NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SUTENT® (sunitinib 12.5 mg capsules)

SUTENT® (sunitinib 25 mg capsules)

SUTENT® (sunitinib 37.5 mg capsules)

SUTENT® (sunitinib 50 mg capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of SUTENT is sunitinib malate. SUTENT capsules contain sunitinib malate equivalent to 12.5 mg, 25 mg, 37.5 mg or 50 mg sunitinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SUTENT is supplied as a hard gelatin capsule for oral administration.

12.5 mg strength: Hard gelatin capsule with Swedish Orange cap and Swedish Orange body, printed with white ink “Pfizer” on the cap, “STN 12.5mg” on the body.

25 mg strength: Hard gelatin capsule with caramel cap and Swedish Orange body, printed with white ink “Pfizer” on the cap, “STN 25mg” on the body.

37.5 mg strength: Hard gelatin capsule with yellow cap and yellow body, printed with black ink “Pfizer” on the cap, “STN 37.5mg” on the body.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUTENT is indicated for the treatment of advanced renal cell carcinoma.

SUTENT is indicated for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesilate treatment due to resistance or intolerance.

SUTENT is indicated for the treatment of unresectable, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET).

4.2 Dose and method of administration

Dose

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

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.

Dose adjustments

For GIST and mRCC, dose modifications in 12.5 mg steps may be applied based on individual safety and tolerability. The daily dose should not exceed 75 mg nor be decreased below 25 mg.

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

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

No adjustment to starting dose is required when administering SUTENT to patients with mild or moderate hepatic impairment or with renal impairment (see section 5.2 and section 4.4). Subsequent dose adjustments should be based on individual safety and tolerability.

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for age, body weight, race, gender or ECOG score.

CYP3A4 inhibitors/inducers

Strong CYP3A4 inhibitors such as ketoconazole may increase SUTENT plasma concentrations. Co-administration of SUTENT with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see section 4.5). 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 pancreatic NET, based on careful monitoring of tolerability.

CYP3A4 inducers such as rifampicin may decrease SUTENT plasma concentrations. Co-administration of SUTENT with potent CYP3A4 inducers, such as rifampicin, should be avoided (see section 4.5). If this is not possible, the dose of SUTENT may need to be increased in 12.5 mg steps (up to 87.5 mg per day for GIST and RCC or 62.5 mg per day for pancreatic NET) based on careful monitoring of tolerability.

Selection of an alternative concomitant medication with no or minimal potential to induce or inhibit CYP3A4 should be considered.

Paediatric population

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

Method of administration

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

SUTENT may be taken with or without food.

4.3 Contraindications

Use of SUTENT is contraindicated in patients with hypersensitivity to sunitinib malate or to any other component of SUTENT capsules.

4.4 Special warnings and precautions for use

Skin and tissues

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

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

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

Haemorrhagic events

Haemorrhagic events reported through post-marketing experience, some of which were fatal, have included gastrointestinal (GI), respiratory, tumour, urinary tract and brain haemorrhages. In clinical trials, treatment-related tumour haemorrhage occurred in approximately 2% of patients with GIST. These events may occur suddenly and, in the case of pulmonary tumours, may present as severe and life-threatening haemoptysis or pulmonary haemorrhage. 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 metastatic non-small cell lung cancer (NSCLC). SUTENT is not approved for use in patients with NSCLC.

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, 28% of patients had bleeding events compared with 7% of patients receiving interferon-α (IFN-α). Seven (1.9%) patients on sunitinib versus 0% of patients on IFN-α experienced Grade 3 or greater treatment-related bleeding events. Of patients receiving sunitinib for cytokine-refractory mRCC, 26% experienced bleeding. Bleeding events, excluding epistaxis, occurred in 19% of patients receiving sunitinib in the phase 3 pancreatic NET study compared to 4% of patients receiving placebo. Epistaxis was reported in 21% of patients receiving SUTENT for pancreatic NET and 5% of patients receiving placebo.

Routine assessment of haemorrhagic events should include complete blood counts and physical examination.

Epistaxis was the most common treatment-related haemorrhagic adverse event reported. Less common bleeding events in mRCC, GIST and pancreatic NET patients included rectal, gingival, upper GI, genital and wound bleeding.

Haematological

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 pancreatic NET 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 pancreatic NET 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 have been reported through post-marketing experience.

Complete blood counts should be performed at the beginning of each treatment cycle or every 4 weeks during continuous therapy for patients receiving treatment with SUTENT.

Cardiovascular

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

In the treatment-naïve mRCC study, 21% and 12% of patients on sunitinib and IFN-α, respectively, had an LVEF value below the LLN. One (<1%) patient who received sunitinib was diagnosed with congestive heart failure (CHF).

In GIST patients, treatment-related adverse events of 'cardiac failure', 'cardiac failure congestive' or 'left ventricular failure' were reported in 0.7% of patients treated with sunitinib and 1% of patients treated with placebo. In the phase 3 GIST study, treatment-related fatal cardiac reactions occurred in 1% of patients on each of the sunitinib and placebo arms of the study. In the 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 pancreatic NET 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 SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischaemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

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

QT interval prolongation

The effect of sunitinib on QT interval was investigated in an open, positive control (moxifloxacin 400 mg) trial of 24 patients, aged 20-87 years with advanced malignancies. At plasma concentrations seen with normal recommended doses, the maximum QTcF (Fridericia's correction) mean change from baseline was 9.6 msec (upper 95% CI 15.1 msec). At plasma concentrations approximately twice those seen with recommended doses, the maximum QTcF mean change from baseline was 15.4 msec (upper 95% CI 22.4 msec). The positive control (moxifloxacin 400 mg) showed a maximum QTcF mean change from baseline of 5.6 msec.

One case of Torsades de Pointes has been reported in a patient receiving sunitinib 50 mg per day. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking other drugs known to prolong the QT interval (e.g. antiarrhythmics), or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with potent CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of sunitinib reduced (see sections 4.5 and 4.2).

Hypertension

Hypertension was a very common adverse reaction reported in clinical trials in subjects with solid tumours. SUTENT dosing was reduced or temporarily delayed in approximately 2.7% of this patient population. None of these patients was discontinued from treatment with SUTENT. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of this patient population. Treatment-related hypertension was reported in approximately 24% of patients receiving sunitinib for treatment-naïve mRCC compared to 1% of patients receiving IFN-α. Severe hypertension occurred in 5% of treatment-naïve patients on sunitinib and 1% of patients on IFN-α. Treatment-related hypertension was reported in 23% of patients receiving sunitinib in a phase 3 pancreatic NET study, compared to 4% of patients receiving placebo. Severe hypertension occurred in 10% of pancreatic NET 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.

Venous thromboembolic events

Treatment-related venous thromboembolic events were reported in approximately 1% of patients with solid tumours who received sunitinib on clinical trials, including GIST and mRCC.

Seven patients (3%) on SUTENT 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.

Seven patients (2%) receiving sunitinib in the phase 3 treatment-naïve mRCC study and four patients (2%) on the two cytokine-refractory mRCC studies had treatment-related venous thromboembolic events reported. Six of these patients had pulmonary embolisms, one was Grade 3 and five were Grade 4, and five of these patients had DVT, one each with Grade 1 and 4, and three with Grade 3. One subject 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, one with Grade 1 and four with Grade 4.

No treatment-related venous thromboembolic events were reported for patients receiving sunitinib and one Grade 2 DVT was reported for a patient receiving placebo in the phase 3 pancreatic NET study. No cases with fatal outcome were reported in GIST, mRCC and pancreatic NET registration studies. Cases with fatal outcome have been reported in the post-marketing setting.

Aneurysms and artery dissections

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

Thyroid dysfunction

Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on sunitinib treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Treatment-emergent acquired hypothyroidism was noted in 4% of GIST patients on SUTENT versus 1% on placebo. Hypothyroidism was reported as an adverse event in 2% of patients on sunitinib in the treatment-naïve mRCC study and one patient (<1%) in the IFN-α arm, and in 4% of patients across the two cytokine-refractory mRCC studies. Additionally, thyroid stimulating hormone (TSH) elevations were reported in 2% of cytokine-refractory mRCC patients. Overall, 7% of the cytokine-refractory mRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. In the phase 3 pancreatic NET study treatment-related hypothyroidism was reported in 5 patients (6%) receiving sunitinib and in one patient (1%) on placebo.

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

Gastrointestinal events

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

Gastrointestinal tract

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

Pancreatitis

Increases in serum lipase and amylase were observed in patients with various solid tumours who received SUTENT. Increases in lipase levels 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.

No treatment-related pancreatitis was reported in the phase 3 pancreatic NET study.

If symptoms of pancreatitis are present, SUTENT should be discontinued and patients provided with appropriate supportive care.

Hepatotoxicity

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

Seizures

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

Surgical procedures

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

Osteonecrosis of the jaw (ONJ)

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 (IV) bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when SUTENT and IV 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 IV bisphosphonates, invasive dental procedures should be avoided if possible.

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. Patients generally at risk of TLS are those with high tumour burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

Necrotising fasciitis

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.

Thrombotic microangiopathy

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

Proteinuria

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

Hypoglycaemia

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

Hyperammonaemic encephalopathy

Hyperammonaemic encephalopathy has been reported with sunitinib. In patients who develop unexplained lethargy or changes in mental status, ammonia level should be measured, and appropriate clinical management should be initiated (see section 4.8).

Tolerability

Dose adjustments and/or interruptions may be required based on individual safety and tolerability. In patients with advanced RCC who are unable to tolerate sunitinib on the 4 weeks on, 2 weeks off (4/2) schedule, completion of the 6 week treatment cycle utilising a planned dose interruption after week 2 lasting for 1 week, or 2 weeks on, 1 week off (2/1) schedule may be considered.

Paediatric use

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

Use in the elderly

Approximately 34% of the subjects in clinical studies of SUTENT were 65 or over. No significant differences in safety or efficacy were observed between younger and older patients.

Use in hepatic insufficiency

No adjustment to starting dose is required when administering SUTENT to patients with mild or moderate (Child-Pugh class A and B) hepatic impairment. SUTENT has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment (see section 5.2).

Use in renal insufficiency

No adjustment to starting dose is required when administering SUTENT to patients with renal impairment (mild-severe) or with ESRD on haemodialysis (see section 5.2).

Laboratory tests

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

4.5 Interaction with other medicines and other forms of interaction

In-vitro studies of CYP inhibition and induction

In-vitro studies indicate that sunitinib does not induce major CYP enzymes, including CYP3A4. The calculated *in vitro* Ki values for inhibition of CYP isoforms, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 AND CYP4A9/11, by sunitinib and its primary active metabolite indicated that neither compound is likely to have any clinically relevant drug-drug interactions with drugs that may be metabolised by these enzymes.

Medicines that may increase sunitinib plasma concentrations

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

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

Medicines that may decrease sunitinib plasma concentrations

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category D

There are no studies in pregnant women using sunitinib. Studies in animals have shown reproductive toxicity including fetal malformations (see section 5.3).

As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT may result in adverse effects on pregnancy.

SUTENT should not be used during pregnancy. Women of childbearing potential must be advised to avoid becoming pregnant while receiving treatment with SUTENT. If the drug is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be apprised

of the potential hazard to the fetus. Adequate contraception should be used during therapy and for at least 4 weeks after completion of therapy.

Breast-feeding

It is not known whether sunitinib or its primary metabolite are excreted in human milk. Sunitinib and/or its metabolites are readily excreted in rat milk (milk:plasma concentration ratio of approximately 5:1). Because of the potential for serious adverse reactions in nursing infants, women should not breastfeed 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 or operate machinery have been performed. Patients should be advised that they may experience fatigue or dizziness during treatment with SUTENT.

4.8 Undesirable effects

The data described below reflect exposure to SUTENT in patients who participated in the placebo-controlled trial for the treatment of GIST, the active-controlled trial for the treatment of mRCC or the placebo-controlled trial for the treatment of pancreatic NET. The GIST and mRCC patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles and the pancreatic NET patients received a starting oral dose of 37.5 mg daily without a scheduled rest period.

Adverse events occurring in the GIST, RCC and pancreatic NET studies are described below.

See section 4.4 for more information on haematological events, seizures, thyroid dysfunction, gastrointestinal disorders, including pancreatitis, and cardiovascular events, including QT interval prolongation, hypertension and venous thromboembolic events, reported during the clinical trials.

Adverse events in placebo-controlled GIST

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

Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 56% vs. 51% of patients on SUTENT versus placebo, respectively. Diarrhoea, hypertension, bleeding, mucositis, skin abnormalities and altered taste were more common in patients receiving SUTENT. Table 1 compares the incidence of common (>10%) treatment-emergent adverse events for patients receiving SUTENT versus those on placebo.

Table 1. Treatment-Emergent Adverse Events Reported in at Least 10% of GIST Patients who received SUTENT or Placebo in the placebo-controlled GIST Study*

	GIST			
	SUTENT (n=202)		Placebo (n=102)	
Adverse Event, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any		114 (56)		52 (51)
Constitutional				
Fatigue	84 (42)	17 (8)	48 (47)	8 (8)
Fever	36 (18)	3 (2)	17 (17)	1 (1)
Gastrointestinal				
Diarrhoea	81 (40)	9 (4)	27 (27)	0 (0)
Nausea	63 (31)	3 (2)	33 (32)	5 (5)
Mucositis/stomatitis	58 (29)	2 (1)	18 (18)	2 (2)
Vomiting	49 (24)	4 (2)	24 (24)	3 (3)
Constipation	41 (20)	0 (0)	14 (14)	2 (2)
Abdominal pain[c]	67 (33)	22 (11)	39 (38)	12 (12)
Cardiac				
Hypertension	31 (15)	9 (4)	11 (11)	0 (0)
Dermatology				
Rash	28 (14)	2 (1)	9 (9)	0 (0)
Skin discolouration	61 (30)	0 (0)	23 (23)	0 (0)
Hand-foot syndrome	28 (14)	9 (4)	10 (10)	3 (3)
Neurology				
Altered taste	42 (21)	0 (0)	12 (12)	0 (0)
Headache	26 (13)	3 (2)	23 (23)	0 (0)
Musculoskeletal				
Arthralgia	24 (12)	2 (1)	16 (16)	0 (0)
Back pain	23 (11)	2 (1)	16 (16)	4 (4)
Myalgia/limb pain	28 (14)	1 (1)	9 (9)	1 (1)
Respiratory				
Dyspnoea	20 (10)	0 (0)	19 (19)	3 (3)
Cough	17 (8)	0 (0)	13 (13)	0 (0)
Metabolism/Nutrition				
Anorexia[d]	67 (33)	1 (1)	30 (29)	5 (5)
Asthenia	45 (22)	10 (5)	11 (11)	3 (3)
Haemorrhage/bleeding				
Bleeding, all sites	37 (18)	14 (7)	17 (17)	9 (9)

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

[a] Grade 4 AEs in patients on SUTENT included abdominal pain (2%) and bleeding (2%).

[b] Grade 4 AEs in patients on placebo included fatigue (3%), mucositis (1%), vomiting (1%), abdominal pain (3%), back pain (1%), and bone pain (1%).

[c] Includes abdominal quadrant, gastric, hypochondrial, abdominal, flank and cancer-related pain.

[d] Includes decreased appetite.

Oral pain other than mucositis/stomatitis occurred in 12 patients (6%) on SUTENT versus 3 (3%) on placebo. Hair colour changes occurred in 15 patients (7%) on SUTENT versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on SUTENT versus 2 (2%) on placebo.

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

Table 2. Treatment-Emergent Laboratory Abnormalities (≥10%) in the placebo-controlled GIST Study *

Adverse Event, n (%)	SUTENT (n=202)		Placebo (n=102)	
	All Grades	Grade 3/4[a]	All Grades	Grade 3/4[b]
Any		68 (34)		22 (22)
Gastrointestinal				
AST / ALT	78 (39)	3 (2)	23 (23)	1 (1)
Alkaline phosphatase	48 (24)	7 (4)	21 (21)	4 (4)
Total Bilirubin	32 (16)	2 (1)	8 (8)	0 (0)
Indirect Bilirubin	20 (10)	0 (0)	4 (4)	0 (0)
Amylase	35 (17)	10 (5)	12 (12)	3 (3)
Lipase	50 (25)	20 (10)	17 (17)	7 (7)
Cardiac				
Decreased LVEF	22 (11)	2 (1)	3 (3)	0 (0)
Renal / Metabolic				
Creatinine	25 (12)	1 (1)	7 (7)	0 (0)
Hypokalaemia	24 (12)	1 (1)	4 (4)	0 (0)
Hypernatraemia	20 (10)	0 (0)	4 (4)	1 (1)
Uric acid	31 (15)	16 (8)	16 (16)	8 (8)
Haematology				
Neutropenia	107 (53)	20 (10)	4 (4)	0 (0)
Lymphopenia	76 (38)	0 (0)	16 (16)	0 (0)
Anaemia	52 (26)	6 (3)	22 (22)	2 (2)
Thrombocytopenia	76 (38)	10 (5)	4 (4)	0 (0)

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

[a] Grade 4 AEs in patients on SUTENT included alkaline phosphatase (1%), lipase (2%), creatinine (1%), hypokalaemia (1%), neutropenia (2%), anaemia (2%), and thrombocytopenia (1%).

[b] Grade 4 AEs in patients on placebo included amylase (1%), lipase (1%), anaemia (2%), and thrombocytopenia (1%).

Grade 3 or 4 treatment-emergent laboratory abnormalities were observed in 68 (34%) versus 22 (22%) patients on SUTENT and placebo, respectively. Elevated liver function tests, pancreatic enzymes and creatinine were more common in patients treated with SUTENT than placebo. Decreased LVEF and myelosuppression were also more common with SUTENT treatment. Treatment-emergent electrolyte disturbances of all types were more common in patients on SUTENT than on placebo, including hyperkalaemia (6% vs. 4%), hypokalaemia (12% vs. 4%), hypernatraemia (10% vs. 4%), hyponatraemia (6% vs. 1%) and hypophosphataemia (9% vs. 0%). Three SUTENT patients (1.5%) had Grade 3 hypophosphataemia. Acquired hypothyroidism was noted in 8 patients (4%) on SUTENT versus 1 (1%) on placebo.

Adverse events in RCC studies

The as-treated patient population for the interim safety analysis of the Phase 3 RCC study included 250 patients, 129 randomised to SUTENT and 121 randomised to interferon-α. Dose reductions occurred in 42 patients (33%) on SUTENT and 15 patients (12%) on interferon-α. Dose interruptions occurred in 45 patients (35%) on SUTENT and 44 patients (36%) on interferon-α. The rates of treatment-emergent, non-fatal adverse events resulting in permanent discontinuation were 9% and 13% in the SUTENT and interferon-α groups, respectively. Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 67% versus 49% of patients on SUTENT versus interferon-α, respectively. Diarrhoea, hypertension, bleeding, mucositis, skin abnormalities and altered taste were more common

in patients receiving SUTENT. Table 3 compares the incidence of common (≥10%) treatment-emergent adverse events for patients receiving SUTENT versus those on interferon-α.

Data on treatment with SUTENT in the 169 patients enrolled in the pivotal and supportive studies in cytokine-refractory mRCC are also included in Table 3. The median duration of treatment was 5.5 months (range: 0.8-11.2) in the pivotal study and 7.7 months (range: 0.2-16.1) in the supportive study. Dose interruptions occurred in 48 patients (45%) in the pivotal study and 45 patients (71%) in the supportive study; one or more dose reductions occurred in 23 patients (22%) in the pivotal study and 22 patients (35%) in the supportive study.

Table 3. Treatment-Emergent Adverse Events Reported in at Least 10% of Patients with mRCC who received SUTENT or Interferon-α*

	Treatment-naïve				Cytokine-refractory	
	SUTENT (n=129)		Interferon-α (n=121)		SUTENT (N=169)	
Adverse Event, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**	**All Grades**	**Grade 3/4[c]**
Any	129 (100)	87 (67)	119 (98)	59 (49)	169 (100)	123 (73)
Constitutional						
Fatigue	81 (63)	12 (9)	77 (64)	21 (17)	125 (74)	19 (11)
Asthenia	20 (16)	6 (5)	26 (22)	7 (6)	16 (9)	4 (2)
Fever	20 (16)	2 (2)	43 (36)	0 (0)	26 (15)	2 (1)
Weight decreased	13 (10)	0 (0)	15 (12)	1 (1)	19 (11)	1 (1)
Chills	12 (9)	0 (0)	45 (37)	0 (0)	18 (11)	0 (0)
Gastrointestinal						
Diarrhoea	78 (60)	9 (7)	24 (20)	0 (0)	93 (55)	8 (5)
Mucositis/stomatitis	63 (49)	6 (5)	4 (3)	2 (2)	90 (53)	7 (4)
Nausea	59 (46)	6 (5)	50 (41)	1 (1)	92 (54)	4 (2)
Vomiting	37 (29)	7 (5)	17 (14)	1 (1)	63 (37)	7 (4)
Dyspepsia	35 (27)	1 (1)	7 (6)	0 (0)	77 (46)	1 (1)
Abdominal pain[d]	31 (24)	5 (4)	16 (13)	2 (2)	34 (20)	5 (3)
Constipation	21 (16)	0 (0)	16 (13)	0 (0)	57 (34)	1 (1)
Flatulence	19 (15)	0 (0)	5 (4)	0 (0)	24 (14)	0 (0)
Dry mouth	14 (11)	0 (0)	9 (7)	1 (1)	10 (6)	0 (0)
Glossodynia	14 (11)	0 (0)	1 (1)	0 (0)	25 (15)	0 (0)
Cardiac						
Hypertension	32 (25)	9 (7)	2 (2)	1 (1)	48 (28)	10 (6)
Oedema, peripheral	15 (12)	1 (1)	7 (6)	0 (0)	28 (17)	1 (1)
Dermatology						
Dry skin	30 (23)	0 (0)	10 (8)	0 (0)	29 (17)	0 (0)
Rash	29 (23)	1 (1)	15 (12)	1 (1)	64 (38)	1 (1)
Hair colour changes	25 (19)	0 (0)	0 (0)	0 (0)	29 (17)	0 (0)
Hand-foot syndrome	26 (20)	5 (4)	0 (0)	0 (0)	21 (12)	5 (3)
Skin discolouration	23 (18)	0 (0)	0 (0)	0 (0)	55 (33)	0 (0)
Alopecia	8 (6)	0 (0)	15 (12)	0 (0)	20 (12)	0 (0)

	Treatment-naïve				Cytokine-refractory	
	SUTENT (n=129)		Interferon-α (n=121)		SUTENT (N=169)	
Adverse Event, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**	**All Grades**	**Grade 3/4[c]**
Neurology						
Altered taste[e]	60 (47)	0 (0)	22 (18)	0 (0)	73 (43)	0 (0)
Headache	27 (21)	1 (1)	22 (18)	0 (0)	43 (25)	2 (1)
Dizziness	9 (7)	0 (0)	22 (18)	1 (1)	27 (16)	3 (2)
Musculoskeletal						
Back pain	31 (24)	5 (4)	14 (12)	2 (2)	29 (17)	1 (1)
Myalgia/limb pain	30 (23)	2 (2)	31 (26)	1 (1)	60 (36)	2 (2)
Arthralgia	25 (19)	0 (0)	22 (18)	0 (0)	48 (28)	2 (1)
Respiratory						
Cough	34 (26)	1 (1)	22 (18)	0 (0)	29 (17)	1 (1)
Dyspnoea	20 (16)	5 (4)	23 (19)	5 (4)	47 (28)	8 (5)
Metabolism/Nutrition						
Anorexia[f]	58 (45)	0 (0)	60 (50)	2 (2)	53 (31)	1 (1)
Dehydration	13 (10)	5 (4)	6 (5)	2 (2)	19 (11)	5 (3)
Haemorrhage/bleeding						
Bleeding, all sites	43 (33)	2 (2)	7 (6)	0 (0)	44 (26)	1 (1)
Psychiatric						
Insomnia	14 (11)	0 (0)	10 (8)	0 (0)	22 (13)	1 (1)
Depression	6 (5)	0 (0)	16 (13)	3 (3)	14 (8)	1 (1)

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

[a] Grade 4 AEs in patients on SUTENT included back pain (2%) and rash (1%).

[b] Grade 4 AEs in patients on interferon-α included dyspnoea (2%), depression (1%) and fatigue (1%).

[c] There were no Grade 4 adverse events among the events reported with a ≥10% incidence in the cytokine-refractory mRCC population.

[d] Includes flank pain. [e] Includes ageusia, hypogeusia and dysgeusia. [f] Includes decreased appetite.

Other significant adverse events occurring in cytokine-refractory mRCC patients receiving SUTENT included peripheral neuropathy (10%), appetite disturbance (9%), blistering of the skin (7%), periorbital oedema (7%) and increased lacrimation (6%).

In the Phase 3 study, 20 (16%) versus 14 patients (12%) experienced treatment-emergent Grade 4 chemistry laboratory abnormalities on SUTENT versus interferon-α, respectively. The most common Grade 4 chemistry abnormalities were hyperuricaemia (10% on each arm) and increased lipase (4% on SUTENT, 2% on interferon-α). The most common Grade 3 chemistry abnormalities observed on both arms were increased lipase (15% on SUTENT, 5% on interferon-α) and hyperglycaemia (4% on each arm). Other common Grade 3 laboratory abnormalities on SUTENT were increased amylase (5%) and hyponatraemia (5%), and on interferon-α were hypophosphataemia (5%) and AST (3%). Common treatment-emergent Grade 3 and 4 chemistry laboratory abnormalities in patients on SUTENT in the cytokine-refractory mRCC studies included increased lipase (16%), increased amylase (5%), hypophosphataemia (10%) and hyperuricaemia (10%).

Haematology laboratory abnormalities are presented in Table 4.

Table 4. Treatment-Emergent Grade 3 and 4 Haematology Laboratory Abnormalities*in Patients with mRCC who received SUTENT or Interferon-α

	Treatment-naïve				Cytokine-refractory	
	SUTENT (n=129)		Interferon-α (n=121)		(N=169)	
Laboratory Test	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**

Haematology, n (%)						
Neutropenia	15 (12)	2 (2)	7 (6)	1 (1)	21 (12)	1 (1)
Anaemia	4 (3)	0 (0)	3 (3)	0 (0)	9 (5)	3 (2)
Lymphopenia	19 (14)	0 (0)	26 (21)	0 (0)	33 (20)	2 (1)
Thrombocytopenia	9 (7)	0 (0)	0 (0)	0 (0)	5 (3)	0 (0)
Leukopenia	8 (6)	0 (0)	2 (2)	0 (0)	12 (7)	0 (0)

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

Long-term safety in mRCC

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

Adverse events in the phase 3 pancreatic NET study

The median number of days on treatment was 139 days (range 13-532 days) for patients on SUTENT and 113 days (range 1-614 days) for patients on placebo. Nineteen patients (23%) on SUTENT and 3 patients (4%) on placebo were on study for >1 year. Dose interruptions occurred in 25 patients (30%) on SUTENT and 10 patients (12%) on placebo. Dose reductions occurred in 26 patients (31%) on SUTENT and 9 patients (11%) on placebo. Discontinuation rates due to adverse events were 22% for SUTENT and 17% for placebo.

Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 54% versus 50% of patients on SUTENT versus placebo, respectively. Table 5 compares the incidence of common (≥10%) treatment-emergent adverse events for patients receiving SUTENT and reported more commonly in patients receiving SUTENT than in patients receiving placebo.

Table 5. Adverse Events Reported in the Phase 3 Pancreatic NET Study in at Least 10% of Patients who Received SUTENT and More Commonly Than in Patients Given Placebo*

Adverse event n (%)	Pancreatic NET			
	SUTENT (n=83)		Placebo (n=82)	
	All Grades	Grade 3/4[a]	All Grades	Grade 3/4
Any	82 (99)	45 (54)	78 (95)	41 (50)
Constitutional				
Asthenia	28 (34)	4 (5)	22 (27)	3 (4)
Fatigue	27 (33)	4 (5)	22 (27)	7 (9)
Weight decreased	13 (16)	1(1)	9 (11)	0 (0)
Gastrointestinal				
Diarrhoea	49 (59)	4 (5)	32 (39)	2 (2)
Stomatitis/oral Syndromes[b]	40 (48)	5 (6)	15 (18)	0 (0)
Nausea	37 (45)	1 (1)	24 (29)	1 (1)
Vomiting	28 (34)	0 (0)	25 (31)	2 (2)
Dyspepsia	12 (15)	0 (0)	5 (6)	0 (0)
Abdominal pain - upper	11 (13)	1 (1)	6 (7)	0 (0)
Cardiac				
Hypertension	22 (27)	8 (10)	4 (5)	1 (1)

Adverse event n (%)	Pancreatic NET			
	SUTENT (n=83)		Placebo (n=82)	
	All Grades	Grade 3/4[a]	All Grades	Grade 3/4
Dermatology				
Hair colour changes	24 (29)	1 (1)	1 (1)	0 (0)
Hand-foot syndrome	19 (23)	5 (6)	2 (2)	0 (0)
Rash	15 (18)	0 (0)	4 (5)	0 (0)
Dry skin	12 (15)	0 (0)	9 (11)	0 (0)
Neurology				
Dysgeusia	17 (21)	0 (0)	4 (5)	0 (0)
Headache	15 (18)	0 (0)	11 (13)	1 (1)
Musculoskeletal				
Arthralgia	12 (15)	0 (0)	5 (6)	0 (0)
Psychiatric				
Insomnia	15 (18)	0 (0)	10 (12)	0 (0)
Haemorrhage/Bleeding				
Bleeding events[c]	18 (22)	0 (0)	8 (10)	3 (4)
Epistaxis	17 (21)	1 (1)	4 (5)	0 (0)

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

[a] Grade 4 AEs in patients on SUTENT included fatigue (1%).

[b] Includes aphthous stomatitis, gingival pain, gingivitis, glossitis, glossodynia, mouth ulceration, oral discomfort, oral pain, tongue ulceration, mucosal dryness, mucosal inflammation, and dry mouth.

[c] Includes hematemesis, hematochezia, hematoma, hemoptysis, hemorrhage, melena, and metrorrhagia.

Table 6 provides common (≥10%) treatment-emergent laboratory abnormalities.

Table 6. Laboratory Abnormalities Reported in the Phase 3 Pancreatic NET Study in at Least 10% of Patients Who Received SUTENT

Laboratory Parameter, n (%)	Pancreatic NET					
	SUTENT			Placebo		
	N	All Grades*	Grade 3/4*[a]	N	All Grades*	Grade 3/4*[b]
Gastrointestinal						
AST	82	59 (72)	4 (5)	80	56 (70)	2 (3)
ALT	82	50 (61)	3 (4)	80	44 (55)	2 (3)
Alkaline phosphatase	82	52 (63)	8 (10)	80	56 (70)	9 (11)
Total bilirubin	82	30 (37)	1 (1)	80	22 (28)	3 (4)
Amylase	74	15 (20)	3 (4)	74	7 (10)	1 (1)
Lipase	75	13 (17)	4 (5)	72	8 (11)	3 (4)
Renal/Metabolic						
Glucose increased	82	58 (71)	10 (12)	80	62 (78)	14 (18)
Albumin	81	33 (41)	1 (1)	79	29 (37)	1 (1)
Phosphorus	81	29 (36)	6 (7)	77	17 (22)	4 (5)
Calcium decreased	82	28 (34)	0 (0)	80	15 (19)	0 (0)
Sodium decreased	82	24 (29)	2 (2)	80	27 (34)	2 (3)
Creatinine	82	22 (27)	4 (5)	80	22 (28)	4 (5)
Glucose decreased	82	18 (22)	2 (2)	80	12 (15)	3 (4)
Potassium decreased	82	17 (21)	3 (4)	80	11 (14)	0 (0)
Magnesium decreased	52	10 (19)	0 (0)	39	4 (10)	0 (0)
Potassium increased	82	15 (18)	1 (1)	80	9 (11)	1 (1)

Haematology						
Neutrophils	82	58 (71)	13 (16)	80	13 (16)	0 (0)
Hemoglobin	82	53 (65)	0 (0)	80	44 (55)	1 (1)
Platelets	82	49 (60)	4 (5)	80	12 (15)	0 (0)
Lymphocytes	82	46 (56)	6 (7)	80	28 (35)	3 (4)

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

[a] Grade 4 laboratory abnormalities in patients on SUTENT included creatinine (4%), lipase (4%), glucose decreased (2%), glucose increased (2%), neutrophils (2%), ALT (1%), AST (1%), platelets (1%), potassium increased (1%) and total bilirubin (1%).

[b] Grade 4 laboratory abnormalities in patients on placebo included creatinine (3%), alkaline phosphatase (1%), glucose increased (1%) and lipase (1%).

Post-marketing experience

The following adverse events have been identified during post-approval use of sunitinib (see also section 4.4). Since these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders

Rare cases of thrombotic microangiopathy, some with fatal outcome, have been reported. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician (see section 4.4, Thrombotic Microangiopathy).

Cardiac disorders

Cardiac failure, cardiomyopathy, myocardial ischaemia, myocardial infarction and left ventricular failure, some with fatal outcome, have been reported. Congestive cardiac failure, prolonged QT interval and torsade de pointes have been reported.

Endocrine disorders

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

Gastrointestinal disorders

Pancreatitis, gastrointestinal perforation and oesophagitis have been reported.

Haemorrhagic events

Cases of pulmonary, GI, tumour, urinary tract and brain haemorrhage, some fatal, have been reported. Cases of fatal haemorrhage associated with thrombocytopenia have been reported.

Hepatobiliary disorders

Cases of hepatic failure and cholecystitis, particularly acalculous cholecystitis, have been reported.

Immune system disorders

Hypersensitivity reactions, including angioedema, have been reported.

Infections and infestations

Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported. The infections observed most commonly with sunitinib treatment are infections typically seen in cancer patients, including respiratory infections (e.g. pneumonia, bronchitis), urinary tract

infections, skin infections (e.g. cellulitis), sepsis/septic shock and abscess (e.g. oral, genital, anorectal, skin, limb, visceral). Infections may be bacterial (e.g. intra-abdominal, osteomyelitis), viral (e.g. nasopharyngitis, oral herpes) or fungal (e.g. candidiasis: oral, oesophageal). Rare cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported (see section 4.4).

Investigations

Increased TSH and blood uric acid have been reported.

Metabolism and nutrition disorders

Cases of tumour lysis syndrome (TLS), some fatal, have been reported in patients treated with sunitinib.

Decreases in blood glucose, in some cases clinically symptomatic, have been reported (see section 4.4, Hypoglycaemia).

Musculoskeletal and connective tissue disorders

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

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

Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with sunitinib, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to IV bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see section 4.4).

Nervous system disorders

Taste disturbances, including ageusia, have been reported.

Hyperammonaemic encephalopathy has been reported.

Renal and urinary disorders

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

Cases of proteinuria and rare cases of nephrotic syndrome have been reported (see section 4.4).

Respiratory, thoracic and mediastinal disorders

Pulmonary embolism, in some cases with fatal outcome, has been reported. Cases of pleural effusion have been reported.

Skin and subcutaneous tissue disorders

Cases of erythema multiforme, pyoderma gangrenosum and Stevens-Johnson syndrome have been reported.

Vascular disorders

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Cases of overdose have been reported; some cases were associated with adverse reactions consistent with the known safety profile of SUTENT.

There is no specific antidote for overdosage with SUTENT and treatment of overdose should consist of general supportive measures.

Sunitinib is not removed from blood by dialysis.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: LO1XE04.

Mechanism of action

Sunitinib is a small molecule that simultaneously inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, pathologic angiogenesis and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a wide range of kinases and was identified as a potent inhibitor of platelet-derived growth factor receptor β (PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R) and the glial cell-line derived neurotrophic factor receptor (RET).

Inhibition of the tyrosine kinase activity of these RTKs by sunitinib has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays in which the activity of PDGFRα was inhibited. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays for inhibition of PDGFRβ, VEGFR2 and KIT tyrosine kinase activities.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumour xenografts expressing RTK targets *in vivo* and demonstrated inhibition of tumour growth or tumour regression, and/or inhibited metastases in some experimental models of cancer. Consistent with its multi-targeted profile, sunitinib demonstrated the ability to directly inhibit growth of tumour cells expressing dysregulated RTK targets (PDGFR, RET, FLT3 or KIT) and to inhibit tumour angiogenesis.

Clinical efficacy and safety

Advanced renal cell carcinoma (RCC)

A 1:1 randomised, multi-centre, Phase 3 study comparing SUTENT with interferon-α is ongoing in over 700 treatment-naïve patients with metastatic RCC (mRCC). The starting dose of SUTENT is sunitinib 50 mg orally once daily as a single agent for 4 consecutive weeks followed by 2 weeks off (Schedule 4/2) and the dosage of interferon-α2a (IFN-α) administered subcutaneously is 9 MIU three times weekly.

The primary endpoint is Progression Free Survival (PFS) and the study is also powered to detect an improvement in Overall Survival (OS). The statistical plan includes an interim analysis of Objective Response Rate (ORR) between the two treatments after 250 patients have completed at least 3 cycles. The results of the planned interim analysis, with ORR as the primary endpoint, are provided in Table 7.

Table 7. SUTENT versus IFN-α in First-Line Treatment of mRCC Objective Response Rate and Progression Interim Results

Core Imaging Laboratory Measurements (N= 235)		
	SUTENT N=129 (%)	**IFN-α N=124 (%)**
Patients with baseline assessment, n (%)	115 (89.1)	106 (85.5)
Best Overall Response		
Complete Response	0 (0.0)	0 (0.0)
Partial Response	33 (25.6)	9 (7.3)
Stable Disease	53 (41.1)	54 (43.5)
Progressive Disease	25 (19.4)	29 (23.4)
Not evaluable (< 6 weeks on study)	4 (3.1)	14 (11.3)
Scans still to assess	14 (10.9)	18 (14.5)
Overall Response Rate (CR+PR), n (%) (95% CI)	33 (25.6) (18.3 – 34.0)	9 (7.3) (3.4 – 13.3)
Patients with progression or death due to any cause while on study[1], n (%)	32 (24.8)	51 (41.1)
Median Progression Free Survival (PFS) in weeks, (95% CI)	NA (NA, NA)	23.0 (16.7, NA)

[1] On study includes a 28-day follow up period after the last dose of study drug.
NA = Could not be calculated because the data were not mature.

The use of single agent SUTENT in the treatment of advanced cytokine-refractory RCC was investigated in two studies, a pivotal Phase 2 study and a supportive Phase 2 study. Both studies were single-arm, non-randomised, multi-centre, open-label studies in patients with mRCC who were refractory to prior cytokine treatment (interferon-α, interleukin-2, or interferon-α plus interleukin-2). The primary endpoint for both studies was ORR. Secondary endpoints included assessment of Time to Tumour Progression (TTP), PFS, Duration of Response (DR) and OS.

The pivotal study enrolled 106 patients and the supportive study enrolled 63 patients. The starting dose in both studies was sunitinib 50 mg daily on Schedule 4/2. Therapy was continued until the patients met withdrawal criteria or had progressive disease. The baseline age, gender, race, ECOG performance status, baseline malignancy and prior treatment history of the patients were comparable between the two studies. Most patients enrolled in the studies (97% of the pooled population) had

undergone nephrectomy; prior nephrectomy was required for patients enrolled in the pivotal study. All patients had received one previous cytokine regimen, to which 9.5% (n=16) had experienced an objective disease response. Metastatic disease present at the time of study entry included lung metastases in 81% of patients. Liver metastases were more common in the pivotal study (27% vs. 16% in the supportive study) and bone metastases were more common in the supportive study (51% vs. 25% in the pivotal study); 52% of patients in the pooled population had at least 3 metastatic sites.

The results of the two studies are provided in Table 8.

Table 8. Efficacy Results in second-line treatment of mRCC

Efficacy Parameter	**Pivotal Study N = 106**	**Supportive Study N = 63**
Objective Response Rate: CR + PR [% (95% CI)]	35.8 (26.8, 45.7)[a]	25.4 (15.3, 37.9) [a]
Median Time to Progression [weeks (95% CI)]	38.0 (34.0, *)[a]	37.7 (24.0, 46.4)[b]
Median Progression Free Survival [weeks (95% CI)]	36.0 (33.9, 62.6)[a]	37.7 (24.0, 46.4) [b]
Median Duration of Response [weeks (95% CI)]	** (42.0, *)	54 (34.3, 70.1)

CI=Confidence interval, CR=Complete response, PR=Partial response.

[a] Assessed by blinded core radiology laboratory.

[b] Assessed by investigator; TTP and PFS were not measured by the core laboratory in the supportive study.

* Data not mature enough to determine upper confidence limit .

** Median DR has not yet been reached.

The primary endpoint for both studies was ORR. The core imaging laboratory reported 38 partial responses (PRs) in the pivotal study resulting in an ORR of 35.8% (95% CI: 26.8, 45.7). Consistent results were observed in the supportive study where an ORR of 25.4% was demonstrated. The majority of objective disease responses were observed during Cycles 2 to 4; responses were observed as late as Cycle 11. Duration of tumour response (DR) data from the pivotal study is premature as only a relatively small number of patients responding to treatment had experienced disease progression (Median DR not yet reached [95% CI: 42.0 weeks,*] using core-laboratory assessment). The median DR in the supportive study, based on investigator assessment, was 54 weeks (95% CI: 34.3, 70.1). These results indicate that disease responses induced by SUTENT in patients with cytokine-refractory RCC were durable.

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 a dose of 50 mg daily at the recommended treatment schedule of 4 weeks on followed by 2 weeks off (Schedule 4/2). In this study the investigator-assessed median TTP was 34.0 weeks (95% CI = 22.0–46.0 weeks).

A randomised, double-blind, placebo-controlled Phase 3 study of SUTENT was conducted in patients with GIST who were intolerant to, or had experienced disease progression during or following treatment with, imatinib (median maximum daily dose 800 mg). In this study, 312 patients were randomised (2:1) to receive either SUTENT 50 mg or placebo orally once daily on Schedule 4/2 until disease progression or withdrawal from the study for another reason (207 patients received SUTENT and 105 patients received placebo).

The results of the dose escalating and Phase 3 studies are provided in Table 9.

Table 9. GIST Efficacy Results[a]

Efficacy Parameter	**Phase 3 Study**[b]		**Dose escalating study**[c]
	SUTENT N = 207	**Placebo N = 105**	**SUTENT N = 55**
Median Time to Progression [weeks (95% CI)]	27.3[d] (16.0, 32.1)	6.4[d] (4.4, 10.0)	34.0 (22.0, 46.0)
Median Progression Free Survival [weeks (95% CI)]	24.6[e] (12.1, 28.3)	6.4[e] (4.4, 10.0)	34.0 (22.0, 46.0)
Median Overall Survival [weeks (95% CI)]	*[f] (43.7, *)	* (30.0, *)	Not measured
Objective Response Rate (ORR): CR+PR [n (%)]	14 (6.8[g])	0	5 (9.1)
Duration of SD ≥ 22 weeks [n (%)]	36 (17.4)	2 (1.9)	28 (50.9)
Clinical benefit rate: SD ≥22 weeks + CR + PR [n (%)]	50 (24.2)	2 (1.9)	33 (60.0)

CI=Confidence interval, CR=Complete response, PR=Partial response, SD=Stable disease.
a Data based on cutoff date of 1 January 2005 for the phase 3 study and 1 December 2004 for the dose-escalating study.
[b] Core Imaging Laboratory Assessment.
[c] Investigator Assessment (Core Imaging not conducted for secondary endpoints).
[d] Hazard Ratio 0.329, 95% CI 0.223, 0.466, p-value <0.0001.
[e] Hazard Ratio 0.333, 95% CI 0.238, 0.467, p-value <0.0001.
[f] Hazard Ratio 0.491, 95% CI 0.290, 0.831, p-value = 0.007.
[g] 95% CI = 3.7, 11.1.
* Unable to calculate due to the low number of deaths in the ongoing study.

In the Phase 3 study, a statistically significant prolongation in the primary endpoint, TTP, was observed between the treatment arms and was considered clinically significant (Figure 1). The median TTP by core imaging laboratory assessment was 27.3 vs. 6.4 weeks for the SUTENT and placebo arms, respectively (Hazard Ratio 0.329, 95% CI 0.222, 0.466, p-value <0.0001). The risk of experiencing progression was 3 times higher for patients in the placebo arm compared to the SUTENT arm (representing a 67% reduction in the risk of developing progressive disease for patients receiving SUTENT). Median TTP for the group of patients treated with SUTENT was more than 4 times longer than that for patients receiving placebo. Results of the dose escalating study with median TTP of 34.0 weeks by investigator assessment are consistent with the results of the Phase 3 study.

In the Phase 3 study, 14 PRs (6.8% ORR), as determined by response evaluation criteria in solid tumours (RECIST) using core laboratory assessment were observed in patients treated with SUTENT, while none was observed in the placebo arm. Results of the dose escalating study were consistent, with 5 PRs reported (9.1% ORR) by investigator assessment.

When evaluated for clinical benefit response (percentage of patients experiencing CR, PR or stable disease [SD] ≥22 weeks), 50 (24.2%) of patients treated with SUTENT in the Phase 3 study experienced clinical benefit, while only 2 (1.9%) placebo-treated patients experienced clinical benefit. In the dose escalating study, the clinical benefit rate was 60%. The difference in clinical benefit response rates between studies is the result of the longer follow-up period in the dose escalating study, resulting in more patients treated for at least 22 weeks compared to the Phase 3 study. These results demonstrate the ability of SUTENT to achieve and maintain disease control in patients with GIST after failure of imatinib.

Figure 1. Kaplan-Meier Curve of TTP in Phase 3 GIST Study (Intent-to-Treat Population)

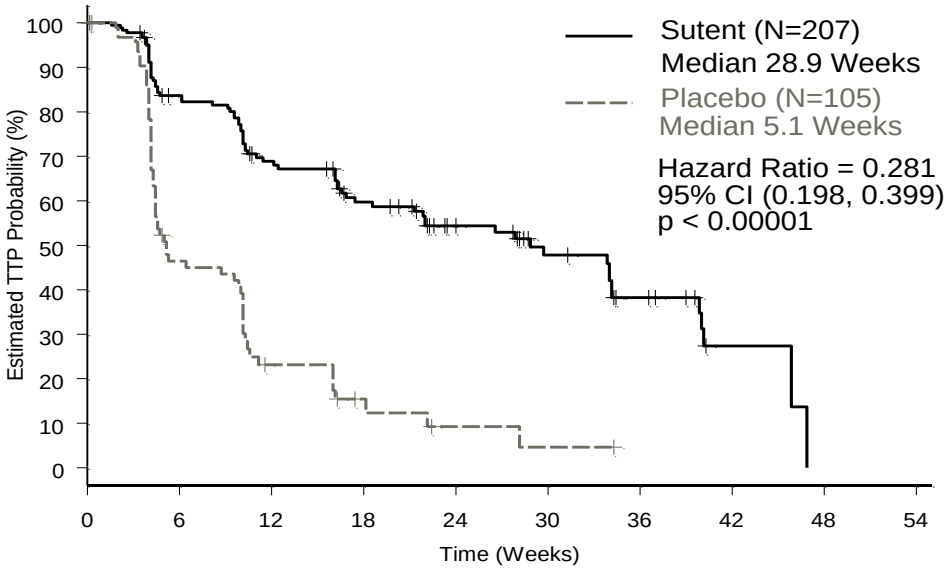
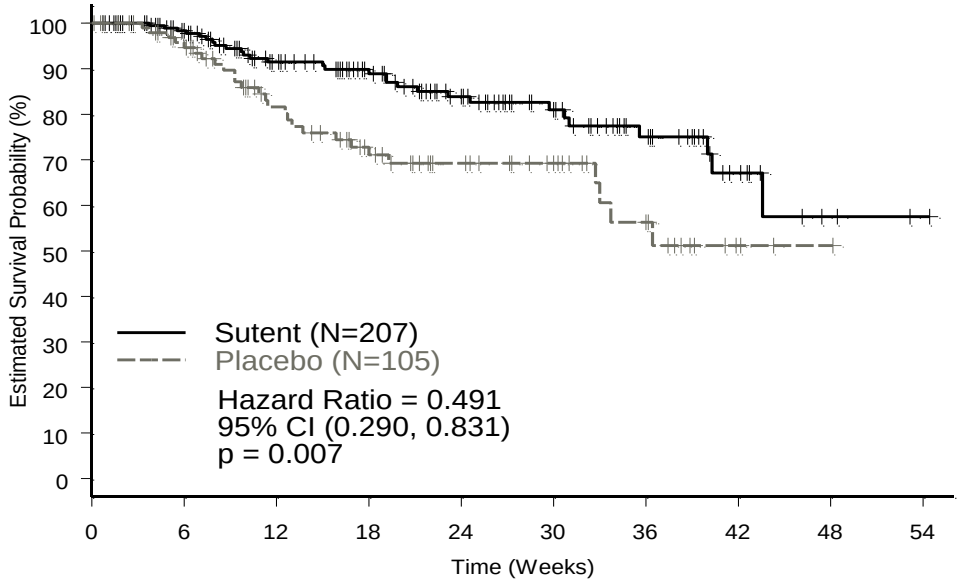


Figure 2. Kaplan-Meier Curve of OS (Intent-to-Treat Population)



The difference in OS was statistically significant (Hazard Ratio 0.491; 95% CI: 0.290, 0.831, p = 0.007) in the Phase 3 study (Figure 2). The risk of death was twice as high in patients in the placebo arm of the study compared to the SUTENT arm. Median OS had not yet been reached in either treatment arm at the time of the analysis. The percentages of deaths were 14% for SUTENT vs. 25% for placebo.

Pancreatic neuroendocrine tumours (pancreatic NET)

A supportive phase 2, open-label, multi-centre study evaluated the efficacy and safety of single-agent SUTENT 50 mg daily on Schedule 4/2 [4 weeks on treatment, 2-week rest period] in patients with unresectable pancreatic NET. In a pancreatic islet cell tumour cohort of 66 patients, the primary endpoint of response rate was 17%. All were partial responses.

A pivotal phase 3, multi-centre, international, randomised, double-blind placebo-controlled study of single-agent SUTENT was conducted in patients with unresectable, well-differentiated pancreatic NET. Patients were required to have documented progression, based on RECIST, within the prior 12 months and were randomised (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 PFS in patients receiving sunitinib versus patients receiving placebo. Other endpoints included OS, ORR, Patient-reported Outcomes (PRO) and safety. Use of somatostatin analogs was allowed in the study.

Demographics were comparable between the SUTENT and placebo groups. Additionally, 49% of SUTENT patients had non-functioning tumours versus 52% of placebo patients and 92% of patients in both arms had liver metastases. A total of 66% of SUTENT patients received prior systemic therapy compared with 72% of placebo patients. In addition, 24% of SUTENT patients had received somatostatin analogs compared with 22% of placebo patients.

A clinically significant advantage in PFS for SUTENT over placebo was seen. 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]. A hazard ratio favouring SUTENT was observed in all subgroups of baseline characteristics evaluated. The results are provided in Table 10.

This study was terminated early at the recommendation of an independent Drug Monitoring Committee and patients offered open-label SUTENT in extension studies.

Table 10. Pancreatic NET Efficacy Results from the Phase 3 Study

Efficacy Parameter	SUTENT (n = 86)	Placebo (n = 85)	P-Value	HR (95% CI)
Progression-Free Survival [median, months] (95% CI)	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	0.0001[a]	0.418 (0.263, 0.662)
Overall Survival [median, months][a] (95% CI)	NR (21.5, NR)	NR (16.3, NR)	0.0644[b]	0.594 (0,340, 1.038)
Objective Response Rate [%] (95% CI)	9.3 (3.2, 15.4)	0	0.0066[c]	NA

CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached.

[a] All subjects originally randomised were included and analysed under the original randomised treatment arm.

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

[c] Fisher's Exact test.

Figure 3. Kaplan-Meier Curve of PFS in the Phase 3 Pancreatic NET Study

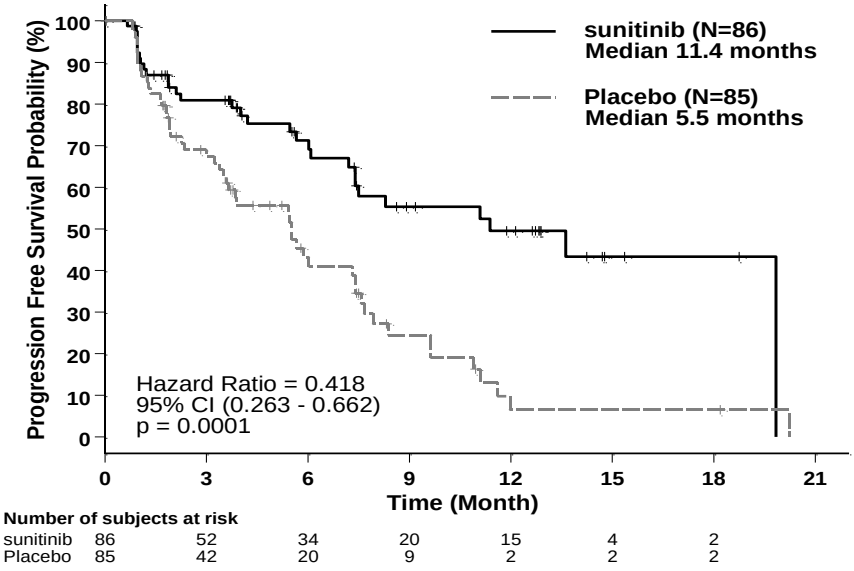
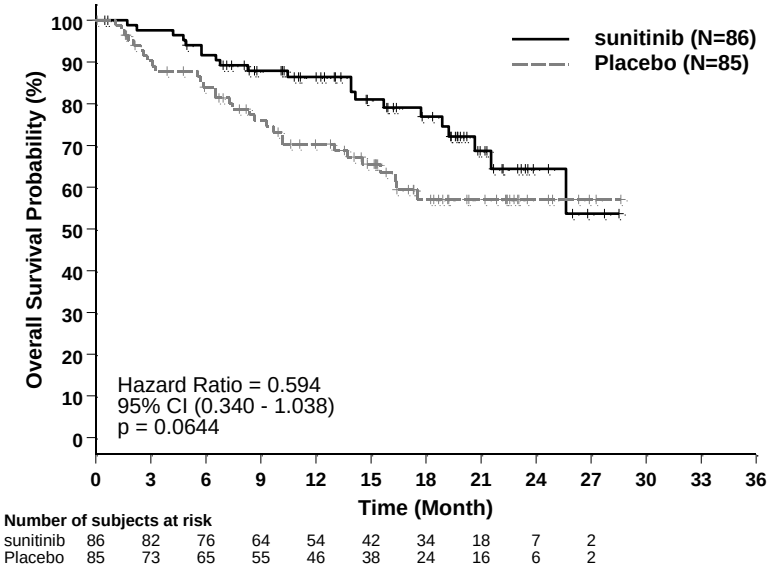


Figure 4. Kaplan-Meier Curve of OS in the Phase 3 Pancreatic NET Study



OS data were not mature at the time of the analysis. There were 21 deaths in the SUTENT arm and 30 deaths in the placebo arm. Patients in the placebo arm were able to receive SUTENT after disease progression, possibly confounding the survival analysis. A statistically significant difference in ORR favouring SUTENT over placebo was observed.

Results from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC-30) demonstrated 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.

5.2 Pharmacokinetic properties

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

Absorption

Absolute bioavailability has not been determined.

Maximum plasma concentrations (C_{max}) are generally observed between 6 - 12 hours (T_{max}) following oral administration. In multiple dose studies in the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionately with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By day 14, combined plasma concentrations of sunitinib and its active metabolite are 62.9-101 ng/mL which are target concentrations predicted from preclinical data to inhibit receptor phosphorylation *in vitro* and result in tumour stasis/growth reduction *in vivo*.

Food has no effect on the bioavailability of sunitinib.

Distribution

Binding of sunitinib and its primary active metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no apparent concentration dependence in the range of 100-4000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was large, 2230 L, indicating distribution into the tissues.

Biotransformation

Sunitinib is metabolised primarily by the cytochrome P450 enzyme, CYP3A4, which produces its primary active metabolite, which is also metabolised by CYP3A4. The primary active metabolite comprises 23 to 37% of the total exposure.

Elimination

Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active metabolite are approximately 40-60 hours and 80-110 hours, respectively.

Excretion is primarily via faeces (61%) with renal elimination of drug and metabolites accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine and faeces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and faeces, but generally were not found in plasma. Total oral clearance (Cl/F) was 34-62 L/hr with an inter-patient variability of 40%.

No significant changes in the pharmacokinetics of sunitinib or the primary, active metabolite are observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

Special populations

The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers.

Hepatic impairment

Sunitinib and its primary metabolite are mainly metabolised by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh class C) hepatic impairment.

Renal impairment

Systemic exposures after a single dose of SUTENT 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 haemodialysis in subjects with end-stage renal disease (ESRD), the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function.

Population pharmacokinetics

Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, gender, race or Eastern Cooperative Oncology Group (ECOG) performance status on the pharmacokinetics of sunitinib or the primary active metabolite.

Paediatric population

There are no pharmacokinetic data available in paediatric patients.

5.3 Preclinical safety data

Genotoxicity

Sunitinib was not genotoxic in *in vitro* tests for bacterial gene mutation and human lymphocyte structural chromosomal aberrations, or in an *in vivo* micronucleus test in rats. Polyploidy (numerical chromosome aberrations) was induced by high sunitinib concentrations in human lymphocytes *in vitro*. The major active metabolite was indirectly evaluated in these tests.

Carcinogenicity

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

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

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

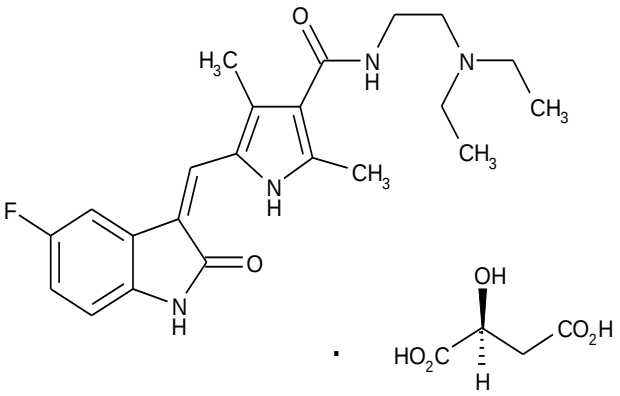
Reproductive and developmental toxicity

Rat fertility was unaffected by doses of up to 10 mg/kg/day (males) or 5 mg/kg/day (females), which resulted in exposures (AUC) to sunitinib plus its primary metabolite that were respectively about 26 times and 5 times the human value with the recommended daily dose of 50 mg. Embryolethality was seen in treated females at 5 mg/kg/day, but not at 1.5 mg/kg/day.

Adverse effects on the female reproductive system were seen in toxicity studies in cynomolgus monkeys (including impaired ovarian follicular development, uterine endometrial atrophy and vaginal epithelial atrophy) and rats (corpora lutea degeneration and uterine atrophy). Adverse effects on the male reproductive system were also seen in toxicity studies in rats (including testicular tubular atrophy). In both species, these effects mainly occurred at doses that elicited major toxicity.

Sunitinib was shown to be embryotoxic and teratogenic when administered to pregnant rats and rabbits. Increased fetal resorptions, decreased fetal weights and skeletal malformations were observed in rats with a dose of 5 mg/kg/day, while increased fetal variations occurred at 3 mg/kg/day. These doses resulted in exposures of sunitinib plus its primary metabolite (AUC) that were about 6 and 2 times the human value with the recommended daily dose of 50 mg, respectively. Limited investigations in rabbits showed the occurrence of cleft lip at doses of 1 and 5 mg/kg/day, which resulted in exposures of sunitinib plus its primary metabolite that were about 0.3 times and 3 times the human value, respectively. Increased fetal resorptions were observed at 5 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS



Chemical Name: (Z)-*N*-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3*H* indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (*S*)-2-hydroxysuccinate

Molecular Formula: $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$

Molecular Weight: 532.57

CAS Registry Number: 341031-54-7

6.1 List of excipients

12.5 mg strength

Capsule content:
Mannitol
Croscarmellose sodium
Povidone
Magnesium stearate

Capsule shell:
Gelatin
Titanium dioxide
Sodium laurilsulfate
Red iron oxide CI77491

Printing ink:
Shellac
Propylene glycol
Sodium hydroxide
Povidone
Titanium dioxide

25 mg strength

Capsule content:
Mannitol
Croscarmellose sodium
Povidone
Magnesium stearate

Capsule shell:
Gelatin
Titanium dioxide
Sodium laurilsulfate
Red iron oxide CI77491
Yellow iron oxide CI77492
Black iron oxide CI77499

Printing ink:
Shellac
Propylene glycol
Sodium hydroxide
Povidone
Titanium dioxide

37.5 mg strength

Capsule content:
Mannitol
Croscarmellose sodium
Povidone
Magnesium stearate

Capsule shell:
Gelatin
Titanium dioxide
Sodium laurilsulfate
Yellow iron oxide CI77492

Printing ink:
Shellac
Propylene glycol

Potassium hydroxide
Black iron oxide

50 mg strength

Capsule content:
Mannitol
Croscarmellose sodium
Povidone
Magnesium stearate

Capsule shell:
Gelatin
Titanium dioxide
Sodium laurilsulfate
Red iron oxide CI77491
Yellow iron oxide CI77492
Black iron oxide CI77499

Printing ink:
Shellac
Propylene glycol
Sodium hydroxide
Povidone
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

HDPE bottles or aluminium/polyvinyl chloride (PVC)/polychlorotriflouroethylene (PCTFE, Aclar) blister packs containing 28 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine.

8. SPONSOR

Pfizer New Zealand Limited
PO Box 3998
Auckland, New Zealand
Toll Free number: 0800 736 363
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 26 October 2006 (12.5 mg, 25 mg, 50 mg), 08 December 2016 (37.5 mg).

10. DATE OF REVISION OF THE TEXT

21 March 2025

Summary table of changes

Section changed	Summary of new information
4.4	Addition of hyperammonaemic encephalopathy precaution.
4.8	Addition of post marketing adverse event - hyperammonaemic encephalopathy. Update to the NZ reporting adverse reactions website.
4.9	Update overdose wording as per NZ Data Sheet Template v1.4 January 2025.
8	Addition of sponsor website address.
All	Minor editorial changes.