothyroidism was reported in 15 (13.6%) subjects on sunitinib and 3 (2.9%) subjects on standard of care. Blood TSH increase was reported in 1 (0.9%) subject on sunitinib and no subjects on standard of care. Hyperthyroidism was reported in no

sunitinib-treated subjects and 1 (1.0%) subject receiving standard of care. In the other study hypothyroidism was reported in a total of 31 (13%) sunitinib subjects and 2 (0.8%) capecitabine subjects. Blood TSH increase was reported in 12 (5.0%) sunitinib subjects and no capecitabine subjects. Hyperthyroidism was reported in 4 (1.7%) sunitinib subjects and no capecitabine subjects. Blood TSH decrease was reported in 3 (1.3%) sunitinib subjects and no capecitabine subjects. T4 increase was reported in 2 (0.8%) sunitinib subjects and 1 (0.4%) capecitabine subject. T3 increase was reported in 1 (0.8%) sunitinib subject and no capecitabine subjects. All thyroid-related events reported were Grade 1-2.
Cases of hyperthyroidism, some followed by hypothyroidism, and cases of thyroiditis have been uncommonly reported in clinical trials and through post-marketing experience.

Pancreatitis
Increases in serum lipase and amylase activities were observed in patients with various solid tumours who received sunitinib. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours.
Pancreatitis has been observed uncommonly (<1%) in patients receiving sunitinib for GIST or MRCC.
Cases of serious pancreatic events, some with fatal outcome, have been reported.
If symptoms of pancreatitis are present, patients should have sunitinib discontinued and be provided with appropriate supportive care.
No treatment-related pancreatitis was reported in the phase 3 pNET study.

Hepatotoxicity
Hepatotoxicity has been observed in patients treated with sunitinib. Cases of hepatic failure, some with a fatal outcome, were observed in <1% of solid tumor patients treated with sunitinib. Monitor liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) before initiation of treatment, during each cycle of treatment, and as clinically indicated. If signs or symptoms of hepatic failure are present, sunitinib should be discontinued and appropriate supportive care should be provided.

Hepatobiliary disorders
Sunitinib treatment may be associated with cholecystitis, including acalculous cholecystitis and emphysematous cholecystitis. In clinical registrational studies the incidence of cholecystitis was 0.5%. Post-marketing cases of cholecystitis have been reported.

Renal function
Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.
Risk factors associated with renal impairment/failure in patients receiving sunitinib included, in addition to underlying renal cell carcinoma, older age, diabetes mellitus, underlying renal impairment, cardiac failure, hypertension, sepsis, dehydration/hypovolemia, and rhabdomyolysis.
The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. Discontinue sunitinib in patients with nephrotic syndrome.

Fistula
If fistula formation occurs, sunitinib treatment should be interrupted. Limited information is available on the continued use of sunitinib in patients with fistulae.

Impaired wound healing
Cases of impaired wound healing have been reported during sunitinib therapy.
No formal clinical studies of the effect of sunitinib on wound healing have been conducted.
Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume

sunitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Osteonecrosis of the Jaw (ONJ)
Cases of ONJ have been reported in patients treated with SUTENT. The majority of cases occurred in patients who had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when SUTENT and intravenous bisphosphonates are used either simultaneously or sequentially.
Invasive dental procedures are also an identified risk factor. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 4.8).

Hypersensitivity/angioedema
If angioedema due to hypersensitivity occurs, sunitinib treatment should be interrupted and standard medical care provided.

Nervous system disorders
Taste disturbance
Dysgeusia was reported in approximately 28% of patients receiving sunitinib in clinical trials.

Seizures
In clinical studies of sunitinib and from post-marketing experience, seizures have been observed in subjects with or without radiological evidence of brain metastases. In addition, there have been few reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning and visual loss, including cortical blindness, should be controlled with medical management including control of hypertension. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Tumour Lysis Syndrome (TLS)
Cases of TLS, some fatal, have been rarely observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib. Risk factors for TLS include high tumour burden, preexisting chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated as clinically indicated, and prophylactic hydration should be considered.

Infections
Serious infections, with or without neutropenia, including some with a fatal outcome, have been reported. The infections observed most commonly with sunitinib treatment are infections typically seen in cancer patients, e.g. respiratory, urinary tract, skin infections and sepsis.
Rare cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported. Sunitinib therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

*Medicinal products that may **increase** sunitinib plasma concentrations*
In healthy volunteers, concomitant administration of a single dose of sunitinib with the potent CYP3A4 inhibitor ketoconazole resulted in an increase of the combined [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values of 49% and 51%, respectively.
Administration of sunitinib with potent CYP3A4 inhibitors (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations.

Combination with CYP3A4 inhibitors should therefore be avoided, or the selection of an alternate concomitant medicinal product with no or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dose of SUTENT may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability (see section 4.2).

*Medicinal products that may **decrease** sunitinib plasma concentrations*
In healthy volunteers, concomitant administration of a single dose of sunitinib with the CYP3A4 inducer rifampicin resulted in a reduction of the combined [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values of 23% and 46%, respectively.
Administration of sunitinib with potent CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort*/Hypericum perforatum*) may decrease sunitinib concentrations. Combination with CYP3A4 inducers should therefore be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered. 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 for GIST and MRCC or 62.5 mg per day for pNET), based on careful monitoring of tolerability (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no studies in pregnant women using sunitinib. Studies in animals have shown reproductive toxicity including foetal malformations (see section 5.3). SUTENT should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the foetus. If SUTENT is used during pregnancy or if the patient becomes pregnant while on treatment with SUTENT, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with SUTENT.

Breast-feeding
Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite is excreted in human milk. Because active substances are commonly excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should not breast-feed while taking SUTENT.

Fertility
Based on nonclinical findings, male and female fertility may be compromised by treatment with sunitinib (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most serious adverse reactions associated with sunitinib, some fatal, are renal failure, heart failure, pulmonary embolism, gastrointestinal perforation, and haemorrhages (e.g. respiratory tract, gastrointestinal, tumour, urinary tract, and brain haemorrhages). The most common adverse reactions of any grade (experienced by at least 20% of the patients in RCC, GIST, and pNET registrational trials) included decreased appetite, taste disturbance, hypertension, fatigue, gastrointestinal disorders (i.e. diarrhoea, nausea, stomatitis, dyspepsia and vomiting), skin discolouration, and palmar-plantar erythrodysaesthesia syndrome. These symptoms may diminish as treatment continues. Hypothyroidism may develop during treatment. Haematological disorders (e.g neutropoenia, thrombocyopoenia, and anaemia) are amongst the most common adverse drug reactions.

Fatal events other than those listed in section 4.4 above or in section 4.8 below that were considered possibly related to sunitinib included multi-system organ failure, disseminated intravascular coagulation, peritoneal haemorrhage, rhabdomyolysis, cerebrovascular accident, dehydration, adrenal insufficiency, renal failure, respiratory failure, pleural effusion, pneumothorax, shock, and sudden death.

Tabulated list of adverse reactions

Adverse reactions that were reported in GIST, MRCC, and pNET patients in the phase 2/3 studies are listed below, by system organ class, frequency and grade of severity (NCI-CTCAE). 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), not known (cannot be estimated from the available data).

Table 1 - Adverse reactions reported in clinical trials

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Infections and infestations	Very common	Viral infections[a]	125 (11.4%)	0 (0.0%)	0 (0.0%)
	Common	Respiratory infections[b]	67 (6.1%)	16 (1.5%)	0 (0.0%)
	Common	Abscess[c]	40 (3.7%)	11 (1.0%)	2 (0.2%)
	Common	Fungal infections[d]	16 (1.5%)	1 (0.1%)	1 (0.1%)
	Common	Urinary tract infection	82 (7.5%)	15 (1.4%)	0 (0.0%)
	Common	Skin infections[e]	19 (1.7%)	1 (0.1%)	1 (0.1%)
	Uncommon	Sepsis[f]	6 (0.5%)	2 (0.2%)	3 (0.3%)
	Uncommon	Bacterial infections[g]	10 (0.9%)	2 (0.2%)	3 (0.3%)
Blood and lymphatic system disorders	Very common	Neutropoenia	200 (18.3%)	93 (8.5%)	18 (1.6%)
	Very common	Thrombocytopoenia	181 (16.6%)	62 (5.7%)	13 (1.2%)
	Very common	Anaemia	240 (22.0%)	68 (6.2%)	17 (1.6%)
	Common	Leukopoenia	95 (8.7%)	36 (3.3%)	3 (0.3%)
	Common	Lymphopoenia	38 (3.5%)	18 (1.6%)	2 (0.2%)
	Uncommon	Pancytopenia	3 (0.3%)	2 (0.2%)	0 (0.0%)
Immune system disorders	Uncommon	Hypersensitivity	10 (0.9%)	0 (0.0%)	0 (0.0%)
Endocrine disorders	Very common	Hypothyroidism	157 (14.4%)	13 (1.2%)	2 (0.2%)
	Uncommon	Hyperthyroidism	6 (0.5%)	2 (0.2%)	0 (0.0%)
Metabolism and nutrition disorders	Very common	Decreased appetite[h]	476 (43.5%)	28 (2.6%)	1 (0.1%)
	Common	Dehydration	97 (8.9%)	27 (2.5%)	3 (0.3%)
	Uncommon	Tumour lysis syndrome	2 (0.2%)	1 (0.1%)	0 (0.0%)
Psychiatric disorders	Very common	Insomnia	179 (16.4%)	5 (0.5%)	0 (0.0%)
	Common	Depression	103 (9.4%)	1 (0.1%)	2 (0.2%)
Nervous system disorders	Very common	Dizziness	149 (13.6%)	7 (0.6%)	0 (0.0%)
	Very common	Headache	290 (26.5%)	18 (1.6%)	0 (0.0%)
	Very common	Taste disturbance[i]	392 (35.9%)	2 (0.2%)	0 (0.0%)
	Common	Neuropathy peripheral	95 (8.7%)	5 (0.5%)	0 (0.0%)
	Common	Paraesthesia	93 (8.5%)	2 (0.2%)	0 (0.0%)
	Common	Hypoaesthesia	68 (6.2%)	1 (0.1%)	0 (0.0%)
	Common	Hyperaesthesia	34 (3.1%)	1 (0.1%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Uncommon	Cerebrovascular accident[j]	1 (0.1%)	0 (0.0%)	1 (0.1%)
	Uncommon	Posterior reversible encephalopathy syndrome	2 (0.2%)	0 (0.0%)	1 (0.1%)
	Uncommon	Transient ischaemic attack	3 (0.3%)	0 (0.0%)	2 (0.2%)
Eye disorders	Common	Periorbital oedema	63 (5.8%)	1 (0.1%)	0 (0.0%)
	Common	Eyelid oedema	35 (3.2%)	1 (0.1%)	0 (0.0%)
	Common	Lacrimation increased	57 (5.2%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	Uncommon	Cardiac failure congestive	4 (0.4%)	3 (0.3%)	0 (0.0%)
	Uncommon	Cardiac failure	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Cardiomyopathy	4 (0.4%)	1 (0.1%)	0 (0.0%)
	Uncommon	Pericardial effusion	9 (0.8%)	2 (0.2%)	1 (0.1%)
	Uncommon	Left ventricular failure	1 (0.1%)	0 (0.0%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	334 (30.6%)	120 (11.0%)	0 (0.0%)
	Common	Deep vein thrombosis	19 (1.7%)	11 (1.0%)	0 (0.0%)
	Common	Hot flush	41 (3.8%)	0 (0.0%)	0 (0.0%)
	Common	Flushing	31 (2.8%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea	261 (23.9%)	46 (4.2%)	3 (0.3%)
	Very common	Epistaxis	195 (17.8%)	8 (0.7%)	0 (0.0%)
	Very common	Oropharyngeal pain[k]	111 (10.2%)	2 (0.2%)	0 (0.0%)
	Very common	Cough	225 (20.6%)	6 (0.5%)	0 (0.0%)
	Common	Pulmonary embolism	21 (1.9%)	2 (0.2%)	18 (1.6%)
	Common	Pleural effusion	45 (4.1%)	13 (1.2%)	3 (0.3%)
	Common	Haemoptysis	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Common	Dyspnoea exertional	56 (5.1%)	4 (0.4%)	0 (0.0%)
	Common	Nasal congestion	40 (3.7%)	0 (0.0%)	0 (0.0%)
	Common	Nasal dryness	24 (2.2%)	0 (0.0%)	0 (0.0%)
	Uncommon	Pulmonary haemorrhage	5 (0.5%)	0 (0.0%)	0 (0.0%)
	Uncommon	Respiratory failure	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Stomatitis[l]	321 (29.4%)	24 (2.2%)	0 (0.0%)
	Very common	Abdominal pain[m]	484 (44.3%)	96 (8.8%)	7 (0.6%)
	Very common	Vomiting	423 (38.7%)	40 (3.7%)	0 (0.0%)
	Very common	Diarrhoea	664 (60.8%)	82 (7.5%)	0 (0.0%)
	Very common	Dyspepsia	338 (30.9%)	14 (1.3%)	0 (0.0%)
	Very common	Glossodynia	109 (10.0%)	0 (0.0%)	0 (0.0%)
	Very common	Oral pain	120 (11.0%)	5 (0.5%)	0 (0.0%)
	Very common	Nausea	583 (53.3%)	45 (4.1%)	0 (0.0%)
	Very common	Constipation	312 (28.5%)	12 (1.1%)	1 (0.1%)
	Very common	Flatulence	155 (14.2%)	0 (0.0%)	0 (0.0%)
	Very common	Dry mouth	115 (10.5%)	0 (0.0%)	0 (0.0%)
	Very common	Gastro-oesophageal reflux disease	125 (11.4%)	4 (0.4%)	0 (0.0%)
	Common	Dysphagia	56 (5.1%)	5 (0.5%)	1 (0.1%)
	Common	Oesophagitis	18 (1.6%)	6 (0.5%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Common	Abdominal discomfort	82 (7.5%)	2 (0.2%)	0 (0.0%)
	Common	Rectal haemorrhage	53 (4.8%)	4 (0.4%)	0 (0.0%)
	Common	Gingival bleeding	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Common	Mouth ulceration	21 (1.9%)	0 (0.0%)	1 (0.1%)
	Common	Proctalgia	39 (3.6%)	3 (0.3%)	0 (0.0%)
	Common	Cheilitis	28 (2. 6%)	1 (0.1%)	1 (0.1%)
	Common	Haemorrhoids	81 (7.4%)	0 (0.0%)	0 (0.0%)
	Common	Oral discomfort	19 (1.7%)	0 (0.0%)	0 (0.0%)
	Common	Eructation	22 (2.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Intestinal perforation	2 (0.2%)	2 (0.2%)	0 (0.0%)
	Uncommon	Pancreatitis	9 (0.8%)	3 (0.3%)	0 (0.0%)
	Uncommon	Anal fistula	8 (0.7%)	2 (0.2%)	1 (0.1%)
Hepatobiliary disorders	Uncommon	Hepatic failure	4 (0.4%)	1 (0.1%)	1 (0.1%)
	Uncommon	Hepatitis	1 (0.1%)	1 (0.1%)	0 (0.0%)
	Uncommon	Cholecystitis	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Hepatic function abnormal	4 (0.4%)	1 (0.1%)	1 (0.1%)
Skin and subcutaneous tissue disorders	Very common	Pigmentation disorder[n]	326 (29.8%)	1 (0.1%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	300 (27.4%)	86 (7.9%)	0 (0.0%)
	Very common	Rash[o]	329 (30.1%)	10 (0.9%)	1 (0.1%)
	Very common	Erythema	109 (10.0%)	2 (0.2%)	0 (0.0%)
	Very common	Alopecia	116 (10.6%)	0 (0.0%)	0 (0.0%)
	Very common	Hair colour changes	200 (18.3%)	1 (0.1%)	0 (0.0%)
	Very common	Dry skin	185 (16.9%)	1 (0.1%)	0 (0.0%)
	Common	Skin exfoliation	74 (6.8%)	5 (0.5%)	0 (0.0%)
	Common	Skin Reaction[p]	29 (2.7%)	3 (0.3%)	0 (0.0%)
	Common	Eczema	19 (1.7%)	1 (0.1%)	0 (0.0%)
	Common	Blister	50 (4.6%)	4 (0.4%)	0 (0.0%)
	Common	Acne	31 (2.8%)	0 (0.0%)	0 (0.0%)
	Common	Pruritus	98 (9.0%)	1 (0.1%)	0 (0.0%)
	Common	Skin hyperpigmentation	17 (1.6%)	0 (0.0%)	0 (0.0%)
	Common	Skin lesion	52 (4.8%)	2 (0.2%)	0 (0.0%)
	Common	Hyperkeratosis	38 (3.5%)	7 (0.6%)	0 (0.0%)
	Common	Dermatitis	35 (3.2%)	6 (0.5%)	0 (0.0%)
	Common	Nail disorder[q]	44 (4.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Stevens-Johnson syndrome	1 (0.1%)	1 (0.1%)	0 (0.0%)
	Uncommon	Toxic epidermal necrolysis	1 (0.1%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity	249 (22.8%)	20 (1.8%)	3 (0.3%)
	Very common	Myalgia	128 (11.7%)	7 (0.6%)	0 (0.0%)
	Very common	Arthralgia	253 (23.1%)	19 (1.7%)	1 (0.1%)
	Very common	Musculoskeletal pain	118 (10.8%)	13 (1.2%)	1 (0.1%)
	Very common	Muscle spasms	110 (10.1%)	5 (0.5%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Very common	Back pain	257 (23.5%)	32 (2.9%)	2 (0.2%)
	Common	Muscular weakness	56 (5.1%)	6 (0.5%)	1 (0.1%)
	Uncommon	Osteonecrosis of the jaw	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Fistula	4 (0.4%)	1 (0.1%)	1 (0.1%)
	Uncommon	Myopathy	1 (0.1%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	Common	Renal failure	21 (1.9%)	7 (0.6%)	1 (0.1%)
	Common	Renal failure acute	12 (1.1%)	5 (0.5%)	1 (0.1%)
	Common	Chromaturia	44 (4.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Nephrotic syndrome	2 (0.2%)	1 (0.1%)	1 (0.1%)
	Uncommon	Proteinuria	9 (0.8%)	6 (0.5%)	0 (0.0%)
General disorders and administration site conditions	Very common	Chest Pain	119 (10.9%)	14 (1.3%)	1 (0.1%)
	Very common	Mucosal inflammation	233 (21.3%)	17 (1.6%)	1 (0.1%)
	Very common	Fatigue[r]	834 (76.3%)	204 (18.7%)	13 (1.2%)
	Very common	Oedema [s]	313 (28.6%)	14 (1.3%)	1 (0.1%)
	Very common	Pyrexia	236 (21.6%)	13 (1.2%)	1 (0.1%)
	Very common	Chills	112 (10.2%)	5 (0.5%)	0 (0.0%)
	Common	Pain	95 (8.7%)	12 (1.1%)	1 (0.1%)
	Common	Influenza like illness	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Impaired healing	3 (0.3%)	0 (0.0%)	0 (0.0%)
Investigations	Very common	Ejection fraction decreased[t]	130 (11.9%)	24 (2.2%)	0 (0.0%)
	Very common	Weight decreased	169 (15.5%)	9 (0.8%)	0 (0.0%)
	Common	White blood cell count decreased	86 (7.9%)	36 (3.3%)	0 (0.0 %)
	Common	Lipase increased	81 (7.4%)	36 (3.3%)	21 (1.9%)
	Common	Platelet count decreased	83 (7.6%)	21 (1.9%)	3 (0.3%)
	Common	Haemoglobin decreased	66 (6.0%)	20 (1.8%)	0 (0.0%)
	Common	Blood creatinine phosphokinase increased	44 (4.0%)	9 (0.8%)	4 (0.4%)
	Common	Amylase increased[u]	49 (4.5%)	25 (2.3%)	2 (0.2%)
	Common	Aspartate aminotransferase increased	50 (4.6%)	13 (1.2%)	1 (0.1%)
	Common	Alanine aminotransferase increased	42 (3.8%)	12 (1.1%)	2 (0.2%)
	Common	Blood creatinine increased	75 (6.9%)	9 (0.8%)	1 (0.1%)
	Common	Blood pressure increased	25 (2.3%)	3 (0.3%)	0 (0.0%)
	Common	Blood uric acid increased	21 (1.9%)	1 (0.1%)	12 (1.1%)
	Uncommon	Blood thyroid stimulating hormone increased	9 (0.8%)	0 (0.0%)	0 (0.0%)
	Uncommon	Electrocardiogram QT prolonged	7 (0.6%)	0 (0.0%)	1 (0.1%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
		Any adverse event	1087 (99.5%)	553 (50.6%)	210 (19.2%)

The following terms have been combined:

[a] Nasopharyngitis and oral herpes
[b] Bronchitis, lower respiratory tract infection, pneumonia and respiratory tract infection
[c] Abscess, abscess limb, anal abscess, gingival abscess, liver abscess, pancreatic abscess, perineal abscess, perirectal abscess, rectal abscess, subcutaneous abscess and tooth abscess
[d] Oesophageal candidiasis and oral candidiasis
[e] Cellulitis and skin infection
[f] Sepsis and sepsis shock
[g] Abdominal abscess, abdominal sepsis, diverticulitis and osteomyelitis
[h] Decreased appetite and anorexia
[i] Dysgeusia, ageusia and taste disturbance
[j] Cerebrovascular accident and cerebral infarction
[k] Oropharyngeal and laryngeal pain
[l] Stomatitis and aphtous stomatitis
[m] Abdominal distension and abdominal pain
[n] Yellow skin, skin discolouration and pigmentation disorder
[o] Dermatitis psoriasiform, exfoliative rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic
[p] Skin reaction and skin disorder
[q] Nail disorder and discolouration
[r] Fatigue and asthenia
[s] Face oedema, oedema and oedema peripheral
[t] Ejection fraction decreased/abnormal
[u] Amylase and amylase increased

Table 2 - Adverse reactions identified through post-marketing experience

The following adverse reactions have been identified during post-approval use of SUTENT. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programmes, clinical pharmacology studies and exploratory studies in unapproved indications.

Infections and infestations	
Uncommon*	Necrotising Fasciitis
Blood and lymphatic system disorders	
Uncommon*	Thrombotic microangiopathy
Immune system disorders	
Uncommon*	Angioedema
Endocrine disorders	
Uncommon*	Thyroiditis
Cardiac disorders	
Uncommon*	Torsade de pointes
Skin and subcutaneous tissue disorders	
Uncommon*	Pyoderma gangrenosum
Uncommon*	Erythema multiforme
Musculoskeletal and connective tissue disorders	
Uncommon*	Rhabdomyolysis

* Frequency of the adverse reaction calculated with the 3/X methodology described in the Guideline on Summary of Product Characteristics.

Description of selected adverse reactions
Infection and infestations: Cases of serious infection (with or without neutropoenia), including cases with fatal outcome, have been reported. Cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported (see also section 4.4).

Blood and lymphatic system disorders: Cases of thrombotic microangiopathy have been reported. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Immune system disorders: Hypersensitivity reactions, including angioedema, have been reported.

Nervous system disorders: There have been few reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS) (See also section 4.4).

Endocrine disorders: Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience (see also section 4.4).

Metabolism and nutrition disorders: Cases of TLS, some fatal, have been reported in patients treated with sunitinib.

Cardiac disorders: Cardiac events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported through post-marketing experience (see also section 4.4).

Respiratory, thoracic and mediastinal disorders: Cases of pulmonary embolism and cases of pulmonary haemorrhage, in some cases with fatal outcome, have been reported.

Gastrointestinal disorders: Cases of oesophagitis, in some cases with fatal outcome, have been reported.

Hepatobiliary disorders: Hepatic dysfunction has been reported and may include Liver Function Test abnormalities, hepatitis or liver failure. Cases of cholecystitis, in some cases with fatal outcome, have been reported (see also section 4.4).

Skin and subcutaneous tissue disorders: Cases of pyoderma gangrenosum, generally reversible after drug discontinuation, have been reported (see also section 4.4).

Musculoskeletal and connective tissue disorders: Cases of myopathy and/or rhabdomyolysis, some with acute renal failure, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.
Cases of fistula formation, sometimes associated with tumour necrosis and regression, in some cases with fatal outcomes, have been reported.
Cases of impaired wound healing have been reported during sunitinib therapy.
Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with SUTENT, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4).

Renal and urinary disorders: Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported. (see also section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote for overdose with sunitinib and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed active substance may be achieved by emesis or gastric lavage. A few cases of overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of sunitinib, or without adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors; ATC code: L01XE04

Mechanism of action
Sunitinib inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, neoangiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (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 efficacy and safety
The clinical safety and efficacy of sunitinib has been studied in the treatment of patients with 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), the treatment of patients with MRCC and the treatment of patients with unresectable pNET.
Efficacy is based on time to tumour progression and an increase in survival in GIST, on progression free survival and objective response rates for treatment-naïve and cytokine-refractory MRCC respectively, and on progression free survival for pNET.

Gastrointestinal stromal tumours (GIST)
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 Tumour Progression (TTP) was 34.0 weeks (95% CI = 22.0 – 46.0 weeks).
A phase 3, randomized, double-blind, placebo-controlled study of sunitinib 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 sunitinib or placebo, orally once daily on Schedule 4/2 until disease progression or withdrawal from the study for another reason (207 patients received sunitinib 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. At the time of the pre-specified interim analysis, the median TTP on sunitinib was 28.9 weeks (95% CI = 21.3-34.1 weeks) as assessed by the Investigator and 27.3 weeks (95% CI = 16.0-32.1 weeks) as assessed by the Independent Review and was statistically significantly longer than the TTP on placebo of 5.1 weeks (95% CI = 4.4-10.1 weeks) as assessed by the Investigator and 6.4 weeks (95% CI = 4.4-10.0 weeks) as assessed by the Independent Review. The difference in overall survival was statistically in favour of

sunitinib [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 sunitinib arm.
After the interim analysis of efficacy and safety, at recommendation of the Independent DSMB, the study was unblinded and patients on the placebo arm were offered open-label sunitinib treatment.
A total of 255 patients received sunitinib in the open-label treatment phase of the study, including 99 patients who were initially treated with placebo.
The analyses of primary and secondary endpoints in the open-label phase of the study reaffirmed the results obtained at the time of the interim analysis, as shown in the table below:

Table 3 - Summary of Efficacy Endpoints (ITT population)

	Double-Blind Treatment [a]				
	Median (95% CI)		Hazard Ratio		Placebo Cross-Over Group
Endpoint	**SUTENT**	**Placebo**	**(95% CI)**	**p**	**Treatment[b]**
Primary: TTP (weeks)					
Interim	27.3 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.329 (0.233 to 0.466)	<0.001	-
Final	26.6 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.339 (0.244 to 0.472)	<0.001	10.4 (4.3 to 22.0)
Secondary					
PFS (weeks) [c]					
Interim	24.1 (11.1 to 28.3)	6.0 (4.4 to 9.9)	0.333 (0.238 to 0.467)	<0.001	-
Final	22.9 (10.9 to 28.0)	6.0 (4.4 to 9.7)	0.347 (0.253 to 0.475)	<0.001	-
ORR (%)[d]					
Interim	6.8 (3.7 to 11.1)	0 (-)	NA	0.006	-
Final	6.6 (3.8 to 10.5)	0 (-)	NA	0.004	10.1 (5.0 to 17.8)
OS (weeks)[e]					
Interim	-	-	0.491 (0.290 to 0.831)	0.007	-
Final	72.7 (61.3 to 83.0)	64.9 (45.7 to 96.0)	0.876 (0.679 to 1.129)	0.306	-

a Results of double-blind treatment are from the ITT population and using central radiologist measurement, as appropriate.
b Efficacy results for the 99 subjects who crossed over from placebo to SUTENT after unblinding. Baseline was reset at cross-over and efficacy analyses were based on investigators assessment
c The interim PFS numbers have been updated based on a recalculation of the original data
d Results for ORR are given as percent of subjects with confirmed response with the 95% CI.
e Median not achieved because the data were not yet mature.

Median overall survival (OS) in the ITT population was 72.7 weeks and 64.9 weeks (HR 0.876, 95% CI 0.679 – 1.129, p=0.306), in the sunitinib and placebo arms respectively. In this analysis, the placebo arm included those patients randomized to placebo who subsequently received open-label sunitinib treatment.

Treatment-naïve metastatic renal cell carcinoma (MRCC)
A phase 3, randomized, multi-centre international study evaluating the efficacy and safety of sunitinib compared with IFN-α in treatment-naïve MRCC patients was conducted. Seven hundred and fifty patients were randomized 1:1 to the treatment arms; they received treatment with either sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily oral administration followed by 2 weeks of rest (schedule 4/2), or IFN-α, administered as a subcutaneous injection of 3 million units (MU) the

first week, 6 MU the second week, and 9 MU the third week and thereafter, on 3 non-consecutive days each week.

The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for sunitinib treatment and 4.1 months (range: 0.1 – 45.6) for IFN- α treatment. Treatment-related serious adverse events (TRSAEs) were reported in 23.7% of patients receiving sunitinib and in 6.9% of patients receiving IFN-α. However, the discontinuation rates due to adverse events were 20% for sunitinib and 23% for IFN-α. Dose interruptions occurred in 202 patients (54%) on sunitinib and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on sunitinib and 98 patients (27%) on IFN-α. Patients were treated until disease progression or withdrawal from the study. The primary efficacy endpoint was progression free survival (PFS). A planned interim analysis showed a statistically significant advantage for sunitinib over IFN-α, in this study, the median PFS for the sunitinib-treated group was 47.3 weeks, compared with 22.0 weeks for the IFN-α-treated group; the hazard ratio was 0.415 (95% CI: 0.320-0.539, p-value <0.001). Other endpoints included objective response rate (ORR), overall survival (OS) and safety. Core radiology assessment was discontinued after the primary endpoint had been met. At the final analysis, the ORR as determined by the investigators' assessment was 46% (95% CI: 41 - 51) for the sunitinib arm and 12.0% (95% CI: 9- 16) for the IFN-α arm (p<0.001).

Sunitinib treatment was associated with longer survival compared to IFN-α. The median OS was 114.6 weeks for the sunitinib arm (95% CI: 100.1 - 142.9 weeks) and 94.9 weeks for the IFN-α arm (95% CI: 77.7 - 117.0 weeks) with a hazard ratio of 0.821 (95% CI: 0.673 - 1.001; p=0.0510 by unstratified log-rank).

The overall PFS and OS, observed in the ITT population, as determined by the core radiology laboratory assessment, are summarized in the table below:

Summary of Efficacy Endpoints (ITT population)

Summary of Progression-Free Survival	**Sunitinib (N=375)**	**IFN-α (N=375)**
Subject did not progress or die [n (%)]	161 (42.9)	176 (46.9)
Subject observed to have progressed or died [n (%)]	214 (57.1)	199 (53.1)
PFS (weeks)		
Quartile (95% CI)		
25%	22.7 (18.0 to 34.0)	10.0 (7.3 to 10.3)
50%	48.3 (46.4 to 58.3)	22.1 (17.1 to 24.0)
75%	84.3 (72.9 to 95.1)	58.1 (45.6 to 82.1)
Unstratified Analysis		
Hazard Ratio (sunitinib vs IFN-α)	0.5268	
95% CI for Hazard Ratio	(0.4316 to 0.6430)	
p-value[a]	<0.0001	

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

Summary of Overall Survival (ITT Population)	**Sunitinib (N = 375)**	**IFN-α (N = 375)**
Subject not known to have died [n (%)]	185 (49.3)	175 (46.7)
Subject observed to have died [n (%)]	190 (50.7)	200 (53.3)
OS (weeks)		
Quartile (95% CI)		
25%	56.6 (48.7 to 68.4)	41.7 (32.6 to 51.6)
50%	114.6 (100.1 to 142.9)	94.9 (77.7 to 117.0)
75%	NA (NA to NA)	NA (NA to NA)
Unstratified Analysis		
Hazard Ratio (sunitinib vs IFN-α)	0.8209	
95% CI for Hazard Ratio	(0.6730 to 1.0013)	
p-value[a]	0.0510	

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

NA: Not Available (Not Reached)

Cytokine-refractory metastatic renal cell carcinoma (MRCC)
A phase 2 study of sunitinib was conducted in patients who were refractory to prior cytokine therapy with interleukin-2 or IFN-α. Sixty-three patients received a starting dose of 50 mg sunitinib 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 sunitinib 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 sunitinib 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 35.8% (95% C.I. 26.8% – 47.5 %). The median DR and OS had not yet been reached.

Pancreatic neuroendocrine tumours (pNET)
A supportive phase 2, open-label, multi-center study evaluated the efficacy and safety of single-agent sunitinib 50 mg daily on Schedule 4/2 [4 weeks on treatment, 2-week rest period] in patients with unresectable pNET. In a pancreatic islet cell tumour cohort of 66 patients, the primary endpoint of response rate was 17%.
A pivotal phase 3, multi-centre, international, randomized, double-blind placebo-controlled study of single-agent sunitinib was conducted in patients with unresectable pNET.
Patients were required to have documented progression, based on RECIST, within the prior 12 months and were randomized (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled rest period (n=86) or placebo (n=85).
The primary objective was to compare Progression-Free Survival (PFS) in patients receiving sunitinib *versus* patients receiving placebo. Other endpoints included Overall Survival (OS), Objective Response Rate (ORR), Patient-reported Outcomes (PRO) and safety.
Demographics were comparable between the sunitinib and placebo groups. Additionally, 49% of sunitinib patients had non-functioning tumours *versus* 52% of placebo patients and 92% patients in both arms had liver metastases.
Use of somatostatin analogs was allowed in the study.
A total of 66% of sunitinib patients received prior systemic therapy compared with 72% of placebo patients. In addition, 24% of sunitinib patients had received somatostatin analogs compared with 22% of placebo patients.
A clinically significant advantage in investigator-assessed PFS for sunitinib over placebo was observed. The median PFS was 11.4 months for the sunitinib arm compared to 5.5 months for the placebo arm [hazard ratio: 0.418 (95% CI 0.263, 0.662), p-value =0.0001]; similar results were observed when derived tumour response assessments based upon application of RECIST to investigator tumour measurements were used to determine disease progression, as shown in Table 4. A hazard ratio favouring sunitinib was observed in all subgroups of baseline characteristics evaluated, including an analysis by number of prior systemic therapies. A total of 29 patients in the sunitinib arm and 24 in the placebo arm had received no prior systemic treatment; among these patients, the hazard ratio for PFS was 0.365 (95% CI 0.156, 0.857), p=0.0156. Similarly, among 57 patients in the sunitinib arm (including 28 with 1 prior systemic therapy and 29 with 2 or more prior systemic therapies) and 61 patients in the placebo arm (including 25 with 1 prior systemic therapy and 36 with 2 or more prior systemic therapies) who had received prior systemic therapy, the hazard ratio for PFS was 0.456 (95% CI 0.264, 0.787), p=0.0036.
A sensitivity analysis of PFS was conducted where progression was based upon investigator-reported tumour measurements and where all subjects censored for reasons other than study termination were treated as PFS events. This analysis provided a conservative estimate of the treatment effect of sunitinib and supported the primary analysis, demonstrating a hazard ratio of 0.507 (95% CI 0.350, 0.733) and p=0.000193. The pivotal study in pancreatic NET was terminated prematurely at the

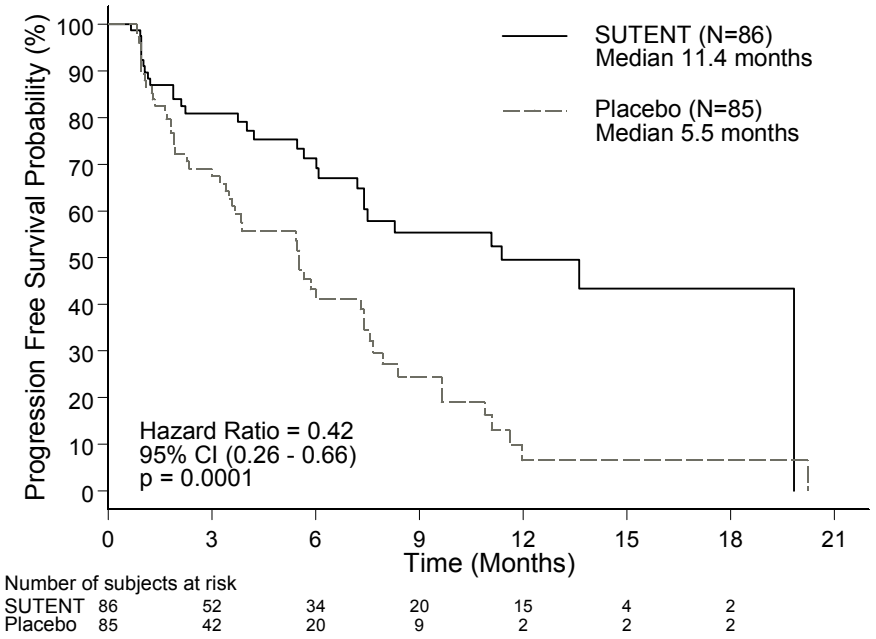
recommendation of an independent Drug Monitoring Committee, and the primary endpoint was based upon investigator assessment, both of which may have affected the estimates of the treatment effect. In order to rule out bias in the investigator-based assessment of PFS, a blinded independent central review of scans was performed and supported the investigator assessment, as shown in Table 4.

Table 4 - pNET Efficacy Results from the Phase 3 Study

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

CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached
[a]2-sided unstratified log-rank test
[b]Fisher's Exact test

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



OS data were not mature at the time of the analysis. There were 9 deaths in the sunitinib arm and 21 deaths in the placebo arm. A statistically significant difference in ORR favouring sunitinib over placebo was observed.
Upon disease progression, patients were unblinded and placebo patients could have been offered access to open-label sunitinib in a separate extension study. As a result of the early study closure, remaining patients were unblinded and offered access to open-label sunitinib in an extension study. A total of 59 patients from the placebo arm received sunitinib in an extension study.
Results from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC-30) showed that the overall global health-related quality of life and the five functioning domains (physical, role, cognitive, emotional and social) were maintained for patients on sunitinib treatment as compared to placebo with limited adverse symptomatic effects.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of the studies with SUTENT in one or more subsets of the paediatric population in gastrointestinal stromal tumours (GIST) (see section 4.2 for information on the paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with SUTENT in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of the studies with SUTENT in all subsets of the paediatric population for treatment of gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of sunitinib have been evaluated in 135 healthy volunteers and 266 patients with solid tumours. The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers.
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 schedules tested.

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

Distribution
In vitro, binding of sunitinib and its primary active metabolite to human plasma protein was 95% and 90%, respectively, with no apparent concentration dependence. The apparent volume of distribution (V_d) for sunitinib was large, 2230 l, indicating distribution into the tissues.

Metabolic interactions
The calculated *in vitro* K_i values for all cytochrome P450 (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 induce metabolism, to any clinically relevant extent, of other active substances that may be metabolised by these enzymes.

Biotransformation
Sunitinib is metabolised primarily by CYP3A4, the cytochrome P450 isoform which produces its primary active metabolitedesethyl sunitinib, which is then further metabolised by the same isoenzyme. Co-administration of sunitinib with potent CYP3A4 inducers or inhibitors should be avoided because the plasma levels of sunitinib may be altered (see sections 4.4 and 4.5).

Elimination
Excretion is primarily via faeces (61%), with renal elimination of unchanged active substance and metabolites accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major 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/h. 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.

Special populations
Hepatic impairment: Sunitinib and its primary metabolite are mainly metabolized by the liver. Systemic exposures after a single dose of sunitinib were similar in subjects with mild or moderate (Child-Pugh class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST > 2.5 x ULN (upper limit of normal) or, if due to liver metastasis, > 5.0 x ULN.

Renal impairment: Population pharmacokinetic analyses indicated that sunitinib apparent clearance (CL/F) was not affected by creatinine clearance within the range evaluated (42 - 347 ml/min). Systemic exposures after a single dose of sunitinib were similar in subjects with severe renal impairment (CLcr<30 ml/min) compared to subjects with normal renal function (CLcr>80 ml/min). Although sunitinib and its primary metabolite were not eliminated through hemodialysis in subjects with ESRD, the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function.

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

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

5.3 Preclinical safety data

In rat and monkey repeated-dose toxicity studies up to 9-months duration, the primary target organ effects were identified in the gastrointestinal tract (emesis and 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 hypocellularity, and lymphoid depletion of thymus, spleen, and lymph node), exocrine pancreas (acinar cell degranulation with single cell necrosis), salivary gland (acinar hypertrophy), bone joint (growth plate thickening), uterus (atrophy) and ovaries (decreased follicular development). All findings occurred at clinically relevant sunitinib plasma exposure levels. Additional effects, observed in other studies included QTc interval prolongation, LVEF reduction, pituitary hypertrophy, and testicular tubular atrophy, increased mesangial cells in kidney, haemorrhage in gastro-intestinal 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 genotoxic potential.

Carcinogenicity

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

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

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

Reproductive and developmental toxicity

No effects on 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 epididymides and colloid depletion in prostate and seminal vesicles at plasma exposure levels 18-fold higher than observed in clinic.

In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions, increased post-implantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5-fold higher than 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 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 5.5-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 observed in clinic.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Mannitol (E421)
Croscarmellose sodium
Povidone (K-25)
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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 polyethylene (HDPE) bottle with a polypropylene closure containing 30 hard capsules.

Poly(chlorotrifluoroethylene)/PVC transparent perforated unit dose blister with aluminium foil coated with heat seal lacquer containing 28 x 1 hard capsules.

Not all pack sizes may be marketed.

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)

EU/1/06/347/007
EU/1/06/347/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 2006
Date of latest renewal: 9 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

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

Gastrointestinal stromal tumour (GIST)
SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance.

Metastatic renal cell carcinoma (MRCC)
SUTENT is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.

Pancreatic neuroendocrine tumours (pNET)
SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.
Experience with SUTENT as first-line treatment is limited (see section 5.1).

4.2 Posology and method of administration

Therapy with sunitinib should be initiated by a physician experienced in the administration of anti-cancer agents.

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

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

Dose adjustments
Safety and tolerability
For GIST and MRCC, dose modifications in 12.5 mg steps may be applied based on individual safety and tolerability. Daily dose should not exceed 75 mg nor be decreased below 25 mg.

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

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

CYP3A4 inhibitors/inducers
Co-administration of sunitinib with potent CYP3A4 inducers, such as rifampicin, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of sunitinib may need to be increased in 12.5 mg steps (up to 87.5 mg per day for GIST and MRCC or 62.5 mg per day for pNET) based on careful monitoring of tolerability.

Co-administration of sunitinib with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of sunitinib may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability.
Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered.

Special populations
Paediatric population
The safety and efficacy of sunitinib in patients below 18 years of age have not been established.
No data are available.
There is no relevant use of sunitinib in children from birth to less than 6 years in the indication of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib treatment due to resistance or intolerance. There is no relevant use of sunitinib in the paediatric population in the indications treatment of advanced/metastatic renal cell carcinoma (MRCC) and treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression.
Use of sunitinib in the paediatric population is not recommended.

Elderly patients (≥ 65 years old)
Approximately one-third of the patients in clinical studies who received sunitinib were 65 years of age or over. No significant differences in safety or effectiveness were observed between younger and older patients.

Hepatic impairment
No starting dose adjustment is recommended when administering sunitinib to patients with mild or moderate (Child-Pugh class A and B) hepatic impairment. Sunitinib has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment and therefore its use in patients with severe hepatic impairment cannot be recommended (see section 5.2).

Renal impairment
No starting dose adjustment is required when administering sunitinib to patients with renal impairment (mild-severe) or with end-stage renal disease (ESRD) on haemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability (see section 5.2).

Method of administration
SUTENT is for oral administration. It 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 the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Co-administration with potent CYP3A4 inducers should be avoided because it may decrease sunitinib plasma concentration (see sections 4.2 and 4.5).

Co-administration with potent CYP3A4 inhibitors should be avoided because it may increase the plasma concentration of sunitinib (see sections 4.2 and 4.5).

Skin and tissue disorders

Skin discolouration, possibly due to the active substance colour (yellow), is a very common adverse reaction occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with sunitinib. Other possible dermatologic effects may include dryness, thickness or cracking of the skin, blisters, or occasional rash on the palms of the hands and soles of the feet.

The above reactions were not cumulative, were typically reversible and generally did not result in treatment discontinuation. Cases of pyoderma gangrenosum, generally reversible after drug discontinuation, have been reported.Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM) and cases suggestive of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). If signs or symptoms of SJS, TEN, or EM (e.g. progressive skin rash often with blisters or mucosal lesions) are present, sunitinib treatment should be discontinued. If the diagnosis of SJS or TEN is confirmed, treatment must not be re-started. In some cases of suspected EM, patients tolerated the reintroduction of sunitinib therapy at a lower dose after resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines.

Haemorrhage and tumour bleeding

Haemorrhagic events, some of which were fatal, reported through post-marketing experience have included gastro-intestinal, respiratory, urinary tract and brain haemorrhages.

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

Epistaxis was the most common haemorrhagic adverse reaction, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. Some of the epistaxis events were severe, but very rarely fatal.

Events of tumour haemorrhage, sometimes associated with tumour necrosis, have been reported; some of these haemorrhagic events were fatal.

In clinical trials, 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. Cases of pulmonary haemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib for MRCC, GIST and lung cancer. SUTENT is not approved for use in patients with lung cancer.

Patients receiving concomitant treatment with anticoagulants (e.g. warfarin, acenocoumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR) and physical examination.

Gastrointestinal disorders

Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia and stomatitis/oral pain were the most commonly reported gastrointestinal adverse reactions; oesophagitis events have been also reported (see section 4.8).

Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with anti-emetic, anti-diarrhoeal or antacid properties.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred in patients with intra-abdominal malignancies treated with sunitinib. Fatal gastrointestinal bleeding occurred in 0.98% of patients receiving placebo in the GIST phase 3 study.

Hypertension
Hypertension was reported in approximately 22.7 of patients with solid tumours. The dose of sunitinib was reduced or its administration temporarily suspended in approximately 2.7% of the patients who experienced hypertension. In none of these patients sunitinib was permanently discontinued. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of patients with solid tumours. Hypertension was reported in approximately 33.9% of patients receiving sunitinib for treatment-naïve MRCC, compared to 3.6% of patients receiving IFN-α. Severe hypertension occurred in 12% of treatment-naïve patients on sunitinib and <1% of patients on IFN-α. Hypertension was reported in 26.5% of patients receiving sunitinib in a phase 3 pNET study, compared to 4.9% of patients receiving placebo. Severe hypertension occurred in 10% of pNET patients on sunitinib and 3% of patients on placebo. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

Haematological disorders
Decreased absolute neutrophil counts of grade 3 and 4 severity respectively were reported in 10% and 1.7% of patients on the phase 3 GIST study, in 16% and 1.6% of patients on the phase 3 MRCC study, and in 13% and 2.4% of patients on the phase 3 pNET study. Decreased platelet counts of grade 3 and 4 severity respectively were reported in 3.7% and 0.4% of patients on the phase 3 GIST study, in 8.2% and 1.1% of patients on the phase 3 MRCC study, and in 3.7% and 1.2% of patients on the phase 3 pNET study. The above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. None of these events in the phase 3 studies were fatal, but rare fatal haematological events, including haemorrhage associated with thrombocytopenia and neutropenic infections, have been reported through post-marketing experience.
Anaemia has been observed to occur early as well as late during treatment with sunitinib; Grade 3 and 4 cases have been reported.
Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with sunitinib.

Cardiac disorders
Cardiovascular events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported in patients treated with sunitinib. These data suggest that sunitinib increases the risk of cardiomyopathy. No specific additional risk factors for sunitinib-induced cardiomyopathy apart from the drug-specific effect have been identified in the treated patients.
In clinical trials, decreases in left ventricular ejection fraction (LVEF) of ≥ 20% and below the lower limit of normal occurred in approximately 2% of sunitinib-treated GIST patients, 4% of cytokine-refractory MRCC patients, and 2% of placebo-treated GIST patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued. In the treatment-naïve MRCC study, 27% patients on sunitinib and 15% of patients on IFN-α had an LVEF value below the lower limit of normal. Two patients (<1%) who received sunitinib were diagnosed with congestive heart failure (CHF).
In GIST patients ‘cardiac failure’, ‘cardiac failure congestive’ or ‘left ventricular failure’ were reported in 1.2% of patients treated with sunitinib and 1% of patients treated with placebo. In the pivotal phase 3 GIST study (n=312), treatment-related fatal cardiac reactions occurred in 1% of patients on each arm of the study (i.e. sunitinib and placebo arms). In a phase 2 study in cytokine-refractory MRCC patients, 0.9% of patients experienced treatment-related fatal myocardial infarction and in the phase 3 study in treatment-naïve MRCC patients, 0.6% of patients on the IFN-α arm and 0% patients on the sunitinib arm experienced fatal cardiac events. In the phase 3 pNET study, one (1%) patient who received sunitinib had treatment-related fatal cardiac failure. 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 sunitinib administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from sunitinib clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction.
Close monitoring for clinical signs and symptoms of CHF should be performed, especially in patients with cardiac risk factors and/or history of coronary artery disease.

Physicians are advised to weigh this risk against the potential benefits of sunitinib. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.
In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. The administration of sunitinib should be interrupted and/or the dose reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

QT interval prolongation
Data from non-clinical (*in vitro* and *in vivo*) studies, at doses higher than the recommended human dose, indicated that sunitinib has the potential to inhibit the cardiac action potential repolarisation process (e.g. prolongation of QT interval).
Increases in the QTc interval to over 500 msec occurred in 0.5%, and changes from baseline in excess of 60 msec occurred in 1.1% of the 450 solid tumour patients; both of these parameters are recognized as potentially significant changes. At approximately twice therapeutic concentrations, sunitinib has been shown to prolong the QTcF Interval (Frederica's Correction).
QTc interval prolongation was investigated in a trial in 24 patients, ages 20-87 years, with advanced malignancies. The results of this study demonstrated that sunitinib had an effect on QTc interval (defined as a mean placebo-adjusted change of > 10 msec with a 90% CI upper limit > 15 msec) at therapeutic concentration (day 3) using the within-day baseline correction method, and at greater than therapeutic concentration (Day 9) using both baseline correction methods. No patients had a QTc interval >500 msec. Although an effect on QTcF interval was observed on Day 3 at 24 hours post-dose (i.e. at therapeutic plasma concentration expected after the recommended starting dose of 50 mg) with the within-day baseline correction method, the clinical significance of this finding is unclear.
Using comprehensive serial ECG assessments at times corresponding to either therapeutic or greater than therapeutic exposures, none of the patients in the evaluable or ITT populations were observed to develop QTc interval prolongation considered as "severe" (i.e. equal to or greater than Grade 3 by CTCAE version 3.0).
At therapeutic plasma concentrations, the maximum QTcF interval (Frederica's correction) mean change from baseline was 9.6 msec (90% CI 15.1msec). At approximately twice therapeutic concentrations, the maximum QTcF interval change from baseline was 15.4 msec (90% CI 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF interval change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 (CTCAE version 3.0).
QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. Torsade de pointes has been observed in <0.1% of sunitinib-exposed patients. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant administration of sunitinib with potent CYP3A4 inhibitors should be limited because of the possible increase in sunitinib plasma concentrations (see section 4.2 and 4.5).

Venous thromboembolic events
Treatment-related venous thromboembolic events were reported in approximately 1.0% of patients with solid tumours who received sunitinib on clinical trials, including GIST and MRCC.
Seven patients (3%) on sunitinib and none on placebo in a phase 3 GIST study experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT) and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.
Thirteen patients (3%) receiving sunitinib in the phase 3 treatment-naïve MRCC study and four patients (2%) on the two cytokine-refractory MRCC studies had venous thromboembolic events reported. Nine of these patients had pulmonary embolisms, one was Grade 2 and eight were Grade 4. Eight of these patients had DVT, one with Grade 1, two with Grade 2, four with Grade 3 and one with Grade 4. One patient with pulmonary embolism in the cytokine-refractory MRCC study experienced dose interruption.In treatment-naïve MRCC patients receiving IFN-α, six (2%) venous

thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolisms, all with Grade 4.
Venous thromboembolic events were reported for 1 (1.2%) subject in the sunitinib arm and 5 (6.1%) subjects in the placebo arm in the phase 3 pNET study. Two of these subjects on placebo had DVT, one with Grade 2 and one with Grade 3.
No cases with fatal outcome were reported in GIST, MRCC and pNET registrational studies. Cases with fatal outcome have been observed in post-marketing setting (see respiratory events and section 4.8).

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

Respiratory events
Patients who presented with pulmonary embolism within the previous 12 months were excluded from sunitinib clinical studies.
In patients who received sunitinib in phase 3 registrational studies, pulmonary events (i.e. dyspnoea, pleural effusion, pulmonary embolism or pulmonary oedema) were reported in approximately 17.8% of patients with GIST, in approximately 26.7% of patients with MRCC and in 12% of patients with pNET.
Approximately 22.2% of patients with solid tumours, including GIST and MRCC, who received sunitinib in clinical trials experienced pulmonary events.
Cases of pulmonary embolism were observed in approximately 3.1% of patients with GIST and in approximately 1.2% of patients with MRCC, who received sunitinib in phase 3 studies (see section 4.4 - Venous thromboembolic events). No pulmonary embolism was reported for patients with pNET who received sunitinib in the phase 3 study. Rare cases with fatal outcome have been observed in post-marketing setting (see section 4.8).

Thyroid dysfunction
Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. During sunitinib treatment, routine monitoring of thyroid function should be performed every 3 months. In addition, patients should be observed closely for signs and symptoms of thyroid dysfunction during treatment, and patients who develop any signs and/or symptoms suggestive of thyroid dysfunction should have laboratory testing of thyroid function performed as clinically indicated. Patients who develop thyroid dysfunction should be treated as per standard medical practice.
Hypothyroidism has been observed to occur early as well as late during treatment with sunitinib. Hypothyroidism was reported as an adverse reaction in 7 patients (4%) receiving sunitinib across the two cytokine-refractory MRCC studies; in 61 patients (16%) on sunitinib and three patients (<1%) in the IFN-α arm in the treatment-naïve MRCC study.
Additionally, TSH elevations were reported in 4 cytokine-refractory MRCC patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Acquired hypothyroidism was noted in 8 GIST patients (4%) on sunitinib *versus* 1 (1%) on placebo. In the phase 3 pNET study hypothyroidism was reported in 6 patients (7.2%) receiving sunitinib and in one patient (1.2%) on placebo.
Thyroid function was monitored prospectively in two studies in patients with breast cancer; SUTENT is not approved for use in breast cancer. In one study, hypothyroidism was reported in 15 (13.6%) subjects on sunitinib and 3 (2.9%) subjects on standard of care. Blood TSH increase was reported in 1 (0.9%) subject on sunitinib and no subjects on standard of care. Hyperthyroidism was reported in no sunitinib-treated subjects and 1 (1.0%) subject receiving standard of care. In the other study hypothyroidism was reported in a total of 31 (13%) sunitinib subjects and 2 (0.8%) capecitabine subjects. Blood TSH increase was reported in 12 (5.0%) sunitinib subjects and no capecitabine subjects. Hyperthyroidism was reported in 4 (1.7%) sunitinib subjects and no capecitabine subjects.

Blood TSH decrease was reported in 3 (1.3%) sunitinib subjects and no capecitabine subjects. T4 increase was reported in 2 (0.8%) sunitinib subjects and 1 (0.4%) capecitabine subject. T3 increase was reported in 1 (0.8%) sunitinib subject and no capecitabine subjects. All thyroid-related events reported were Grade 1-2.
Cases of hyperthyroidism, some followed by hypothyroidism, and cases of thyroiditis have been uncommonly reported in clinical trials and through post-marketing experience.

Pancreatitis
Increases in serum lipase and amylase activities were observed in patients with various solid tumours who received sunitinib. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours.
Pancreatitis has been observed uncommonly (<1%) in patients receiving sunitinib for GIST or MRCC.
Cases of serious pancreatic events, some with fatal outcome, have been reported.
If symptoms of pancreatitis are present, patients should have sunitinib discontinued and be provided with appropriate supportive care.
No treatment-related pancreatitis was reported in the phase 3 pNET study.

Hepatotoxicity
Hepatotoxicity has been observed in patients treated with sunitinib. Cases of hepatic failure, some with a fatal outcome, were observed in <1% of solid tumor patients treated with sunitinib. Monitor liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) before initiation of treatment, during each cycle of treatment, and as clinically indicated. If signs or symptoms of hepatic failure are present, sunitinib should be discontinued and appropriate supportive care should be provided.

Hepatobiliary disorders
Sunitinib treatment may be associated with cholecystitis, including acalculous cholecystitis and emphysematous cholecystitis. In clinical registrational studies the incidence of cholecystitis was 0.5%. Post-marketing cases of cholecystitis have been reported.

Renal function
Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.
Risk factors associated with renal impairment/failure in patients receiving sunitinib included, in addition to underlying renal cell carcinoma, older age, diabetes mellitus, underlying renal impairment, cardiac failure, hypertension, sepsis, dehydration/hypovolemia, and rhabdomyolysis.
The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. Discontinue sunitinib in patients with nephrotic syndrome.

Fistula
If fistula formation occurs, sunitinib treatment should be interrupted. Limited information is available on the continued use of sunitinib in patients with fistulae.

Impaired wound healing
Cases of impaired wound healing have been reported during sunitinib therapy.
No formal clinical studies of the effect of sunitinib on wound healing have been conducted.
Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sunitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Osteonecrosis of the Jaw (ONJ)
Cases of ONJ have been reported in patients treated with SUTENT. The majority of cases occurred in patients who had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when SUTENT and intravenous bisphosphonates are used either simultaneously or sequentially.
Invasive dental procedures are also an identified risk factor. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 4.8).

Hypersensitivity/angioedema
If angioedema due to hypersensitivity occurs, sunitinib treatment should be interrupted and standard medical care provided.

Nervous system disorders
Taste disturbance
Dysgeusia was reported in approximately 28% of patients receiving sunitinib in clinical trials.

Seizures
In clinical studies of sunitinib and from post-marketing experience, seizures have been observed in subjects with or without radiological evidence of brain metastases. In addition, there have been few reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning and visual loss, including cortical blindness, should be controlled with medical management including control of hypertension. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Tumour Lysis Syndrome (TLS)
Cases of TLS, some fatal, have been rarely observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib. Risk factors for TLS include high tumour burden, preexisting chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated as clinically indicated, and prophylactic hydration should be considered.

Infections
Serious infections, with or without neutropenia, including some with a fatal outcome, have been reported. The infections observed most commonly with sunitinib treatment are infections typically seen in cancer patients, e.g. respiratory, urinary tract, skin infections and sepsis.
Rare cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported. Sunitinib therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

*Medicinal products that may **increase** sunitinib plasma concentrations*
In healthy volunteers, concomitant administration of a single dose of sunitinib with the potent CYP3A4 inhibitor ketoconazole resulted in an increase of the combined [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values of 49% and 51%, respectively.
Administration of sunitinib with potent CYP3A4 inhibitors (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations.
Combination with CYP3A4 inhibitors should therefore be avoided, or the selection of an alternate concomitant medicinal product with no or minimal potential to inhibit CYP3A4 should be considered.

If this is not possible, the dose of SUTENT may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability (see section 4.2).

*Medicinal products that may **decrease** sunitinib plasma concentrations*
In healthy volunteers, concomitant administration of a single dose of sunitinib with the CYP3A4 inducer rifampicin resulted in a reduction of the combined [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values of 23% and 46%, respectively.
Administration of sunitinib with potent CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort/*Hypericum perforatum*) may decrease sunitinib concentrations. Combination with CYP3A4 inducers should therefore be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered. 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 for GIST and MRCC or 62.5 mg per day for pNET), based on careful monitoring of tolerability (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no studies in pregnant women using sunitinib. Studies in animals have shown reproductive toxicity including foetal malformations (see section 5.3). SUTENT should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the foetus. If SUTENT is used during pregnancy or if the patient becomes pregnant while on treatment with SUTENT, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with SUTENT.

Breast-feeding
Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite is excreted in human milk. Because active substances are commonly excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should not breast-feed while taking SUTENT.

Fertility
Based on nonclinical findings, male and female fertility may be compromised by treatment with sunitinib (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most serious adverse reactions associated with sunitinib, some fatal, are renal failure, heart failure, pulmonary embolism, gastrointestinal perforation, and haemorrhages (e.g. respiratory tract, gastrointestinal, tumour, urinary tract, and brain haemorrhages). The most common adverse reactions of any grade (experienced by at least 20% of the patients in RCC, GIST, and pNET registrational trials) included decreased appetite, taste disturbance, hypertension, fatigue, gastrointestinal disorders (i.e. diarrhoea, nausea, stomatitis, dyspepsia and vomiting), skin discolouration, and palmar-plantar erythrodysaesthesia syndrome. These symptoms may diminish as treatment continues.
Hypothyroidism may develop during treatment. Haematological disorders (e.g neutropoenia, thrombocyopoenia, and anaemia) are amongst the most common adverse drug reactions.
Fatal events other than those listed in section 4.4 above or in section 4.8 below that were considered possibly related to sunitinib included multi-system organ failure, disseminated intravascular

coagulation, peritoneal haemorrhage, rhabdomyolysis, cerebrovascular accident, dehydration, adrenal insufficiency, renal failure, respiratory failure, pleural effusion, pneumothorax, shock, and sudden death.

Tabulated list of adverse reactions
Adverse reactions that were reported in GIST, MRCC, and pNET patients in the phase 2/3 studies are listed below, by system organ class, frequency and grade of severity (NCI-CTCAE). 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), not known (cannot be estimated from the available data).

Table 1 - Adverse reactions reported in clinical trials

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Infections and infestations	Very common	Viral infections[a]	125 (11.4%)	0 (0.0%)	0 (0.0%)
	Common	Respiratory infections[b]	67 (6.1%)	16 (1.5%)	0 (0.0%)
	Common	Abscess[c]	40 (3.7%)	11 (1.0%)	2 (0.2%)
	Common	Fungal infections[d]	16 (1.5%)	1 (0.1%)	1 (0.1%)
	Common	Urinary tract infection	82 (7.5%)	15 (1.4%)	0 (0.0%)
	Common	Skin infections[e]	19 (1.7%)	1 (0.1%)	1 (0.1%)
	Uncommon	Sepsis[f]	6 (0.5%)	2 (0.2%)	3 (0.3%)
	Uncommon	Bacterial infections[g]	10 (0.9%)	2 (0.2%)	3 (0.3%)
Blood and lymphatic system disorders	Very common	Neutropoenia	200 (18.3%)	93 (8.5%)	18 (1.6%)
	Very common	Thrombocytopoenia	181 (16.6%)	62 (5.7%)	13 (1.2%)
	Very common	Anaemia	240 (22.0%)	68 (6.2%)	17 (1.6%)
	Common	Leukopoenia	95 (8.7%)	36 (3.3%)	3 (0.3%)
	Common	Lymphopoenia	38 (3.5%)	18 (1.6%)	2 (0.2%)
	Uncommon	Pancytopenia	3 (0.3%)	2 (0.2%)	0 (0.0%)
Immune system disorders	Uncommon	Hypersensitivity	10 (0.9%)	0 (0.0%)	0 (0.0%)
Endocrine disorders	Very common	Hypothyroidism	157 (14.4%)	13 (1.2%)	2 (0.2%)
	Uncommon	Hyperthyroidism	6 (0.5%)	2 (0.2%)	0 (0.0%)
Metabolism and nutrition disorders	Very common	Decreased appetite[h]	476 (43.5%)	28 (2.6%)	1 (0.1%)
	Common	Dehydration	97 (8.9%)	27 (2.5%)	3 (0.3%)
	Uncommon	Tumour lysis syndrome	2 (0.2%)	1 (0.1%)	0 (0.0%)
Psychiatric disorders	Very common	Insomnia	179 (16.4%)	5 (0.5%)	0 (0.0%)
	Common	Depression	103 (9.4%)	1 (0.1%)	2 (0.2%)
Nervous system disorders	Very common	Dizziness	149 (13.6%)	7 (0.6%)	0 (0.0%)
	Very common	Headache	290 (26.5%)	18 (1.6%)	0 (0.0%)
	Very common	Taste disturbance[i]	392 (35.9%)	2 (0.2%)	0 (0.0%)
	Common	Neuropathy peripheral	95 (8.7%)	5 (0.5%)	0 (0.0%)
	Common	Paraesthesia	93 (8.5%)	2 (0.2%)	0 (0.0%)
	Common	Hypoaesthesia	68 (6.2%)	1 (0.1%)	0 (0.0%)
	Common	Hyperaesthesia	34 (3.1%)	1 (0.1%)	0 (0.0%)
	Uncommon	Cerebrovascular accident[j]	1 (0.1%)	0 (0.0%)	1 (0.1%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Uncommon	Posterior reversible encephalopathy syndrome	2 (0.2%)	0 (0.0%)	1 (0.1%)
	Uncommon	Transient ischaemic attack	3 (0.3%)	0 (0.0%)	2 (0.2%)
Eye disorders	Common	Periorbital oedema	63 (5.8%)	1 (0.1%)	0 (0.0%)
	Common	Eyelid oedema	35 (3.2%)	1 (0.1%)	0 (0.0%)
	Common	Lacrimation increased	57 (5.2%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	Uncommon	Cardiac failure congestive	4 (0.4%)	3 (0.3%)	0 (0.0%)
	Uncommon	Cardiac failure	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Cardiomyopathy	4 (0.4%)	1 (0.1%)	0 (0.0%)
	Uncommon	Pericardial effusion	9 (0.8%)	2 (0.2%)	1 (0.1%)
	Uncommon	Left ventricular failure	1 (0.1%)	0 (0.0%)	0 (0.0%)
Vascular disorders	Very common	Hypertension	334 (30.6%)	120 (11.0%)	0 (0.0%)
	Common	Deep vein thrombosis	19 (1.7%)	11 (1.0%)	0 (0.0%)
	Common	Hot flush	41 (3.8%)	0 (0.0%)	0 (0.0%)
	Common	Flushing	31 (2.8%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea	261 (23.9%)	46 (4.2%)	3 (0.3%)
	Very common	Epistaxis	195 (17.8%)	8 (0.7%)	0 (0.0%)
	Very common	Oropharyngeal pain[k]	111 (10.2%)	2 (0.2%)	0 (0.0%)
	Very common	Cough	225 (20.6%)	6 (0.5%)	0 (0.0%)
	Common	Pulmonary embolism	21 (1.9%)	2 (0.2%)	18 (1.6%)
	Common	Pleural effusion	45 (4.1%)	13 (1.2%)	3 (0.3%)
	Common	Haemoptysis	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Common	Dyspnoea exertional	56 (5.1%)	4 (0.4%)	0 (0.0%)
	Common	Nasal congestion	40 (3.7%)	0 (0.0%)	0 (0.0%)
	Common	Nasal dryness	24 (2.2%)	0 (0.0%)	0 (0.0%)
	Uncommon	Pulmonary haemorrhage	5 (0.5%)	0 (0.0%)	0 (0.0%)
	Uncommon	Respiratory failure	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	Very common	Stomatitis[l]	321 (29.4%)	24 (2.2%)	0 (0.0%)
	Very common	Abdominal pain[m]	484 (44.3%)	96 (8.8%)	7 (0.6%)
	Very common	Vomiting	423 (38.7%)	40 (3.7%)	0 (0.0%)
	Very common	Diarrhoea	664 (60.8%)	82 (7.5%)	0 (0.0%)
	Very common	Dyspepsia	338 (30.9%)	14 (1.3%)	0 (0.0%)
	Very common	Glossodynia	109 (10.0%)	0 (0.0%)	0 (0.0%)
	Very common	Oral pain	120 (11.0%)	5 (0.5%)	0 (0.0%)
	Very common	Nausea	583 (53.3%)	45 (4.1%)	0 (0.0%)
	Very common	Constipation	312 (28.5%)	12 (1.1%)	1 (0.1%)
	Very common	Flatulence	155 (14.2%)	0 (0.0%)	0 (0.0%)
	Very common	Dry mouth	115 (10.5%)	0 (0.0%)	0 (0.0%)
	Very common	Gastro-oesophageal reflux disease	125 (11.4%)	4 (0.4%)	0 (0.0%)
	Common	Dysphagia	56 (5.1%)	5 (0.5%)	1 (0.1%)
	Common	Oesophagitis	18 (1.6%)	6 (0.5%)	0 (0.0%)
	Common	Abdominal discomfort	82 (7.5%)	2 (0.2%)	0 (0.0%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Common	Rectal haemorrhage	53 (4.8%)	4 (0.4%)	0 (0.0%)
	Common	Gingival bleeding	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Common	Mouth ulceration	21 (1.9%)	0 (0.0%)	1 (0.1%)
	Common	Proctalgia	39 (3.6%)	3 (0.3%)	0 (0.0%)
	Common	Cheilitis	28 (2. 6%)	1 (0.1%)	1 (0.1%)
	Common	Haemorrhoids	81 (7.4%)	0 (0.0%)	0 (0.0%)
	Common	Oral discomfort	19 (1.7%)	0 (0.0%)	0 (0.0%)
	Common	Eructation	22 (2.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Intestinal perforation	2 (0.2%)	2 (0.2%)	0 (0.0%)
	Uncommon	Pancreatitis	9 (0.8%)	3 (0.3%)	0 (0.0%)
	Uncommon	Anal fistula	8 (0.7%)	2 (0.2%)	1 (0.1%)
Hepatobiliary disorders	Uncommon	Hepatic failure	4 (0.4%)	1 (0.1%)	1 (0.1%)
	Uncommon	Hepatitis	1 (0.1%)	1 (0.1%)	0 (0.0%)
	Uncommon	Cholecystitis	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Hepatic function abnormal	4 (0.4%)	1 (0.1%)	1 (0.1%)
Skin and subcutaneous tissue disorders	Very common	Pigmentation disorder[n]	326 (29.8%)	1 (0.1%)	0 (0.0%)
	Very common	Palmar-plantar erythrodysaesthesia syndrome	300 (27.4%)	86 (7.9%)	0 (0.0%)
	Very common	Rash[o]	329 (30.1%)	10 (0.9%)	1 (0.1%)
	Very common	Erythema	109 (10.0%)	2 (0.2%)	0 (0.0%)
	Very common	Alopecia	116 (10.6%)	0 (0.0%)	0 (0.0%)
	Very common	Hair colour changes	200 (18.3%)	1 (0.1%)	0 (0.0%)
	Very common	Dry skin	185 (16.9%)	1 (0.1%)	0 (0.0%)
	Common	Skin exfoliation	74 (6.8%)	5 (0.5%)	0 (0.0%)
	Common	Skin Reaction[p]	29 (2.7%)	3 (0.3%)	0 (0.0%)
	Common	Eczema	19 (1.7%)	1 (0.1%)	0 (0.0%)
	Common	Blister	50 (4.6%)	4 (0.4%)	0 (0.0%)
	Common	Acne	31 (2.8%)	0 (0.0%)	0 (0.0%)
	Common	Pruritus	98 (9.0%)	1 (0.1%)	0 (0.0%)
	Common	Skin hyperpigmentation	17 (1.6%)	0 (0.0%)	0 (0.0%)
	Common	Skin lesion	52 (4.8%)	2 (0.2%)	0 (0.0%)
	Common	Hyperkeratosis	38 (3.5%)	7 (0.6%)	0 (0.0%)
	Common	Dermatitis	35 (3.2%)	6 (0.5%)	0 (0.0%)
	Common	Nail disorder[q]	44 (4.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Stevens-Johnson syndrome	1 (0.1%)	1 (0.1%)	0 (0.0%)
	Uncommon	Toxic epidermal necrolysis	1 (0.1%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity	249 (22.8%)	20 (1.8%)	3 (0.3%)
	Very common	Myalgia	128 (11.7%)	7 (0.6%)	0 (0.0%)
	Very common	Arthralgia	253 (23.1%)	19 (1.7%)	1 (0.1%)
	Very common	Musculoskeletal pain	118 (10.8%)	13 (1.2%)	1 (0.1%)
	Very common	Muscle spasms	110 (10.1%)	5 (0.5%)	0 (0.0%)
	Very common	Back pain	257 (23.5%)	32 (2.9%)	2 (0.2%)
	Common	Muscular weakness	56 (5.1%)	6 (0.5%)	1 (0.1%)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Uncommon	Osteonecrosis of the jaw	5 (0.5%)	2 (0.2%)	0 (0.0%)
	Uncommon	Fistula	4 (0.4%)	1 (0.1%)	1 (0.1%)
	Uncommon	Myopathy	1 (0.1%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	Common	Renal failure	21 (1.9%)	7 (0.6%)	1 (0.1%)
	Common	Renal failure acute	12 (1.1%)	5 (0.5%)	1 (0.1%)
	Common	Chromaturia	44 (4.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Nephrotic syndrome	2 (0.2%)	1 (0.1%)	1 (0.1%)
	Uncommon	Proteinuria	9 (0.8%)	6 (0.5%)	0 (0.0%)
General disorders and administration site conditions	Very common	Chest Pain	119 (10.9%)	14 (1.3%)	1 (0.1%)
	Very common	Mucosal inflammation	233 (21.3%)	17 (1.6%)	1 (0.1%)
	Very common	Fatigue[r]	834 (76.3%)	204 (18.7%)	13 (1.2%)
	Very common	Oedema [s]	313 (28.6%)	14 (1.3%)	1 (0.1%)
	Very common	Pyrexia	236 (21.6%)	13 (1.2%)	1 (0.1%)
	Very common	Chills	112 (10.2%)	5 (0.5%)	0 (0.0%)
	Common	Pain	95 (8.7%)	12 (1.1%)	1 (0.1%)
	Common	Influenza like illness	33 (3.0%)	0 (0.0%)	0 (0.0%)
	Uncommon	Impaired healing	3 (0.3%)	0 (0.0%)	0 (0.0%)
Investigations	Very common	Ejection fraction decreased[t]	130 (11.9%)	24 (2.2%)	0 (0.0%)
	Very common	Weight decreased	169 (15.5%)	9 (0.8%)	0 (0.0%)
	Common	White blood cell count decreased	86 (7.9%)	36 (3.3%)	0 (0.0 %)
	Common	Lipase increased	81 (7.4%)	36 (3.3%)	21 (1.9%)
	Common	Platelet count decreased	83 (7.6%)	21 (1.9%)	3 (0.3%)
	Common	Haemoglobin decreased	66 (6.0%)	20 (1.8%)	0 (0.0%)
	Common	Blood creatinine phosphokinase increased	44 (4.0%)	9 (0.8%)	4 (0.4%)
	Common	Amylase increased[u]	49 (4.5%)	25 (2.3%)	2 (0.2%)
	Common	Aspartate aminotransferase increased	50 (4.6%)	13 (1.2%)	1 (0.1%)
	Common	Alanine aminotransferase increased	42 (3.8%)	12 (1.1%)	2 (0.2%)
	Common	Blood creatinine increased	75 (6.9%)	9 (0.8%)	1 (0.1%)
	Common	Blood pressure increased	25 (2.3%)	3 (0.3%)	0 (0.0%)
	Common	Blood uric acid increased	21 (1.9%)	1 (0.1%)	12 (1.1%)
	Uncommon	Blood thyroid stimulating hormone increased	9 (0.8%)	0 (0.0%)	0 (0.0%)
	Uncommon	Electrocardiogram QT prolonged	7 (0.6%)	0 (0.0%)	1 (0.1%)
		Any adverse event	1087 (99.5%)	553 (50.6%)	210 (19.2%)

The following terms have been combined:

[a] Nasopharyngitis and oral herpes
[b] Bronchitis, lower respiratory tract infection, pneumonia and respiratory tract infection
[c] Abscess, abscess limb, anal abscess, gingival abscess, liver abscess, pancreatic abscess, perineal abscess, perirectal abscess, rectal abscess, subcutaneous abscess and tooth abscess
[d] Oesophageal candidiasis and oral candidiasis
[e] Cellulitis and skin infection
[f] Sepsis and sepsis shock
[g] Abdominal abscess, abdominal sepsis, diverticulitis and osteomyelitis
[h] Decreased appetite and anorexia
[i] Dysgeusia, ageusia and taste disturbance
[j] Cerebrovascular accident and cerebral infarction
[k] Oropharyngeal and laryngeal pain
[l] Stomatitis and aphtous stomatitis
[m] Abdominal distension and abdominal pain
[n] Yellow skin, skin discolouration and pigmentation disorder
[o] Dermatitis psoriasiform, exfoliative rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic
[p] Skin reaction and skin disorder
[q] Nail disorder and discolouration
[r] Fatigue and asthenia
[s] Face oedema, oedema and oedema peripheral
[t] Ejection fraction decreased/abnormal
[u] Amylase and amylase increased

Table 2 - Adverse reactions identified through post-marketing experience

The following adverse reactions have been identified during post-approval use of SUTENT. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programmes, clinical pharmacology studies and exploratory studies in unapproved indications.

Infections and infestations	
Uncommon*	Necrotising Fasciitis
Blood and lymphatic system disorders	
Uncommon*	Thrombotic microangiopathy
Immune system disorders	
Uncommon*	Angioedema
Endocrine disorders	
Uncommon*	Thyroiditis
Cardiac disorders	
Uncommon*	Torsade de pointes
Skin and subcutaneous tissue disorders	
Uncommon*	Pyoderma gangrenosum
Uncommon*	Erythema multiforme
Musculoskeletal and connective tissue disorders	
Uncommon*	Rhabdomyolysis

* Frequency of the adverse reaction calculated with the 3/X methodology described in the Guideline on Summary of Product Characteristics.

Description of selected adverse reactions

Infection and infestations: Cases of serious infection (with or without neutropoenia), including cases with fatal outcome, have been reported. Cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported (see also section 4.4).

Blood and lymphatic system disorders: Cases of thrombotic microangiopathy have been reported. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Immune system disorders: Hypersensitivity reactions, including angioedema, have been reported.

Nervous system disorders: There have been few reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS) (see also section 4.4).

Endocrine disorders: Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience (see also section 4.4).

Metabolism and nutrition disorders: Cases of TLS, some fatal, have been reported in patients treated with sunitinib.

Cardiac disorders: Cardiac events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported through post-marketing experience (see also section 4.4).

Respiratory, thoracic and mediastinal disorders: Cases of pulmonary embolism and cases of pulmonary haemorrhage, in some cases with fatal outcome, have been reported.

Gastrointestinal disorders: Cases of oesophagitis, in some cases with fatal outcome, have been reported.

Hepatobiliary disorders: Hepatic dysfunction has been reported and may include Liver Function Test abnormalities, hepatitis or liver failure. Cases of cholecystitis, in some cases with fatal outcome, have been reported (see also section 4.4).

Skin and subcutaneous tissue disorders: Cases of pyoderma gangrenosum, generally reversible after drug discontinuation, have been reported (see also section 4.4).

Musculoskeletal and connective tissue disorders: Cases of myopathy and/or rhabdomyolysis, some with acute renal failure, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.
Cases of fistula formation, sometimes associated with tumour necrosis and regression, in some cases with fatal outcomes, have been reported.
Cases of impaired wound healing have been reported during sunitinib therapy.
Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with SUTENT, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4).

Renal and urinary disorders: Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported (see also section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote for overdose with sunitinib and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed active substance may be achieved by emesis or gastric lavage. A few cases of overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of sunitinib, or without adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors; ATC code: L01XE04

Mechanism of action
Sunitinib inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, neoangiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (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 efficacy and safety
The clinical safety and efficacy of sunitinib has been studied in the treatment of patients with 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), the treatment of patients with MRCC and the treatment of patients with unresectable pNET.
Efficacy is based on time to tumour progression and an increase in survival in GIST, on progression free survival and objective response rates for treatment-naïve and cytokine-refractory MRCC respectively, and on progression free survival for pNET.

Gastrointestinal stromal tumours (GIST)
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 Tumour Progression (TTP) was 34.0 weeks (95% CI = 22.0 – 46.0 weeks).
A phase 3, randomized, double-blind, placebo-controlled study of sunitinib 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 sunitinib or placebo, orally once daily on Schedule 4/2 until disease progression or withdrawal from the study for another reason (207 patients received sunitinib 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. At the time of the pre-specified interim analysis, the median TTP on sunitinib was 28.9 weeks (95% CI = 21.3-34.1 weeks) as assessed by the Investigator and 27.3 weeks (95% CI = 16.0-32.1 weeks) as assessed by the Independent Review and was statistically significantly longer than the TTP on placebo of 5.1 weeks (95% CI = 4.4-10.1 weeks) as assessed by the Investigator and 6.4 weeks (95% CI = 4.4-10.0 weeks) as assessed by the Independent Review. The difference in overall survival was statistically in favour of sunitinib [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 sunitinib arm.
After the interim analysis of efficacy and safety, at recommendation of the Independent DSMB, the study was unblinded and patients on the placebo arm were offered open-label sunitinib treatment.

A total of 255 patients received sunitinib in the open-label treatment phase of the study, including 99 patients who were initially treated with placebo.
The analyses of primary and secondary endpoints in the open-label phase of the study reaffirmed the results obtained at the time of the interim analysis, as shown in the table below:

Table 3 - Summary of Efficacy Endpoints (ITT population)

	Double-Blind Treatment [a]				
	Median (95% CI)		Hazard Ratio		Placebo Cross-Over Group
Endpoint	**SUTENT**	**Placebo**	**(95% CI)**	**p**	**Treatment[b]**
Primary: TTP (weeks)					
Interim	27.3 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.329 (0.233 to 0.466)	<0.001	-
Final	26.6 (16.0 to 32.1)	6.4 (4.4 to 10.0)	0.339 (0.244 to 0.472)	<0.001	10.4 (4.3 to 22.0)
Secondary					
PFS (weeks) [c]					
Interim	24.1 (11.1 to 28.3)	6.0 (4.4 to 9.9)	0.333 (0.238 to 0.467)	<0.001	-
Final	22.9 (10.9 to 28.0)	6.0 (4.4 to 9.7)	0.347 (0.253 to 0.475)	<0.001	-
ORR (%)[d]					
Interim	6.8 (3.7 to 11.1)	0 (-)	NA	0.006	-
Final	6.6 (3.8 to 10.5)	0 (-)	NA	0.004	10.1 (5.0 to 17.8)
OS (weeks)[e]					
Interim	-	-	0.491 (0.290 to 0.831)	0.007	-
Final	72.7 (61.3 to 83.0)	64.9 (45.7 to 96.0)	0.876 (0.679 to 1.129)	0.306	-

a Results of double-blind treatment are from the ITT population and using central radiologist measurement, as appropriate.
b Efficacy results for the 99 subjects who crossed over from placebo to SUTENT after unblinding. Baseline was reset at cross-over and efficacy analyses were based on investigators assessment
c The interim PFS numbers have been updated based on a recalculation of the original data
d Results for ORR are given as percent of subjects with confirmed response with the 95% CI.
e Median not achieved because the data were not yet mature.

Median overall survival (OS) in the ITT population was 72.7 weeks and 64.9 weeks (HR 0.876, 95% CI 0.679 – 1.129, p=0.306), in the sunitinib and placebo arms respectively. In this analysis, the placebo arm included those patients randomized to placebo who subsequently received open-label sunitinib treatment.

Treatment-naïve metastatic renal cell carcinoma (MRCC)
A phase 3, randomized, multi-centre international study evaluating the efficacy and safety of sunitinib compared with IFN-α in treatment-naïve MRCC patients was conducted. Seven hundred and fifty patients were randomized 1:1 to the treatment arms; they received treatment with either sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily oral administration followed by 2 weeks of rest (schedule 4/2), or IFN-α, administered as a subcutaneous injection of 3 million units (MU) the first week, 6 MU the second week, and 9 MU the third week and thereafter, on 3 non-consecutive days each week.
The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for sunitinib treatment and 4.1 months (range: 0.1 – 45.6) for IFN- α treatment. Treatment-related serious adverse events

(TRSAEs) were reported in 23.7% of patients receiving sunitinib and in 6.9% of patients receiving IFN-α. However, the discontinuation rates due to adverse events were 20% for sunitinib and 23% for IFN-α. Dose interruptions occurred in 202 patients (54%) on sunitinib and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on sunitinib and 98 patients (27%) on IFN-α. Patients were treated until disease progression or withdrawal from the study. The primary efficacy endpoint was progression free survival (PFS). A planned interim analysis showed a statistically significant advantage for sunitinib over IFN-α, in this study, the median PFS for the sunitinib-treated group was 47.3 weeks, compared with 22.0 weeks for the IFN-α-treated group; the hazard ratio was 0.415 (95% CI: 0.320-0.539, p-value <0.001). Other endpoints included objective response rate (ORR), overall survival (OS) and safety. Core radiology assessment was discontinued after the primary endpoint had been met. At the final analysis, the ORR as determined by the investigators' assessment was 46% (95% CI: 41 - 51) for the sunitinib arm and 12.0% (95% CI: 9 - 16) for the IFN-α arm (p<0.001).
Sunitinib treatment was associated with longer survival compared to IFN-α. The median OS was 114.6 weeks for the sunitinib arm (95% CI: 100.1 - 142.9 weeks) and 94.9 weeks for the IFN-α arm (95% CI: 77.7 - 117.0 weeks) with a hazard ratio of 0.821 (95% CI: 0.673 - 1.001; p=0.0510 by unstratified log-rank).

The overall PFS and OS, observed in the ITT population, as determined by the core radiology laboratory assessment, are summarized in the table below:

Summary of Efficacy Endpoints (ITT population)

Summary of Progression-Free Survival	**Sunitinib (N=375)**	**IFN-α (N=375)**
Subject did not progress or die [n (%)]	161 (42.9)	176 (46.9)
Subject observed to have progressed or died [n (%)]	214 (57.1)	199 (53.1)
PFS (weeks)		
Quartile (95% CI)		
25%	22.7 (18.0 to 34.0)	10.0 (7.3 to 10.3)
50%	48.3 (46.4 to 58.3)	22.1 (17.1 to 24.0)
75%	84.3 (72.9 to 95.1)	58.1 (45.6 to 82.1)
Unstratified Analysis		
Hazard Ratio (sunitinib vs IFN-α)	0.5268	
95% CI for Hazard Ratio	(0.4316 to 0.6430)	
p-value[a]	<0.0001	

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

Summary of Overall Survival	**Sunitinib (N = 375)**	**IFN-α (N = 375)**
Subject not known to have died [n (%)]	185 (49.3)	175 (46.7)
Subject observed to have died [n (%)]	190 (50.7)	200 (53.3)
OS (weeks)		
Quartile (95% CI)		
25%	56.6 (48.7 to 68.4)	41.7 (32.6 to 51.6)
50%	114.6 (100.1 to 142.9)	94.9 (77.7 to 117.0)
75%	NA (NA to NA)	NA (NA to NA)
Unstratified Analysis		
Hazard Ratio (sunitinib vs IFN-α)	0.8209	
95% CI for Hazard Ratio	(0.6730 to 1.0013)	
p-value [a]	0.0510	

[a] From a 2-sided log-rank test.
NA: Not Available (Not Reached)

Cytokine-refractory metastatic renal cell carcinoma (MRCC)
A phase 2 study of sunitinib was conducted in patients who were refractory to prior cytokine therapy with interleukin-2 or IFN-α. Sixty-three patients received a starting dose of 50 mg sunitinib 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 sunitinib 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 sunitinib 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 35.8% (95% C.I. 26.8% – 47.5 %). The median DR and OS had not yet been reached.

Pancreatic neuroendocrine tumours (pNET)
A supportive phase 2, open-label, multi-center study evaluated the efficacy and safety of single-agent sunitinib 50 mg daily on Schedule 4/2 [4 weeks on treatment, 2-week rest period] in patients with unresectable pNET. In a pancreatic islet cell tumour cohort of 66 patients, the primary endpoint of response rate was 17%.
A pivotal phase 3, multi-centre, international, randomized, double-blind placebo-controlled study of single-agent sunitinib was conducted in patients with unresectable pNET.
Patients were required to have documented progression, based on RECIST, within the prior 12 months and were randomized (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled rest period (n=86) or placebo (n=85).
The primary objective was to compare Progression-Free Survival (PFS) in patients receiving sunitinib *versus* patients receiving placebo. Other endpoints included Overall Survival (OS), Objective Response Rate (ORR), Patient-reported Outcomes (PRO) and safety.
Demographics were comparable between the sunitinib and placebo groups. Additionally, 49% of sunitinib patients had non-functioning tumours *versus* 52% of placebo patients and 92% patients in both arms had liver metastases.
Use of somatostatin analogs was allowed in the study.
A total of 66% of sunitinib patients received prior systemic therapy compared with 72% of placebo patients. In addition, 24% of sunitinib patients had received somatostatin analogs compared with 22% of placebo patients.
A clinically significant advantage in investigator-assessed PFS for sunitinib over placebo was observed. The median PFS was 11.4 months for the sunitinib arm compared to 5.5 months for the placebo arm [hazard ratio: 0.418 (95% CI 0.263, 0.662), p-value =0.0001]; similar results were observed when derived tumour response assessments based upon application of RECIST to investigator tumour measurements were used to determine disease progression, as shown in Table. A hazard ratio favouring sunitinib was observed in all subgroups of baseline characteristics evaluated, including an analysis by number of prior systemic therapies. A total of 29 patients in the sunitinib arm and 24 in the placebo arm had received no prior systemic treatment; among these patients, the hazard ratio for PFS was 0.365 (95% CI 0.156, 0.857), p=0.0156. Similarly, among 57 patients in the sunitinib arm (including 28 with 1 prior systemic therapy and 29 with 2 or more prior systemic therapies) and 61 patients in the placebo arm (including 25 with 1 prior systemic therapy and 36 with 2 or more prior systemic therapies) who had received prior systemic therapy, the hazard ratio for PFS was 0.456 (95% CI 0.264, 0.787), p=0.0036.
A sensitivity analysis of PFS was conducted where progression was based upon investigator-reported tumour measurements and where all subjects censored for reasons other than study termination were treated as PFS events. This analysis provided a conservative estimate of the treatment effect of sunitinib and supported the primary analysis, demonstrating a hazard ratio of 0.507 (95% CI 0.350, 0.733) and p=0.000193. The pivotal study in pancreatic NET was terminated prematurely at the recommendation of an independent Drug Monitoring Committee, and the primary endpoint was based upon investigator assessment, both of which may have affected the estimates of the treatment effect.

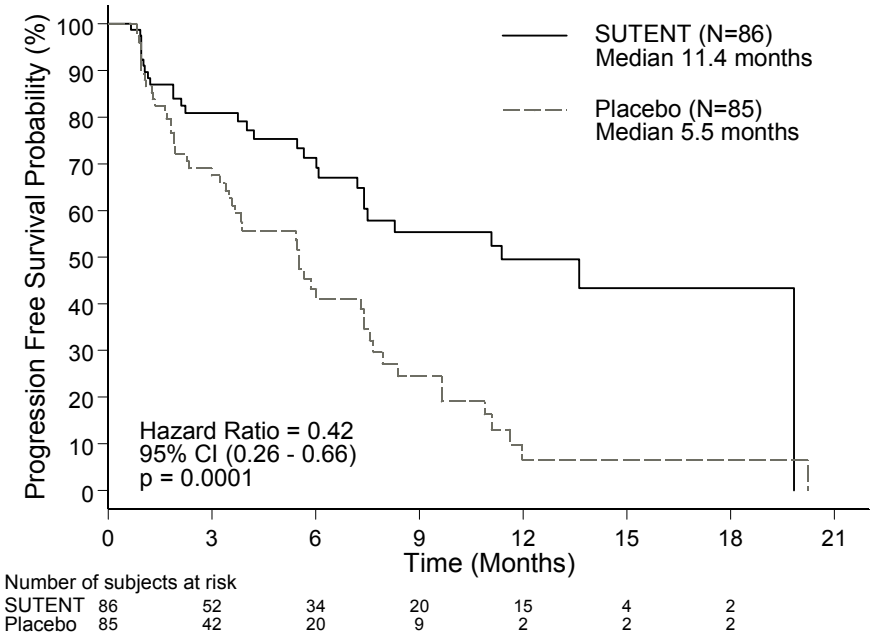
In order to rule out bias in the investigator-based assessment of PFS, a blinded independent central review of scans was performed and supported the investigator assessment, as shown in Table.

Table 4 - pNET Efficacy Results from the Phase 3 Study

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

CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached
[a]2-sided unstratified log-rank test
[b]Fisher's Exact test

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



OS data were not mature at the time of the analysis. There were 9 deaths in the sunitinib arm and 21 deaths in the placebo arm. A statistically significant difference in ORR favouring sunitinib over placebo was observed.
Upon disease progression, patients were unblinded and placebo patients could have been offered access to open-label sunitinib in a separate extension study. As a result of the early study closure, remaining patients were unblinded and offered access to open-label sunitinib in an extension study. A total of 59 patients from the placebo arm received sunitinib in an extension study.
Results from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC-30) showed that the overall global health-related quality of life and the five functioning domains (physical, role, cognitive, emotional and social) were maintained for patients on sunitinib treatment as compared to placebo with limited adverse symptomatic effects.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of the studies with SUTENT in one or more subsets of the paediatric population in gastrointestinal stromal tumours (GIST) (see section 4.2 for information on the paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with SUTENT in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of the studies with SUTENT in all subsets of the paediatric population for treatment of gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, phaeochromocytoma) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and 266 patients with solid tumours. The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers.
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 schedules tested.

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

Distribution
In vitro, binding of sunitinib and its primary active metabolite to human plasma protein was 95% and 90%, respectively, with no apparent concentration dependence. The apparent volume of distribution (V_d) for sunitinib was large, 2230 l, indicating distribution into the tissues.

Metabolic interactions
The calculated *in vitro* Ki values for all cytochrome P450 (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 induce metabolism, to any clinically relevant extent, of other active substance that may be metabolised by these enzymes.

Biotransformation
Sunitinib is metabolised primarily by CYP3A4, the cytochrome P450 isoform which produces its primary active metabolite, desethyl sunitinib, which is then further metabolised by CYP3A4 the same isoenzyme.
Co-administration of sunitinib with potent CYP3A4 inducers or inhibitors should be avoided because the plasma levels of sunitinib may be altered (see sections 4.4 and 4.5).

Elimination
Excretion is primarily via faeces (61%), with renal elimination of unchanged active substance and metabolites accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major 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/h. 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.

Special populations
Hepatic impairment: Sunitinib and its primary metabolite are mainly metabolized by the liver. Systemic exposures after a single dose of sunitinib were similar in subjects with mild or moderate (Child-Pugh class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN (upper limit of normal) or, if due to liver metastasis, > 5.0 x ULN.

Renal impairment: Population pharmacokinetic analyses indicated that sunitinib apparent clearance (CL/F) was not affected by creatinine clearance within the range evaluated (42 - 347 ml/min). Systemic exposures after a single dose of sunitinib were similar in subjects with severe renal impairment (CLcr<30 ml/min) compared to subjects with normal renal function (CLcr>80 ml/min). Although sunitinib and its primary metabolite were not eliminated through hemodialysis in subjects with ESRD, the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function.

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

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

5.3 Preclinical safety data

In rat and monkey repeated-dose toxicity studies up to 9-months duration, the primary target organ effects were identified in the gastrointestinal tract (emesis and 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 hypocellularity, and lymphoid depletion of thymus, spleen, and lymph node), exocrine pancreas (acinar cell degranulation with single cell necrosis), salivary gland (acinar hypertrophy), bone joint (growth plate thickening), uterus (atrophy) and ovaries (decreased follicular development). All findings occurred at clinically relevant sunitinib plasma exposure levels. Additional effects, observed in other studies included QTc interval prolongation, LVEF reduction, pituitary hypertrophy, and testicular tubular atrophy, increased mesangial cells in

kidney, haemorrhage in gastro-intestinal 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 genotoxic potential.

Carcinogenicity

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

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

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

Reproductive and developmental toxicity

No effects on 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 epididymides and colloid depletion in prostate and seminal vesicles at plasma exposure levels 18-fold higher than observed in clinic.

In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions, increased post-implantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5-fold higher than 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 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 5.5-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 observed in clinic.

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

were observed during the pre-weaning and post-weaning periods at 3 mg/kg/day. No development toxicity was observed at 1 mg/kg/day (approximate exposure ≥0.9 times the AUC in patients administered the RDD).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Mannitol (E421)
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

3 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 polyethylene (HDPE) bottle with a polypropylene closure containing 30 hard capsules.

Poly(chlorotrifluoroethylene)/PVC transparent perforated unit dose blister with aluminium foil coated with heat seal lacquer containing 28 x 1 hard capsules.

Not all pack sizes may be marketed.

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)

EU/1/06/347/003
EU/1/06/347/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 2006
Date of latest renewal: 9 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

PFIZER Italia S.r.l
Via del Commercio
Zona Industriale
IT-63100 Marino del Tronto (Ascoli Piceno)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP .

An updated RMP should be submitted:

- At the request of the European Medicine Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To provide the final overall survival analysis from Study A6181111, a multinational, randomized, double-blind, placebo-controlled, Phase 3 clinical trial in patients with progressive, well-differentiated pancreatic islet cell tumours (pNET), not amenable to surgery, radiation, or combined modality therapy with curative intent.	31/12/2014

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

HDPE BOTTLE 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

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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)

EU/1/06/347/001

13. BATCH NUMBER

Batch

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

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 capsules

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

HDPE BOTTLE 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

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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)

EU/1/06/347/002

13. BATCH NUMBER

Batch

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
Sunitinib
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 capsules

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

HDPE BOTTLE OUTER CARTON – 37.5 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Sutent 37.5 mg hard capsules
Sunitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains sunitinib malate, equivalent to 37.5 mg of sunitinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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)

EU/1/06/347/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sutent 37.5 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

HDPE BOTTLE – 37.5 MG CAPSULES

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

Sutent 37.5 mg hard capsules
Sunitinib
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 capsules

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

HDPE BOTTLE 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

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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)

EU/1/06/347/003

13. BATCH NUMBER

Batch

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

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 capsules

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ACLAR/PVC BLISTER 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

4. PHARMACEUTICAL FORM AND CONTENTS

28 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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)

EU/1/06/347/004

13. BATCH NUMBER

Batch

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 BLISTERS OR STRIPS

ACLAR/PVC BLISTER – 12.5 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Sutent 12.5 mg hard capsules
Sunitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

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PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ACLAR/PVC BLISTER 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

4. PHARMACEUTICAL FORM AND CONTENTS

28 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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)

EU/1/06/347/005

13. BATCH NUMBER

Batch

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 BLISTERS OR STRIPS

ACLAR/PVC BLISTER – 25 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Sutent 25 mg hard capsules
Sunitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

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PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ACLAR/PVC BLISTER OUTER CARTON – 37.5 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Sutent 37.5 mg hard capsules
Sunitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains sunitinib malate, equivalent to 37.5 mg of sunitinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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)

EU/1/06/347/008

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sutent 37.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ACLAR/PVC BLISTER – 37.5 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Sutent 37.5 mg hard capsules
Sunitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

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PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ACLAR/PVC BLISTER 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

4. PHARMACEUTICAL FORM AND CONTENTS

28 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

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)

EU/1/06/347/006

13. BATCH NUMBER

Batch

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 BLISTERS OR STRIPS

ACLAR/PVC BLISTER – 50 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Sutent 50 mg hard capsules
Sunitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

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B. PACKAGE LEAFLET

Package leaflet: Information for the user

SUTENT 12.5 mg hard capsules
SUTENT 25 mg hard capsules
SUTENT 37.5 mg hard capsules
SUTENT 50 mg hard capsules
Sunitinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sutent is and what it is used for

Sutent contains the active substance sunitinib, which is a protein kinase inhibitor. It is 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 the use of anti-cancer medicinal products.

Sutent is used to treat adults with the following types of cancer:

- Gastrointestinal stromal tumour (GIST), a type of cancer of the stomach and bowel, where imatinib (another anticancer medicine) no longer works or you cannot take imatinib.
- Metastatic renal cell carcinoma (MRCC), a type of kidney cancer, that has spread to other parts of the body.
- Pancreatic neuroendocrine tumours (pNET) (tumours of the hormone-producing cells in the pancreas) that have progressed or cannot be removed with surgery.

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

2. What you need to know before you take Sutent

Do not take Sutent
- If you are allergic to sunitinib or any of the other ingredients of Sutent (listed in section 6).

Warnings and precautions

Talk to your doctor before taking Sutent:

- **If you have high blood pressure.** Sutent can raise blood pressure. Your doctor may check your blood pressure during treatment with Sutent, and you may be treated with medicines to reduce the blood pressure, if needed.

- **If you have or have had blood disease, bleeding problems, or bruising.** Treatment with Sutent may lead to a higher risk of bleeding or lead to changes in the number of certain cells in the blood which may lead to anemia or affect the ability of your blood to clot. If you are taking warfarin or acenocoumarole, medicines which thin the blood to prevent blood clots, there may be a greater risk of bleeding. Tell your doctor if you have any bleeding while on treatment with Sutent.

- **If you have heart problems.** Sutent can cause heart problems. Tell your doctor if you feel very tired, are short of breath, or have swollen feet and ankles.

- **If you have abnormal heart rhythm changes.** Sutent can cause abnormality of your heart rhythm. Your doctor may obtain electrocardiograms to evaluate for these problems during your treatment with Sutent. Tell your doctor if you feel dizzy, faint, or have abnormal heartbeats while taking Sutent.

- **If you have had a recent problem with blood clots in your veins and/or arteries (types of blood vessels), including stroke, heart attack, embolism, or thrombosis.** Call your doctor immediately if you get symptoms such as chest pain or pressure, pain in your arms, back, neck or jaw, shortness of breath, numbness or weakness on one side of your body, trouble talking, headache, or dizziness while on treatment with Sutent.

- **If you have thyroid glands problems.** Sutent can cause thyroid gland problems. Tell your doctor if you get tired more easily, generally feel colder than other people or your voice deepens whilst taking Sutent. Your thyroid function should be checked before you take Sutent and regularly while you are taking it. If your thyroid gland is not producing enough thyroid hormone, you may be treated with thyroid hormone replacement.

- **If you have or have had pancreatic or gallbladder disorders.** Tell your doctor if you develop any of the following signs and symptoms: pain in the area of the stomach (upper abdomen), nausea, vomiting, and fever. These may be caused by inflammation of the pancreas or gallbladder.

- **If you have or have had liver problems.** Tell your doctor if you develop any of the following signs and symptoms of liver problems during Sutent treatment: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor should do blood tests to check your liver function before and during treatment with Sutent, and as clinically indicated.

- **If you have or have had kidney problems.** Your doctor will monitor your kidney function.

- **If you are going to have surgery or if you had an operation recently.** Sutent may affect the way your wounds heal. You will usually be taken off Sutent if you are having an operation. Your doctor will decide when to start Sutent again.

- **You may be advised to have a dental check-up before you start treatment with Sutent.**
  - if you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth tell your doctor and dentist immediately.
  - if you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with Sutent in particular when you are also receiving or have received intravenous bisphosphonates. Bisphosphonates are medicines used to prevent bone complications that may have been given for another medical condition.

- **If you have or have had skin and subcutaneous tissue disorders.** While you are on this medicine "pyoderma gangrenosum" (painful skin ulceration) or “necrotising fasciitis” (rapidly spreading infection of the skin/soft tissue that may be life-threatening) may occur. This event is generally

reversible after drug discontinuation. Severe skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) have been reported with the use of sunitinib, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. The rash may progress to widespread blistering or peeling of the skin and may be life-threatening. If you develop a rash or these skin symptoms, seek immediate advice from a doctor.

- **If you have or have had seizures.** Notify your doctor as soon as possible if you have high blood pressure, headache, loss of sight.

Children and adolescents
Sutent is not recommended for people aged under 18. Sutent has not been studied in children and adolescents.

Other medicines and Sutent
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription even those not prescribed.

Some medicines can affect the levels of Sutent in your body. You should inform your doctor if you are taking medicines containing the following active substances:
- ketoconazole, itraconazole – used to treat fungal infections
- erythromycin, clarithromycin, rifampicin –used to treat infections
- ritonavir –used to treat HIV
- dexamethasone – a corticosteroid used for various conditions
- phenytoin, carbamazepine, phenobarbital – used to treat epilepsy and other neurological conditions
- herbal preparations containing St. John's Wort (Hypericum perforatum) – used to treat depression and anxiety

Sutent with food and drink
You should avoid drinking grapefruit juice while on treatment with Sutent.

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.
If you might get pregnant, you should use reliable method of 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

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor will prescribe a dose that is right for you, depending on the type of cancer to be treated. If you are being treated for GIST or MRCC, the usual dose is 50 mg once daily taken for 28 days (4 weeks), followed by 14 days (2 weeks) of rest (no medicine), in 6-week cycles. If you are being treated for pNET, the usual dose is 37.5 mg once daily without a rest period.
Your doctor will determine the appropriate dose you need to take as well as if and when you need to stop treatment with Sutent.
Sutent can be taken with or without food.

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, this medicine can cause side effects, although not everybody gets them.

You must immediately contact your doctor if you experience any of those serious side effects (see also **What you need to know before you take Sutent**):

Heart problems. Tell your doctor if you feel very tired, are short of breath, or have swollen feet and ankles. These may be symptoms of heart problems that may include heart failure and heart muscle problems (cardiomyopathy).

Lung or breathing problems. Tell you doctor if you develop cough, chest pain, sudden onset of shortness of breath or coughing up blood. These may be symptoms of a condition called pulmonary embolism that occurs when blood clots travel to your lungs.

Kidney disorders. Tell your doctor if you experience altered frequency or absence of urination which may be symptoms of kidney failure.

Bleeding. Tell your doctor right away if you have any of these symptoms or a serious bleeding problem during treatment with Sutent: painful, swollen stomach (abdomen), vomiting blood, black, sticky stools, bloody urine, headache or change in your mental status, coughing up of blood or bloody sputum from the lungs or airway.

Tumour destruction leading to hole in the intestine. Tell your doctor if you have severe abdominal pain, fever, nausea, vomiting, blood in your stool, or changes in bowel habits.

Other side effects with Sutent may include:

Very common side effects (may affect more than 1 user in 10)

- Reduction in the number of platelets, red blood cells and/or white blood cells (e.g. neutrophils).
- Chest pain.
- Shortness of breath.
- Decreased activity of the thyroid gland (hypothyroidism).
- High blood pressure.
- Decreased in the amount of blood pumped by the heart.
- Infections.
- Mouth pain/irritation, mouth sores/inflammation/dryness, taste disturbances, burning or painful sensation in the tongue, upset stomach, nausea, vomiting, diarrhoea, inflammation of the digestive tract lining, excessive gas in the stomach or intestine, constipation, abdominal pain, loss/decrease of appetite, loss of strength, weight loss.
- Rapid tissue swelling caused by fluid under the skin.
- Extreme tiredness.
- Dizziness.
- Back pain, joint pain, muscle pain.
- Acid heartburn.
- Musculoskeletal pain (pain in muscles and bones).

- Pain in arms and legs.
- Muscle spasms.
- Headache.
- Nose bleeding.
- Yellow skin/skin discoloration, hair colour change, hair loss, rash on the palms of the hands and soles of the feet, blisters, rash, dryness of the skin.
- Cough.
- Chills, fever.
- Difficulty in falling asleep.

Common side effects (may affect 1 to 10 user in 100)

- Blood clots in the blood vessels.
- Fluid retention including around the lungs.
- Influenza-like syndrome.
- Depression.
- Haemorrhoids, pain in the rectum, gingival bleeding, difficulty in swallowingor inability to swallow.
- Difficulty in speaking.
- Inflammation of the oesophagus.
- Nasal dryness, congested nose.
- Excessive tear flow.
- Swelling of the limbs or around the eyes.
- Abnormal sensation of the skin, dry skin, itching, flaking and inflammation of the skin, blisters, acne, excess pigmentation of the skin.
- Abnormal sensations in extremities.
- Abnormally decreased/increased sensitivity, particularly to touch.
- High level of uric acid in the blood.
- Dehydration.
- Hot flushes.
- Abnormally coloured urine.
- Nail discolouration.

Uncommon side effects (may affect 1 to 10 user in 1,000)

- Stroke.
- Changes in the electrical activity or abnormal rhythm of the heart.
- Fluid around the heart (pericardial effusion).
- Liver failure.
- Severe reaction of the skin and/or mucous membranes (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).
- Painful skin ulceration (pyoderma gangrenosum).
- Abnormal muscle breakdown which can lead to kidney problems (rhabdomyolysis).
- Pain in the stomach (abdomen) caused by inflammation of the pancreas.
- Tumour lysis syndrome (TLS) – TLS consists of a group of metabolic complications that can occur during treatment of cancer. These complications are caused by the break-down products of dying cancer cells and may include the following: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizure, clouding of urine and tiredness associated with abnormal laboratory test results (high potassium, uric acid and phosphorous levels and low calcium levels in the blood) that can lead to changes in kidney function and acute renal failure.
- Tumour destruction leading to hole in the intestine (perforation).
- Inflammation of the liver (hepatitis).
- Inflammation (swelling and redness) of the gallbladder with or without associated gallstones.
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss (reversible posterior leukoencephalopathy syndrome).

- Abnormal tube like passage from one normal body cavity to another body cavity or the skin. Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs and symptoms of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience any of them.
- Overproduction of thyroid hormones which increases the amount of energy the body uses at rest. Inflammation of the thyroid gland.
- Problems with wound healing after surgery.
- Abnormal blood tests including pancreatic and liver enzymes.
- Loss of protein in the urine sometime resulting in swelling.
- Inappropriate and excessive reaction to an allergen.
- Muscular weakness, muscular fatigue.

Rare side effect (may affect 1 to 10 user in 10,000)

- Life-threatening infection of the soft tissue including the ano-genital region. Contact your doctor immediately if symptoms of infection occur around a skin injury, including fever, pain, redness, swelling, or drainage of pus or blood.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Sutent

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer pack and label after "EXP". The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Sutent contains

Sutent 12.5 mg hard capsules
The active substance is sunitinib. Each capsule contains sunitinib malate equivalent to 12.5 mg sunitinib.
The other ingredients are:
- *Capsule content:* mannitol (E421), croscarmellose sodium, povidone (K-25) and magnesium stearate.
- *Capsule shell:* gelatin, red iron oxide (E172) and titanium dioxide (E171).
- *Printing ink:* shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide (E171).

Sutent 25 mg hard capsules
The active substance is sunitinib. Each capsule contains sunitinib malate equivalent to 25 mg.
The other ingredients are:
- *Capsule content:* mannitol, croscarmellose sodium, povidone (K-25) and 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 and titanium dioxide (E171).

Sutent 37.5 mg hard capsules
The active substance is sunitinib. Each capsule contains sunitinib malate equivalent to 37.5 mg.
The other ingredients are:
- *Capsule content:* mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate.
- *Capsule shell:* gelatin, titanium dioxide (E171), yellow iron oxide (E172).
- *Printing ink:* shellac, propylene glycol, potassium hydroxide, black iron oxide (E172).

Sutent 50 mg hard capsules
The active substance is sunitinib. Each capsule contains sunitinib malate equivalent to 50 mg.
The other ingredients are:
- *Capsule content:* mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate.
- *Capsule shell:* gelatin, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172).
- *Printing ink:* shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide (E171).

What Sutent looks like and contents of the pack
Sutent 12.5 mg 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, containing yellow to orange granules.

Sutent 25 mg 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, containing yellow to orange granules.

Sutent 37.5 mg is supplied as hard gelatin capsules with yellow cap and yellow body, printed with black ink “Pfizer” on the cap, “STN 37.5 mg” on the body, containing yellow to orange granules.

Sutent 50 mg 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, containing yellow to orange granules.

It is available in plastic bottles of 30 capsules and in perforated unit dose blisters containing 28 x 1 capsules.
Not all pack sizes may be marketed.

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

Manufacturer
Pfizer Italia S.r.l.
Via del Commercio – Zona Industriale
63100 Marino del Tronto (Ascoli Piceno)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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