SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SUTENT® 12,5 mg capsules

SUTENT® 25 mg capsules

SUTENT® 50 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 12,5 mg capsule contains 12,5 mg of sunitinib (as malate).

Each 25 mg capsule contains 25 mg of sunitinib (as malate).

Each 50 mg capsule contains 50 mg of sunitinib (as malate).

Contains sugar (mannitol)

Excipients with known effect

Each SUTENT 12,5 mg capsule contains 80,0 mg mannitol.

Each SUTENT 25 mg capsule contains 39,663 mg mannitol.

Each SUTENT 50 mg capsule contains 79,326 mg mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

SUTENT 12,5 mg capsules: 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 capsules: 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 50 mg capsules: 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gastrointestinal stromal tumour (GIST)

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

Metastatic renal cell carcinoma (MRCC)

SUTENT is indicated for the treatment of treatment-naïve advanced and/or metastatic renal cell carcinoma.

SUTENT is also indicated for the treatment of metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy (interferon α, interleukin-2).

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

Efficacy and safety has not been demonstrated for more than 12 months.

Pancreatic neuroendocrine tumours (pNET)

SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

4.2 Posology and method of administration

Therapy should be initiated by a medical practitioner experienced in the treatment of renal cell carcinoma, GIST or pNET.

Posology

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

For pNET, the recommended dose of SUTENT is 37,5 mg taken orally once daily without a scheduled rest period.

Dose modifications

Safety and tolerability

For GIST and MRCC, dose modifications in 12,5 mg increments 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

In patients receiving SUTENT with a potent CYP3A4 inducer such as rifampicin, its use should be avoided (see section 4.5). If this is not possible, the dosage of SUTENT may need to be increased in 12,5 mg increments (up to 87,5 mg per day for GIST and MRCC or 62,5 mg per day for pNET). Clinical response and tolerability should be carefully monitored.

In patients receiving SUTENT with a CYP3A4 inhibitor such as ketoconazole, its use should be avoided (see section 4.5). If this is not possible, the doses 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 tolerability and/or clinical response. Selection of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP34 should be considered.

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for age, body weight, creatinine clearance, race, gender or ECOG (Eastern Cooperative Oncology Group) score.

Special populations

Elderly patients

No significant differences in safety or efficacy were observed between younger and older patients.

Hepatic insufficiency

No dosage adjustment is necessary when administering SUTENT to patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. SUTENT was not studied in patients with severe (Child-Pugh Class C) hepatic impairment (see section 5.2).

Renal insufficiency

No starting dose adjustment is required when administering SUTENT 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.

Paediatric population

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

Method of administration

For oral use.

SUTENT may be taken with or without food.

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

4.3 Contraindications

- SUTENT is contraindicated in patients with hypersensitivity to sunitinib malate or to any of the other excipients of SUTENT (listed in section 6.1).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Skin and tissues

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

Mouth pain/irritation was reported in approximately 14 % of patients. Dysgeusia (taste disturbance) was reported in approximately 28 % of patients.

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

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 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 at a lower dose after resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines.

Haemorrhage

Haemorrhagic events reported through post-marketing experience, some of which were fatal, have included gastrointestinal (GI), respiratory, tumour, urinary tract and brain haemorrhage. 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 or life-threatening haemoptysis or pulmonary haemorrhage. Tumour haemorrhage has not been observed in patients with MRCC or other solid tumours. 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 SUTENT for MRCC, GIST, and metastatic non-small cell lung cancer (NSCLC). SUTENT is not approved for use in patients with NSCLC.

In patients receiving SUTENT for treatment-naïve MRCC, 39 % had bleeding events. Of patients receiving SUTENT for cytokine-refractory MRCC, 26 % experienced bleeding. Bleeding events, excluding epistaxis, occurred in 21,7 % of patients receiving SUTENT in a Phase 3 pNET study compared to 9,85 % of subjects receiving placebo. Routine assessment of these events should include complete blood counts and physical examination.

Treatment-related epistaxis was reported in 8 % of patients with solid tumours. Epistaxis was the most common treatment related haemorrhagic adverse event, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events.

Gastrointestinal events

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

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.

Pancreatitis

Pancreatitis has been reported in clinical trials of SUTENT. 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. If symptoms of pancreatitis are present, patients should have proper medical follow-up.

Hepatotoxicity

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

Haematological

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

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

Cardiovascular

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischaemia, angina pectoris and myocardial infarction, some of which were fatal, have been reported in clinical trials and through post-marketing experience. 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 MRCC patients and 2 % of placebo-treated patients.

In the treatment-naïve MRCC study, 27 % patients on SUTENT had an LVEF value below the lower limit of normal. Two patients (< 1 %) who received SUTENT were diagnosed with congestive heart failure.

Cardiac failure, congestive cardiac failure or left ventricular failure were reported in 0,8 % of patients with solid tumours and 1 % of patients treated with placebo. In the Phase 3 pNET study, one (1,2 %) patient who received SUTENT had treatment-related fatal cardiac failure.

The relationship between receptor tyrosinase kinase (RTK) inhibition and cardiac function remains unclear but seems to be a class effect. Data from non-clinical (*in vitro* and *in vivo*) studies, at doses higher than the recommended human dose, indicate that SUTENT 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 these parameters are recognised as potentially significant changes.

QT interval prolongation

At approximately twice the therapeutic concentrations, SUTENT has been shown to prolong the QTcF (Fredericia's correction) interval. QT interval prolongation may lead to an increased risk for ventricular dysrhythmias including torsade de pointes. Torsade de pointes has been observed in < 0,1 % of SUTENT-exposed patients. SUTENT should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antidysrhythmics or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with strong CYP3A4 inhibitors, which may increase SUTENT plasma concentrations, should be used with caution and the dose of SUTENT reduced (see section 4.2 and 4.5).

Hypertension

Patients treated with SUTENT should have regular blood pressure assessments.

Hypertension was a very common adverse event reported in clinical trials in patients with solid tumours, including primarily GIST and cytokine-refractory RCC. SUTENT dosing was reduced or temporarily delayed in approximately 2,7 % of this patient population. None of these patients were discontinued from treatment with SUTENT. Severe hypertension (> 200 mmHg systolic or 110 mmHg diastolic) occurred in 4,7 % of this patient population. Hypertension was reported in approximately 33,9 % of patients receiving SUTENT for treatment-naïve MRCC. Severe hypertension occurred in 12 % of treatment-naïve patients on SUTENT. Hypertension was reported in 26,5 % of patients receiving SUTENT in a Phase 3 pNET study, compared to 4,9 % of patients receiving placebo.

Severe hypertension occurred in 10 % of pNET patients on SUTENT and 3 % of patients on placebo. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension of SUTENT therapy is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

Aneurysms and artery dissections

The use of vascular endothelial growth factor (VEGF) pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating 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 treatment prior to the start of SUTENT treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction whilst on SUTENT treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Acquired hypothyroidism was noted in 6,2 % of GIST patients. Hypothyroidism was reported as an adverse event in 16 % of patients on SUTENT in the treatment-naïve MRCC study and in 4 % of subjects across 2 cytokine-refractory MRCC studies. Overall 7 % of the cytokine-refractory MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. In a Phase 3 pNET study, hypothyroidism was reported in six patients (7,2 %) receiving SUTENT and in one (1,2 %) patient on placebo.

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

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 therapy is recommended in patients with seizures or RPLS. Following resolution, treatment may be resumed at the discretion of the treating medical practitioner.

Surgical procedures

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

Osteonecrosis of the Jaw (ONJ)

ONJ has been uncommonly observed in clinical trials and has been reported in post-marketing experience 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 for ONJ. Prior to treatment with SUTENT, a dental examination and appropriate preventative dentistry should be considered. In patients being treated with SUTENT, who have previously received or are receiving IV bisphosphonates, invasive dental procedures should be avoided, if possible.

Venous thromboembolic events

Seven patients (3 %) on SUTENT in a GIST study experienced venous thromboembolic events; five of the seven were Grade 3 deep vein thrombosis (DVT). Thirteen patients (3 %) receiving SUTENT for treatment-naïve MRCC had venous thrombolic events reported such as pulmonary embolism.

Pulmonary embolism

Pulmonary embolism was reported in approximately 2,2 % of patients with solid tumours who received SUTENT. None of these events resulted in a patient discontinuing treatment with SUTENT; however a dose reduction or temporary delay in treatment occurred in a few cases. There were no further occurrences of pulmonary embolism in these patients after treatment was resumed.

Tumour Lysis Syndrome (TLS)

Cases of TLS, some fatal, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with SUTENT. 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

Cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported. SUTENT 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), frequently leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA.

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 SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUTENT in patients with nephrotic syndrome.

Hypoglycaemia

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

Viral reactivation

Hepatitis B reactivation, including fatal outcomes have occurred in patients treated with SUTENT. Hepatitis B virus (HBV) status should be established before initiating treatment with SUTENT. Patients should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in SUTENT

Although TKIs may have different kinase inhibition profiles and/or off target binding profiles, there is

some evidence that the TKIs share to a variable degree, class related cerebrovascular adverse events (e.g. cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction).

These cerebrovascular adverse events may occur in patients on treatment with TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

Patients on treatment with SUTENT should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

Treatment with SUTENT should be discontinued, and alternative treatment options be considered in patients who developed these class related cerebrovascular adverse events.

Mannitol

SUTENT contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

When SUTENT is co-administered with other medicines, there is a potential for medicine interaction.

In vitro studies indicate that SUTENT neither induces nor inhibits major CYP enzymes, including CYP3A4. The dose of SUTENT may need to be reduced based on tolerability when co-administered with CYP3A4 inhibitors. The dose of SUTENT may need to be increased when it is co-administered with potent CYP3A4 inducers.

Medicines that may increase SUTENT plasma concentrations

Concurrent administration of SUTENT with the CYP3A4 inhibitor, ketoconazole, resulted in 49 % and 51 % increases in sunitinib C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers.

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

Medicines that may decrease SUTENT plasma concentrations

Concomitant use of SUTENT with the CYP3A4 inducer, rifampicin, resulted in a more than 23 % and 46 % reduction in sunitinib 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, phenobarbitone or *Hypericum perforatum* known also as St. John's Wort) may decrease SUTENT concentrations. To maintain SUTENT target concentrations, dose adjustment of SUTENT, or selection of co-medications with less enzyme induction potential, should be considered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Teratogenicity has been observed in animal studies. Women of childbearing potential should use effective contraceptive measures during SUTENT treatment and 4 weeks after the last dose of SUTENT.

Pregnancy

SUTENT is contraindicated in pregnancy as safety has not been demonstrated.

Breastfeeding

SUTENT is secreted in breast milk. Women using SUTENT should not breastfeed their infants, because of the potential for serious adverse reactions in nursing infants.

Fertility

Based on the findings of pre-clinical studies, fertility in males and females may be compromised by treatment with SUTENT.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most important serious adverse events associated with SUTENT treatment of solid tumour patients were pulmonary embolism, thrombocytopenia, tumour haemorrhage, febrile neutropenia, and hypertension.

The most very common adverse events of any grade included: fatigue; gastrointestinal disorders, such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting; skin discolouration; rash; hand-foot syndrome (palmar-plantar erythrodysaesthesia); dry skin; hair colour changes; mucosal inflammation; asthenia; dysgeusia; anorexia and hypertension. Fatigue, hypertension and neutropenia were the most common adverse events of Grade 3 maximum severity; and increased lipase was the most frequently occurring adverse event of Grade 4 maximum severity in patients with solid tumours.

Tabulated summary of adverse reactions

The treatment-emergent, all causality frequency of adverse events reported in patients who received SUTENT in single-medicine studies in advanced RCC, GIST and pNET and from post-marketing experience are listed below, by system organ class, frequency category and grade of severity.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000).

Adverse events reported in SUTENT single-medicine studies in advanced RCC, GIST and pNET experience:

System organ class	Adverse Event	SUTENT (n=7115)		
Frequency		All grades (%)	Grade 3 (%)	Grade 4 (%)
Infections and infestations				
Very common	Infections*	2 956 (41,5)	528 (7,4)	83 (1,2)
Blood and lymphatic system disorders				
Very common	Neutropenia	1 224 (17,2)	484 (6,8)	46 (0,6)
	Leukopenia	725 (10,2)	141 (2,0)	9 (0,1)
	Thrombocytopenia	1 563 (22,0)	460 (6,5)	115 (1,6)
	Anaemia	1 697 (23,9)	462 (6,5)	103 (1,4)
Common	Lymphopenia	155 (2,2)	49 (0,7)	2 (0,028)
Rare	Thrombotic microangiopathy[a,**]	4 (0,06)	3 (0,04)	1 (0,01)

Immune system disorders				
Uncommon	Hypersensitivity	45 (0,6)	7 (0,098)	0 (0,0)
Rare	Angioedema	7 (0,098)	3 (0,042)	0 (0,0)
Endocrine disorders				
Very common	Hypothyroidism	890 (12,5)	52 (0,7)	6 (0,084)
Uncommon	Hyperthyroidism	52 (0,7)	5 (0,07)	0 (0,0)
	Thyroiditis	6 (0,084)	0 (0,0)	0 (0,0)
Metabolism and nutrition disorders				
Very common	Decreased appetite	2 644 (37,2)	218 (3,1)	3 (0,0042)
Common	Dehydration**	501 (7,0)	192 (2,7)	15 (0,2)
	Hypoglycaemia	106 (1,5)	28 (0,4)	16 (0,2)
Rare	Tumour lysis syndrome**	4 (0,056)	3 (0,042)	0 (0,0)
Psychiatric disorders				
Very common	Insomnia	759 (10,7)	12 (0,2)	0 (0,0)
Common	Depression	379 (5,3)	18 (0,3)	3 (0,042)
Nervous system disorders				
Very common	Dysgeusia	2 048 (28,8)	32 (0,4)	0 (0,0)
	Headache	1 406 (19,8)	85 (1,2)	5 (0,070)
Common	Dizziness	684 (9,6)	34 (0,5)	3 (0,042)

	Paraesthesia	382 (5,4)	13 (0,2)	1 (0,014)
Uncommon	Cerebral haemorrhage**	23 (0,3)	2 (0,028)	4 (0,056)
	Cerebrovascular accident**	32 (0,4)	8 (0,1)	11 (0,2)
	Ischaemic stroke	3 (0,0)	1 (0,0)	1 (0,0)
	Transient ischaemic attack	21 (0,3)	8 (0,1)	3 (0,042)
Rare	Cerebral infarction	6 (0,084)	2 (0,028)	2 (0,028)
	Reversible posterior encephalopathy syndrome	5 (0,070)	3 (0,042)	1 (0,014)
	Ageusia	3 (0,042)	-	-
Eye disorders				
Common	Periorbital oedema	333 (4,7)	3 (0,042)	0 (0,0)
	Eyelid oedema	276 (3,9)	9 (0,1)	0 (0,0)
	Increased lacrimation	394 (5,5)	1 (0,01)	0 (0,0)
Cardiac disorders				
Common	Myocardial ischaemia[b,**]	87 (1,2)	27 (0,4)	3 (0,0)
	Decreased ejection fraction[c]	152 (2,1)	27 (0,4)	0 (0,0)
Uncommon	Myocardial infarction[d,**]	62 (0,9)	10 (0,1)	33 (0,5)
	Cardiac failure**	51 (0,7)	22 (0,3)	8 (0,1)

	Congestive cardiac failure	32 (0,4)	22 (0,3)	4 (0,056)
	Prolonged electrocardiogram QT	23 (0,3)	4 (0,056)	2 (0,028)
	Cardiomyopathy**	15 (0,2)	5 (0,070)	1 (0,014)
	Left ventricular failure**	7 (0,098)	5 (0,070)	0 (0,0)
Rare	Torsade de pointes	1 (0,014)	0 (0,0)	1 (0,014)
Vascular disorders				
Very common	Hypertension	1 991 (28,0)	505 (7,1)	15 (0,2)
Common	Deep vein thrombosis	91 (1,3)	50 (0,7)	6 (< 0,1)
Uncommon	Tumour haemorrhage**	49 (0,7)	26 (0,4)	3 (0,042)
	Aneurysms and artery dissections[e]	9 (0,1)	4 (0,056)	2 (0,028)
Respiratory, thoracic and mediastinal disorders				
Very common	Dyspnoea	1 443 (20,3)	322 (4,5)	75 (1,1)
	Epistaxis	1 080 (15,2)	43 (0,6)	4 (0,056)
Common	Oropharyngeal pain[f]	455 (6,4)	6 (0,1)	0 (0,0)
	Haemoptysis[g,**]	360 (5,1)	25 (0,4)	5 (0,070)
	Pleural effusion	292 (4,1)	119 (1,7)	15 (0,2)

	Pulmonary embolism**	119 (1,7)	33 (0,5)	52 (0,7)
Gastrointestinal disorders				
Very common	Diarrhoea	3 729 (52,4)	430 (6,0)	13 (0,2)
	Nausea	3 035 (42,7)	246 (3,5)	4 (0,056)
	Vomiting	2 416 (34,0)	287 (4,0)	17 (0,2)
	Abdominal pain[h]	2 162 (30,4)	406 (5,7)	38 (0,5)
	Stomatitis[i]	2 011 (28,3)	189 (2,7)	2 (0,028)
	Constipation	1 653 (23,2)	67 (0,9)	3 (0,042)
	Dyspepsia	1 564 (22,0)	36 (0,5)	1 (0,014)
Common	Gastrointestinal haemorrhage**	121 (1,7)	56 (0,8)	20 (0,3)
	Oesophagitis	143 (2,0)	21 (0,3)	0 (0,0)
	Gastro-oesophageal reflux disease	465 (6,5)	13 (0,2)	0 (0,0)
	Oral pain	582 (8,2)	23 (0,3)	0 (0,0)
	Glossodynia	430 (6,0)	13 (0,2)	0 (0,0)
	Abdominal distension	451 (6,3)	32 (0,4)	2 (0,028)
	Gingival bleeding	147 (2,1)	6 (0,1)	0 (0,0)
	Dry mouth	483 (6,8)	2 (0,028)	0 (0,0)

	Flatulence	501 (7,0)	2 (0,028)	0 (0,0)
Uncommon	Pancreatitis	17 (0,2)	6 (0,084)	1 (0,014)
	Gastrointestinal perforation**	15 (0,2)	7 (0,098)	4 (0,056)
Hepato-biliary disorders				
Uncommon	Cholecystitis[ij]	33 (0,5)	16 (0,2)	4 (0,056)
	Hepatic failure** [hepatitis B reactivation (including fatal events)]	23 (0,3)	4 (0,056)	8 (0,1)
Skin and subcutaneous tissue disorders				
Very common	Hand-foot syndrome (Palmar-plantar erythrodysaesthesia syndrome)	1 984 (27,9)	551 (7,7)	3 (0,042)
	Skin discolouration[ijk]	1 761 (24,8)	13 (0,2)	0 (0,0)
	Rash[l]	1 595 (22,4)	73 (1,0)	2 (0,028)
	Hair colour changes	858 (12,1)	10 (0,1)	0 (0,0)
	Dry skin	805 (11,3)	5 (0,070)	0 (0,0)
Common	Alopecia	564 (7,9)	1 (0,014)	0 (0,0)
	Erythema	488 (6,9)	15 (0,2)	0 (0,0)
	Pruritus	460 (6,5)	3 (0,042)	0 (0,0)
	Skin exfoliation	373 (5,2)	15 (0,2)	0 (0,0)
	Blister	257 (3,6)	27 (0,4)	1 (0,014)

	Skin lesion	190 (2,7)	14 (0,2)	0 (0,0)
	Skin reaction	180 (2,5)	11 (0,2)	0 (0,0)
	Nail disorder	176 (2,5)	3 (0,042)	0 (0,0)
Uncommon	Exfoliative dermatitis	21 (0,3)	2 (0,028)	0 (0,0)
Rare	Erythema multiforme**	5 (0,070)	0 (0,0)	0 (0,0)
	Stevens-Johnson syndrome**	2 (0,028)	1 (0,014)	1 (0,014)
	Pyoderma gangrenosum	1 (0,014)	0 (0,0)	0 (0,0)
Musculoskeletal and connective tissue disorders				
Very common	Pain in extremity	1 237 (17,4)	125 (1,8)	13 (0,2)
	Arthralgia	1 023 (14,4)	97 (1,4)	5 (0,070)
Common	Myalgia	650 (9,1)	34 (0,5)	0 (0,0)
Uncommon	Osteonecrosis of jaw	31 (0,4)	12 (0,2)	0 (0,0)
	Fistula formation**	13 (0,2)	3 (0,042)	2 (0,028)
Rare	Rhabdomyolysis**	7 (0,098)	2 (0,028)	1 (0,014)
	Myopathy	7 (0,098)	0 (0,0)	0 (0,0)
Renal and urinary disorders				
Common	Renal failure**	153 (2,2)	66 (0,9)	18 (0,3)
	Chromaturia	197 (2,8)	0 (0,0)	0 (0,0)
	Proteinuria	105 (1,5)	39 (0,5)	4 (0,056)
Uncommon	Renal impairment	29 (0,4)	9 (0,1)	1 (0,0)

	Urinary tract haemorrhage	8 (0,1)	2 (0,028)	0 (0,0)
Rare	Nephrotic syndrome	7 (0,098)	1 (0,014)	4 (0,056)
General disorders and administration site conditions				
Very common	Fatigue[m]	4 746 (66,7)	1 211 (17,0)	87 (1,2)
	Mucosal inflammation	1 928 (27,1)	180 (2,5)	10 (0,1)
	Oedema[n]	1 723 (24,2)	87 (1,2)	2 (0,028)
	Pyrexia	1 252 (17,6)	72 (1,0)	8 (0,1)
Common	Chills	430 (6,0)	11 (0,2)	1 (0,014)
	Influenza like illness	155 (2,2)	4 (0,056)	0 (0,0)
Investigations				
Common	Increased lipase	105 (1,5)	46 (0,6)	26 (0,4)
	Increased amylase[o]	76 (1,1)	31 (0,4)	4 (0,056)
	Increased blood uric acid	98 (1,4)	4 (0,056)	22 (0,3)
	Decreased white blood cell count	274 (3,9)	95 (1,3)	7 (0,098)
	Decreased platelet count	307 (4,3)	94 (1,3)	15 (0,2)
	Decreased haemoglobin	269 (3,8)	62 (0,9)	12 (0,2)
	Decreased weight	701 (9,9)	29 (0,4)	1 (0,014)

Uncommon	Increased blood creatine phosphokinase	60 (0,8)	12 (0,2)	5 (0,07)
	Increased blood thyroid stimulating hormone	45 (0,6)	7 (0,098)	0 (0,0)

[a] Thrombotic microangiopathy: The following terms have been combined: thrombotic microangiopathy, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome

[b] Myocardial ischaemia: The following terms have been combined: acute coronary syndrome, angina pectoris, unstable angina, coronary artery occlusion, myocardial ischaemia

[c] Decreased ejection fraction: The following terms have been combined: decreased ejection fraction and abnormal ejection fraction

[d] Myocardial infarction: The following terms have been combined: acute myocardial infarction, myocardial infarction, silent myocardial infarction

[e] Aneurysms and artery dissections: The following terms have been combined: aneurysm ruptured, aortic aneurysm, aortic aneurysm rupture and aortic dissection.

[f] Oropharyngeal pain: The following terms have been combined: pharyngolaryngeal pain and oropharyngeal pain

[g] Haemoptysis: The following terms have been combined: hemoptysis and pulmonary haemorrrhage

[h] Abdominal pain: The following terms have been combined: abdominal pain, lower abdominal pain, upper abdominal pain

[i] Stomatitis: The following terms have been combined: stomatitis and aphthous stomatitis

[j] Cholecystitis: The following terms have been combined: cholecystitis and acalculous cholecystitis

[k] Skin discolouration: The following terms have been combined: skin discolouration, yellow skin, pigmentation disorder

[l] Rash: The following terms have been combined: dermatitis psoriasiform, exfoliative rash, rash, erythematous rash, follicular rash, generalized rash, macular rash, maculopapular rash, papular

rash, pruritic rash

[m] Fatigue: The following terms have been combined: fatigue and asthenia

[n] Oedema: The following terms have been combined: face oedema, oedema, peripheral oedema

[o] Increased amylase: The following terms have been combined: amylase, increased amylase

* Infections and infestations are described in the post-marketing experience section

** Event may be fatal

Post-marketing experience

The following adverse events have been identified during post-approval use of SUTENT.

Infections and infestations

Cases of serious infection (with or without neutropenia) in some cases with fatal outcome have been reported. The infections most commonly observed with SUTENT treatment were 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 or fungal. Cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported (see section 4.4).

Blood and lymphatic system disorders

Cases of thrombotic microangiopathy, in some cases with fatal outcome and haemolytic uraemic syndrome have been reported. Temporary suspension of SUTENT is recommended. Following resolution, treatment may be resumed at the discretion of the treating medical practitioner.

Immune system disorders

Hypersensitivity reactions, including angioedema.

Endocrine disorders

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

Metabolism and nutrition disorders

Cases of Tumour Lysis Syndrome, some fatal, have been reported in patients treated with SUTENT.

Decreases in blood glucose, in some cases clinically symptomatic, have been reported during SUTENT treatment.

Nervous system disorders

Taste disturbance, including ageusia.

Cardiac disorders

Cardiac failure, congestive cardiac failure, prolonged QT interval and torsade de pointes have been reported. Cardiomyopathy, myocardial ischaemia, left ventricular failure and myocardial infarction, in some cases with fatal outcome, have been observed.

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

Pulmonary embolism, in some cases with fatal outcome.

Gastrointestinal disorders

Pancreatitis, gastrointestinal perforation, oesophagitis.

Hepato-biliary disorders

Hepatic failure (including fatal events), hepatitis B reactivation (including fatal events) and cholecystitis, particularly acalculous cholecystitis have been reported.

Skin and subcutaneous tissue disorders

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

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 medicines 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.

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 IV bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see section 4.4).

Renal and urinary disorders

Cases of renal impairment and/or failure, in some cases with fatal outcome. Cases of proteinuria and cases of nephrotic syndrome have been reported (see section 4.4).

Investigations

Increased TSH and increased blood uric acid have been reported.

Haemorrhagic events

Cases of pulmonary, gastrointestinal, tumour, urinary tract, and brain haemorrhage, some fatal, have been reported in patients treated with SUTENT.

Long-term safety in MRCC

The long-term safety of SUTENT in patients with metastatic RCC 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 SUTENT was not associated with new types or increased severity of treatment-related adverse events and except for hypothyroidism, toxicity was not cumulative.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no specific antidote for overdosage with SUTENT.

Treatment of overdose is symptomatic and supportive. Cases of overdose have been reported; some cases were associated with adverse reactions consistent with the known adverse effects profile of sunitinib (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic Agents

Sunitinib malate 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 variety of kinases (> 80 kinases) and was identified as a potent inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), 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). 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. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib malate demonstrated inhibition of activity of target RTKs (PDGFRβ, VEGFR2, KIT) in tumours *in vivo* and demonstrated the ability to inhibit tumour growth, cause tumour regression, and/or inhibit metastatic progression in a variety of rodent cancer models. Consistent with its multi-targeted profile, sunitinib malate demonstrated the ability to directly inhibit growth of tumour cells expressing dysregulated RTK targets (PDGFR, RET, or KIT) and to inhibit PDGFRβ- and VEGFR2-dependent tumour angiogenesis.

5.2 Pharmacokinetic properties

Absorption

Sunitinib is absorbed after oral administration with maximum concentrations (C_{max}) generally observed from 6 - 12 hours (T_{max}) post-dose. Food has no effect on the bioavailability of sunitinib.

Distribution

Binding of sunitinib and its primary active metabolite to human plasma protein in *in vitro* assays was 95 % and 90 %, respectively, with no apparent concentration dependence.

Metabolism

The calculated *in vitro* Ki values for all CYP isoforms tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11) indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant interactions with medicines that may be metabolised by these enzymes.

Sunitinib is metabolised primarily by CYP3A4, the cytochrome P450 enzyme, which produces its primary active metabolite, which is then further metabolised by CYP3A4.

Elimination

Excretion is primarily via faeces (61 %) with renal elimination of sunitinib and metabolites accounting for 16 % of the administered dose. Sunitinib and its primary active metabolite were the major sunitinib-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.

Pharmacokinetics in special patient groups

Hepatic insufficiency

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

Renal insufficiency

Population pharmacokinetic analyses have been performed and were not altered in 224 subjects with a calculated creatinine clearance (CL_{cr}) of > 80 mL/min, 46 subjects with CL_{cr} of 50 – 80 mL/min and 7 subjects with CL_{cr} of 30 – 49 mL/min. Systemic exposures after a single dose of SUTENT were similar in subjects with severe renal impairment (CL_{cr} < 30 mL/min) compared to subjects with normal renal function (CL_{cr} > 80 mL/min). Although sunitinib and its primary metabolite were not eliminated through 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.

Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40 - 60 hours, and 80 - 110 hours, respectively. In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By day 14, combined plasma concentrations of sunitinib and is active metabolite are 62,9 - 101 ng/mL which are target concentrations predicted from preclinical data to inhibit receptor phosphorylation *in vitro* and result in tumour stasis/growth reduction *in vivo*. The primary active metabolite comprises 23 % to 37 % of the total exposure. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite are observed with repeated daily administration or with repeated cycles in the dosing

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule

Croscarmellose sodium

Magnesium stearate

Mannitol (E421)

Povidone

Capsule shell

Gelatin

Red iron oxide (CI 77491) (E172)

Titanium dioxide (CI 77891) (E171)

SUTENT 25 mg and 50 mg: Black iron oxide (CI 77499) (E172)

SUTENT 25 mg and 50 mg: Yellow iron oxide (CI 77492) (E172)

Imprinting ink

Povidone

Propylene glycol

Shellac

Sodium hydroxide

Titanium dioxide (CI 77891) (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ºC.

6.5 Nature and contents of container

Opaque white high density polyethylene bottles with a white child resistant polypropylene closure and a heat induction seal liner containing 28 or 30 hard gelatin capsules.

SUTENT capsules are available in blister strips of 28 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

SUTENT 12,5 mg capsules: 41/26/0197

SUTENT 25 mg capsules: 41/26/0195

SUTENT 50 mg capsules: 41/26/0196

9. DATE OF FIRST AUTHORISATION

08 February 2008

10. DATE OF REVISION OF THE TEXT

12 July 2021

Manufacturer: Pfizer Italia S.r.l., Ascoli Piceno, Italy

NAMIBIA: S2

SUTENT 12,5 mg: Reg.No: 08/26/0148

SUTENT 25 mg: Reg.No: 08/26/0147

SUTENT 50 mg: Reg.No: 08/26/0149