NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Sunitinib (sunitinib 12.5 mg capsules)
Sunitinib (sunitinib 25 mg capsules)
Sunitinib (sunitinib 50 mg capsules)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sunitinib capsules contain the active ingredient sunitinib malate comparable to 12.5 mg, 25 mg or 50 mg sunitinib.

For the full list of excipients, section 6.1.

3 PHARMACEUTICAL FORM

Capsule

12.5 mg strength: Hard gelatin capsule with opaque red body and opaque red cap.
25 mg strength: Hard gelatin capsule with opaque red body and opaque orange cap.
50 mg strength: Hard gelatin capsule with opaque orange body and opaque orange cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

4.2 Dose and method of administration

Dose

GIST and mRCC
The recommended Sunitinib dose is 50 mg taken orally once per day for four successive weeks, followed by a rest period of two weeks (Schedule 4/2). The complete cycle of treatment is six weeks.

Based on individual safety and medicine tolerance, dose adjustments may be used in 12.5 mg steps.

The daily dosage of sunitinib should not surpass 75 mg or go below 25 mg.

If a patient forgets to take a dose, they should take the normal prescribed dose the next day. The patient should not take an extra dose.

Pancreatic NET

The recommended Sunitinib dose is 37.5 mg taken orally once per day with no planned rest period.

Based on individual safety and medicine tolerance, dose adjustments may be used in 12.5 mg steps.

The maximum dosage as per the Phase 3 pancreatic NET study was 50 mg per day.

Dose adjustments

Dose adjustments may be essential due to individual safety and tolerability.

Dose initiation with sunitinib does not need modification in patients with mild kidney dysfunction or moderate hepatic impairment (refer to section 5.2 Pharmacokinetic properties and section 4.4 Special warnings and precautions of use). Any following dose adjustments should be on the basis of individual safety and tolerability.

No dose adjustments are required for age, body weight, ECOG score, gender or race as per population pharmacokinetic analyses of demographic data.

Paediatric population

Safety and efficacy has not been established for the use of sunitinib in paediatric patients.

CYP3A4 inhibitors/inducers

Strong CYP3A4 inhibitors may increase concentrations of sunitinib in plasma. Therefore, concomitant use of sunitinib with potent CYP3A4 inhibitors, such as ketoconazole, must be avoided (refer to section 4.5 Interaction with other medicines and other forms of interaction). In the event that this is not feasible, the sunitinib dosage may need to be decreased to a minimum of 37.5 mg per day for GIST and mRCC or 25 mg per day for pancreatic NET, on the basis of vigilant tolerability monitoring.

CYP3A4 inducers may reduce sunitinib plasma concentrations. Therefore, concomitant use of sunitinib with potent CYP3A4 inducers, such as rifampicin, must be avoided (refer to section 4.5 Interaction with other medicines and other forms of interaction). In the event that this is not feasible, the sunitinib dosage may need to be increased in steps of 12.5 mg steps (up to 87.5 mg daily for GIST and RCC or 62.5 mg daily for pancreatic NET) on the basis of vigilant tolerability monitoring.

A variety of an alternative concomitant medicine should be considered with no or limited potential to induce or inhibit CYP3A4.

Method of administration

Treatment should be introduced by an experienced physician in agents used for anti-cancer administration.

Sunitinib can be taken with food or on an empty stomach.

4.3 Contraindications

Any known hypersensitivity to sunitinib malate, or to any of the excipients is a contraindication for Sunitinib capsules.

4.4 Special warnings and precautions for use

Aneurysms and artery dissections

The administration of Vascular Endothelial Growth Factor (VEGF) pathway inhibitors in patients with or without hypertension might cause the formation of aneurysms and/or artery dissections. Prior to sunitinib initiation, this risk should be carefully considered in patients with risk factors for example, a history of aneurysm or hypertension.

Cardiovascular

Through post-marketing experience, cardiovascular events involving cardiomyopathy, heart failure, myocardial ischaemia and myocardial infarction, (in some cases fatal), have been reported. In at-risk patients or patients with a history of cardiovascular events, sunitinib should be used with caution. In clinical studies, a reduction in left ventricular ejection fraction (LVEF) of ≥20% and below the lower limit of normal (LLN) was recorded in approximately 2% of GIST patients treated with sunitinib, 4% of cytokine-refractory mRCC patients and 2% of patients treated with placebo. The decline of LVEF does not seem to have been progressive and as treatment continued, often improved.

In the study involving treatment-naïve mRCC patients, 21% of those receiving sunitinib alone and 12% of those receiving sunitinib with IFN-α had LVEF values below the lower limit of normal (LLN). One (<1%) patient was diagnosed with congestive heart failure (CHF) whom was receiving sunitinib.

Reports of adverse cardiovascular events - specifically cardiac failure, congestive heart failure or left ventricular failure were reported in 0.7% and 1% of patients treated with sunitinib and placebo, respectively. In the Phase 3 GIST study, fatal cardiac reactions that were treatment-related happened in 1% of both treatment arms. In the Phase 2 study in cytokine-refractory mRCC patients, treatment-related fatal myocardial infarction was experienced in 0.9% of patients and in the Phase 3 study in treatment-naïve mRCC patients, 0.6% and 0% of patients experienced fatal cardiac events on the IFN-α arm and sunitinib arm, respectively. In the Phase 3 study on pancreatic NET, treatment-related cardiac failure resulting in death occurred in one patient (1%) receiving sunitinib. The relationship remains unclear (if any) between receptor tyrosine kinase (RTK) inhibition and cardiac function.

Patients were excluded from the clinical studies who had exhibited cardiac events within 12 months preceding sunitinib treatment, for example, cerebrovascular accident or transient ischaemic attack, coronary/peripheral artery bypass graft, myocardial infarction (includes severe/unstable angina), symptomatic congestive heart failure (CHF), or pulmonary embolism. It is not known whether there is a higher risk in patients with these associated conditions of developing drug-related left ventricular dysfunction. The risk should be evaluated against the potential benefits of this medicine. While receiving sunitinib, these patients must be carefully monitored for clinical symptoms and signs of CHF. For a patient given sunitinib, baseline and periodic evaluations of LVEF should be considered. An ejection fraction baseline evaluation should be considered in patients

without cardiac risk factors.

In the occurrence of CHF clinical manifestations, sunitinib discontinuation is recommended. Sunitinib dosage should be interrupted and/or decreased in patients without CHF clinical evidence but with an ejection fraction of <50% and >20% under baseline.

Gastrointestinal events

The most common treatment-related gastrointestinal effects reported were diarrhoea, dyspepsia, nausea, stomatitis and vomiting. Treatment to support the care of gastrointestinal adverse events may comprise of an anti-emetic or anti-diarrhoea medication.

Gastrointestinal tract

Serious and occasionally fatal gastrointestinal complications, such as gastrointestinal perforation, have been infrequently reported in patients with intra-abdominal cancers undergoing treatment with sunitinib.

Haemorrhagic events

Reports of haemorrhagic events via post-marketing setting, including fatal outcomes in some instances, have included brain, gastrointestinal (GI), respiratory, tumour and urinary tract haemorrhages. In clinical studies, treatment-related tumour haemorrhages happened in approximately 2% of GIST patients. These events can appear rapidly and, in the case of pulmonary tumours, may appear as severe and life-threatening pulmonary haemorrhage or haemoptysis. In patients on sunitinib treatment for GIST, mRCC, and metastatic non-small cell lung cancer (NSCLC), instances of pulmonary haemorrhage (in some cases fatal) have been seen in clinical studies and post-marketing experience. For patients with NSCLC, sunitinib treatment is not approved.

In a Phase 3 GIST study, bleeding events occurred in 18% and 17% of patients receiving sunitinib and placebo, respectively. For treatment-naïve mRCC patients receiving sunitinib had a 28% bleeding event occurrence in comparison with 7% of patients receiving interferon-α (IFN-α). Seven (1.9%) patients receiving sunitinib treatment versus 0% of patients on IFN-α treatment experienced bleeding events (considered Grade 3 or greater). 26% of patients given sunitinib for cytokine-refractory mRCC experienced bleeding. In the Phase 3 pancreatic NET study, bleeding events, excluding epistaxis, were recorded in 19% and 4% of patients on sunitinib treatment in comparison to patients receiving placebo, respectively. Epistaxis was recorded in 21% and 5% of patients receiving sunitinib and placebo for pancreatic NET, respectively.

Regular evaluation of haemorrhagic events must include a physical examination and complete blood counts.

The most common haemorrhagic adverse event reported that was related to treatment was epistaxis. Bleeding events considered less common in GIST, mRCC, and pancreatic NET patients involved genital, gingival, rectal, upper GI and wound bleeding.

Haematological

In the Phase 3 GIST study, the reduced absolute neutrophil counts of Grade 3 and 4

severity were 10% and 1.7% of patients, respectively. In the Phase 3 mRCC study this was 16% and 1.6% and in the Phase 3 pancreatic NET study it was 13% and 2.4%, respectively. In the Phase 3 GIST study, the reduced platelet counts of Grade 3 and 4 severity were reported in 3.7% and 0.4% of patients. In the Phase 3 mRCC study this was 8.2% and 1.1% and for the Phase 3 pancreatic NET study this was 3.7% and 1.2%, respectively. These events were not cumulative, did not result in the discontinuation of treatment and were typically reversible. In the Phase 3 studies, none of these events were fatal, although uncommon, fatal blood-related events have been reported following post-approval.

At the commencement of each cycle of treatment or every four weeks during treatment, complete blood counts should be completed for patients receiving sunitinib treatment.

Hepatotoxicity

Hepatotoxicity has been recorded in some patients on sunitinib treatment. Reports of hepatic failure, in some cases fatal, were recorded in <1% of solid tumour patients on sunitinib treatment. Prior to treatment initiation, liver function tests (alanine transaminase [ALT], aspartate transaminase [AST] and bilirubin levels) should be monitored (during each treatment cycle and as clinically indicated). In the event of Grade 3 or 4 hepatic related adverse reactions, sunitinib should be interrupted and discontinued if there is no explanation.

Hyperammonaemic encephalopathy

Hyperammonaemic encephalopathy has been reported with sunitinib. Changes in mental status or unexplained lethargy in patients should have ammonia levels measured with appropriate clinical management (section 4.8 Undesirable effects).

Hypertension

Clinical trials in patients with solid tumours showed hypertension was a very common adverse reaction. Within this population, sunitinib dosing was decreased or temporarily postponed in approximately 2.7% of patients. No patients from this group were discontinued from sunitinib treatment. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) appeared in 4.7% of this group. Reports of treatment-related hypertension were reported in approximately 24% and 1% of patients receiving sunitinib for treatment-naïve mRCC in comparison to patients receiving IFN-α, respectively. In treatment-naïve patients taking sunitinib, severe hypertension was reported in 5% of the group in comparison to 1% of patients on IFN-α. In a Phase 3 pancreatic NET study, treatment-related hypertension was observed in 23% and 4% of patients receiving sunitinib compared to patients receiving placebo, respectively. In pancreatic NET patients, severe hypertension was reported in 10% of the population in comparison to 3% of patients on placebo. If appropriate, patients should be controlled and assessed for hypertension. If hypertension is not controlled with management, temporary postponement of sunitinib is recommended. Once hypertension is suitably controlled, treatment may recommence.

Hypoglycaemia

There are reports of blood glucose decreases throughout treatment with sunitinib. In some of these cases they are clinically symptomatic. For diabetic patients, blood glucose levels should be monitored regularly to assess if the dose of the anti-diabetic medication

needs to be modified to decrease the risk of hypoglycaemia.

Necrotising fasciitis

There are reports of rare cases of necrotising fasciitis, in some cases fatal and including of the perineum. Sunitinib treatment should be withdrawn in patients who present with necrotising fasciitis and suitable treatment should be promptly initiated.

Osteonecrosis of the jaw (ONJ)

There are reports of ONJ in patients having sunitinib treatment. Most of these cases happened in patients who had previously received or had concomitant therapy with intravenous (IV) bisphosphonates, for which there is an identified risk of ONJ. Therefore, caution should be taken when sunitinib and IV bisphosphonates are prescribed either concurrently or successively.

Another identified risk factor is invasive dental procedures. Before sunitinib treatment, a dental examination and suitable preventive dentistry should be planned. Invasive dental procedure should be avoided in patients who have received in the past or are currently receiving IV bisphosphonates, if possible.

Pancreatitis

Patients with numerous solid tumours and whom were given sunitinib treatment were observed to have serum lipase and amylase increases. Increases in the lipase levels were temporary and signs and symptoms of pancreatitis were generally not seen. In patients with GIST or mRCC and receiving sunitinib, pancreatitis is uncommon (<1%). There have been reports of serious pancreatic events and in some cases with fatal outcome.

In the Phase 3 pancreatic NET trial, no treatment-related pancreatitis was observed.

If pancreatitis signs and symptoms are present, sunitinib should be withdrawn and patients given appropriate supportive care.

Proteinuria

There are reports of proteinuria and nephrotic syndrome cases. Patients should be observed for worsening or the development of proteinuria and baseline urinalysis is recommended. The safety in patients with moderate to severe proteinuria of continued treatment with sunitinib has not been thoroughly evaluated. Sunitinib treatment should be discontinued in patients with nephrotic syndrome.

QT interval prolongation

An open, positive control trial with moxifloxacin 400 mg investigated the effect of sunitinib on QT interval in 24 patients, with advance malignancies, aged between 20 and 87 years. At plasma concentrations observed with standard recommended doses, mean change from baseline of the maximum QTcF (Fridericia's correction) was 9.6 msec (upper 95% CI 15.1 msec). At plasma concentrations about twice observed with standard doses, the mean change from baseline of the maximum QTcF was 15.4 msec (upper 95% CI 22.4 msec). The positive control of moxifloxacin 400 mg resulted in a mean change from baseline of maximum QTcF of 5.6 msec.

In one patient taking sunitinib 50 mg daily, Torsades de Pointes was reported. In patients with an identified history of QT interval prolongation caution should be used when administering sunitinib. Caution should also be used in patients who are using other medicines acknowledged to prolong QT interval (for example antiarrhythmics), or patients with applicable pre-existing bradycardia, cardiac disease, or electrolyte disturbances. Sunitinib treatment used concomitantly with potent CYP3A4 inhibitors, may escalate sunitinib plasma concentrations and therefore should be used with caution alongside a decreased sunitinib dosage (refer to sections 4.5 Interaction with other medicines and other forms of interaction and 4.2 Dose and method of administration).

Seizures

In sunitinib clinical trials, seizures have been recorded in patients with evidence of radiological brain metastases. Furthermore, there have been rare (<1%) reports, in some instances fatal, of patients appearing with seizures and radiological evidence of Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Individuals with seizures and signs/symptoms consistent with RPLS, for example, altered mental functioning, decreased alertness, headache, hypertension, and visual loss (including cortical blindness), should be regulated with medical management including hypertension control. It is recommended that sunitinib be temporarily suspended; following resolution, sunitinib treatment may be continued at the discretion of the treating physician.

Skin and tissues

In the clinical trials, a very common adverse reaction was skin discolouration. This may have occurred due to the active drug substance colour (yellow). When having sunitinib treatment, patients should be informed that depigmentation of the skin or hair may happen. Other likely adverse effects may include blisters or an occasional rash on the soles of the feet or palms of the hands, cracking or thickness of the skin and dryness.

These events were not accumulative, did not result in discontinuation of treatment and were in most cases reversible.

There are reports of severe cutaneous reactions, which includes instances of erythema multiforme (EM) and cases indicative of Stevens-Johnson syndrome (SJS), some which had fatal outcomes. If indications or symptoms of SJS or EM (for example, progressive skin rash frequently with blisters or mucosal lesions) appear, the treatment with sunitinib should be discontinued. If a SJS diagnosis is confirmed, sunitinib treatment must not recommence. In some cases of alleged EM, patients tolerated the reintroduction of sunitinib at a reduced dosage after the reaction had been resolved. Some of these patients were also given treatment with antihistamines and/or corticosteroids.

Surgical procedures

There are reports of impaired wound healing during sunitinib treatment. In the case of patients having major surgery, temporary interruption of sunitinib treatment is recommended for precautionary reasons. Regarding reinitiation with the timing of sunitinib treatment, there is limited clinical experience following major surgical intervention. Hence, the evaluation to recommend sunitinib treatment following major surgical intervention must be grounded upon clinical judgment of surgery recovery.

Thrombotic microangiopathy

In clinical studies and post-marketing experience, thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS), (in some cases resulting in renal failure or a fatal result), has been reported of sunitinib as monotherapy and concomitantly with bevacizumab. Sunitinib should be discontinued in patients with the development of TMA. Following treatment discontinuation, the effects of TMA have been observed to be reversed.

Thyroid dysfunction

It is advisable to conduct a baseline laboratory assessment of thyroid function before initiating sunitinib treatment, with appropriate management for hypothyroidism or hyperthyroidism based on standard medical protocols. Continuous monitoring for signs and symptoms of thyroid dysfunction during sunitinib treatment is essential. If patients exhibit indications of thyroid dysfunction, they should undergo periodic laboratory thyroid function assessments and receive treatment in accordance with established medical guidelines.

In the context of sunitinib treatment, treatment-emergent acquired hypothyroidism occurred in 4% of patients with GIST compared to 1% in the placebo group. In the treatment-naïve mRCC study, hypothyroidism was noted as an adverse event in 2% of patients on sunitinib and in one patient (<1%) in the IFN-α arm. Moreover, hypothyroidism was reported in 4% of patients across the two cytokine-refractory mRCC studies, with 2% experiencing thyroid stimulating hormone (TSH) elevations. In total, 7% of the cytokine-refractory mRCC population exhibited either clinical or laboratory evidence of treatment-emergent hypothyroidism. In the phase 3 pancreatic NET study, 6% (5 patients) receiving sunitinib reported treatment-related hypothyroidism, while only 1% (1 patient) on placebo did.

Clinical trials and post-marketing occurrences have documented cases of hyperthyroidism, some of which were followed by hypothyroidism.

Tumour lysis syndrome (TLS)

In clinical studies, rare cases of TLS, in some instances fatal, have been observed. These have been described in patients having sunitinib treatment in post-marketing experience. Patients commonly at risk of TLS tend to have a high tumour burden before treatment commences. Careful monitoring and clinically indicated treatment should be provided for these patients.

Venous thromboembolic events

In clinical studies on patients receiving sunitinib with solid tumours, treatment-related venous thromboembolic events were seen in approximately 1% of the group (includes GIST and mRCC).

In a Phase 3 GIST study, seven patients (3%) on sunitinib and none on placebo had venous thromboembolic events; two were Grade 1 or 2 and five were Grade 3 deep venous thrombosis (DVT). In the seven GIST patients, four discontinued sunitinib treatment after the first observation of DVT.

In the Phase 3 treatment-naïve mRCC trial, seven patients (2%) on sunitinib and four

patients (2%) on the two cytokine-refractory mRCC trials had treatment-related venous thromboembolic reactions reported. Six patients had pulmonary embolisms (one x Grade 3, five x Grade 4), and five patients had DVT (one x Grade 1, one x Grade 4, and three x Grade 3). One patient experienced an interruption with their dose who had a pulmonary embolism in the cytokine-refractory mRCC trial.

In the population group with patients receiving IFN-α, with treatment-naïve mRCC, six patients (2%) had venous thromboembolic events; five patients (1%) experienced pulmonary embolisms (one x Grade 1 and four x Grade 4) and one patient (<1%) experienced a Grade 3 DVT.

No venous thromboembolic events related to treatment were identified in sunitinib-treated patients in the Phase 3 pancreatic NET study and for one patient receiving placebo a Grade 2 DVT was reported. No fatal outcome cases were reported in GIST, mRCC and pancreatic NET registration trials. However, in the post-marketing setting, there are reports of fatal outcome cases.

Tolerability

On the basis of individual patient tolerability and safety, dose adjustments and/or interruptions may be required. Patients with advanced RCC who are not able to tolerate sunitinib treatment on the four weeks on, two weeks off (4/2) therapy schedule, may consider a (2/1) schedule following completion of the six week treatment cycle using a scheduled dose interruption after week two lasting for one week, or two weeks on, one week off.

Sunitinib use in Paediatrics

The safety and efficacy of sunitinib has not been established in paediatric patients.

Sunitinib use in the elderly

In clinical trials with sunitinib, approximately 34% were 65 years or over. No significant safety or efficacy differences were detected between younger and older patients.

Sunitinib use in hepatic insufficiency

In patients with mild to moderate (Child-Pugh class A and B) hepatic impairment, no starting dose adjustment is required. In patients with severe hepatic impairment (Child-Pugh class C), sunitinib has not been examined (refer to section 5.2 Pharmacokinetic properties).

Sunitinib use in renal insufficiency

In patients with mild to severe renal impairment or patients with ESRD on haemodialysis, no starting dose adjustment is required (refer to section 5.2 Pharmacokinetic properties).

Laboratory tests

At the commencement of each cycle of sunitinib treatment, complete blood counts should be performed.

4.5 Interaction with other medicines and other forms of interaction

In-vitro studies of CYP inhibition and induction

In-vitro trials suggest sunitinib has not been shown to significantly induce major cytochrome P450 enzymes, including CYP3A4. The calculated *in vitro* Ki values for CYP isoforms inhibition by sunitinib and its primary active metabolite for, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 AND CYP4A9/11 suggest that neither sunitinib or its primary active metabolite is unlikely to result in significant drug-drug interactions involving substrates of these enzymes.

Medications that may increase plasma concentrations of sunitinib

In health participants, following the administration of a single dose of sunitinib malate concomitantly with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 49% increase of the complex [sunitinib + primary active metabolite] C_{max} and 51% $AUC_{0-\alpha}$ value.

The administration of sunitinib with strong inhibitors of the CYP3A4 family (for example clarithromycin, erythromycin, grapefruit juice, itraconazole and ritonavir) may increase the concentration of sunitinib. The administration of sunitinib with inhibitors should therefore be prevented or the choice of an alternative associated medication with minimal or no potential to inhibit CYP3A4 should be considered. In the event that this is not possible, the sunitinib dosage may need to be decreased (refer to section 4.2 Dose and method of administration).

Medications that may decrease plasma concentrations of sunitinib

In healthy participants, following the administration of a single dose of sunitinib concomitantly with the CYP3A4 inducer, rifampicin, resulted in a 23% reduction of the complex [sunitinib + primary active metabolite] C_{max} and 46% $AUC_{0-\alpha}$ values.

The administration of sunitinib with strong inducers of the CYP3A4 family (for example, carbamazepine, dexamethasone, *Hypericum perforatum* known also as St. John's wort phenobarbital (phenobarbitone), phenytoin, or rifampicin) may decrease the concentration of sunitinib. The administration of sunitinib, together with inducers should therefore be prevented, or the choice of an alternative associated medication with minimal or no potential to induce CYP3A4 should be considered. In the event that this is not possible, the sunitinib dosage may need to be increased (refer to section 4.2 Dose and method of administration).

4.6 Fertility, pregnancy and lactation

Pregnancy
Pregnancy Category D

No studies have been completed using sunitinib in pregnant women. Trials in animals have indicated reproductive toxicity involving fetal malformations (refer to section 5.3 Preclinical safety data).

A significant element of embryonic and fetal development is angiogenesis. Following sunitinib administration the inhibition of angiogenesis may cause pregnancy adverse effects.

Use of sunitinib is not recommended during pregnancy.

While receiving sunitinib treatment, women of reproductive age must be clearly warned to avoid becoming pregnant. If sunitinib is consumed during pregnancy or if the patient becomes pregnant while taking this medicine, the patient should be explained of the potential danger to the fetus. Suitable contraception must be used during sunitinib treatment and for at least four weeks following therapy completion.

Breast-feeding

The excretion of sunitinib and its primary metabolite into human breast milk has not been established. In rats, sunitinib and/or its metabolites are readily excreted into milk (milk:plasma concentration ratio of approximately 5:1). Women should be advised to not breastfeed when on sunitinib treatment due to the potential for serious adverse reactions in nursing infants.

Fertility

Male and female fertility may be compromised by sunitinib treatment based on nonclinical research (refer to section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

There are no studies conducted to assess the impact of sunitinib on driving or using machinery. Patients should be informed that treatment with sunitinib may cause dizziness or fatigue.

4.8 Undesirable effects

The information below displays patients exposed to sunitinib who took part in the GIST treatment placebo-controlled trial, the mRCC treatment active-controlled trial or the pancreatic NET treatment placebo-controlled trial. Patients receiving treatment for GIST and mRCC were administered an oral dose of 50 mg per day to start on Schedule 4/2 within repeated cycles, and the patients receiving treatment for pancreatic NET were administered an oral dose of 37.5 mg per day to start without an organised rest period.

Undesirable effects that occurred in the GIST, RCC and pancreatic NET research are explained below.

Refer to Section 4.4 Special warnings and precautions of use for more information on cardiovascular events (including hypertension, venous thromboembolic and QT interval prolongation), gastrointestinal disorders (including pancreatitis), haematological cases, seizures and thyroid dysfunction, recorded during the clinical studies.

Placebo-controlled GIST adverse events

The median treatment duration in a blinded study treatment for patients on sunitinib and placebo were two cycles (mean 3.0, range 1-9) and one cycle (mean 1.8, range 1-6), respectively. A reduction in dose was required in 23 patients (11%) taking sunitinib and none in patients taking placebo. Interruptions in dosage was required in 59 (29%) and 31 (30%) for patients taking sunitinib and placebo, respectively. The permanent discontinuation rates due to treatment-emergent, non-fatal adverse events for patients

taking sunitinib was 7% and for patients taking placebo 6%.

The majority of treatment-emergent undesirable effects in both study arms were of the severity of Grade 1 or 2. In patients taking sunitinib versus placebo, Grade 3 or 4 treatment-emergent undesirable effects were reported in 56% versus 51%, respectively. In patients on sunitinib, altered taste, bleeding, diarrhoea, hypertension, mucositis and skin abnormalities were more common. Table 1 shows the comparison of incidence for TEAE considered common (>10%) in patients taking sunitinib versus placebo.

Table 1. Reports of Treatment-Emergent Adverse Events of GIST Patients (≥10%) who were given Sunitinib or Placebo in the placebo-controlled GIST Study*

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

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.
[a] Grade 4 Adverse Events in patients on sunitinib which includes abdominal pain (2%) and bleeding (2%).
[b] Grade 4 Adverse Events in patients on placebo which includes abdominal pain (3%), back pain (1%), bone pain (1), fatigue (3%), mucositis (1%) and vomiting (1%).
[c] Includes abdominal, abdominal quadrant, cancer-related, flank, gastric, and hypochondrial pain.
[d] Includes reduction of appetite.

Oral pain (not including mucositis/stomatitis) was reported in 12 (6%) and 3 (3%) patients on sunitinib versus placebo, respectively. Hair colour changes was reported in 15 (7%) and 4 (4%) patients on sunitinib versus on placebo, respectively. Alopecia was reported in 10 (5%) and 2 (2%) of patients on sunitinib versus placebo, respectively.

Table 2 shows frequently occurring (≥10%) laboratory abnormalities that emerged during treatment.

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

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

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.
[a] Grade 4 Adverse Events in patients on sunitinib which includes alkaline phosphatase (1%), anaemia (2%), creatinine (1%), hypokalaemia (1%), lipase (2%), neutropenia (2%), and thrombocytopenia (1%).
[b] Grade 4 Adverse Events in patients on placebo which includes amylase (1%), anaemia (2%), lipase (1%), and thrombocytopenia (1%).

Grade 3 or 4 treatment-emergent laboratory abnormalities were reported in 68 (34%) patients on sunitinib versus 22 (22%) patients on placebo. In patients treated with sunitinib, elevated creatinine, liver function tests and pancreatic enzymes were more common than placebo. It was more common to have decreased LVEF and

myelosuppression in patients with sunitinib treatment than on placebo. This was also evident with treatment-emergent electrolyte disturbances (of all types), including hyperkalaemia (6% sunitinib vs. 4% placebo), hypokalaemia (12% sunitinib vs. 4% placebo), hypernatraemia (10% sunitinib vs. 4% placebo), hyponatraemia (6% sunitinib vs. 1% placebo) and hypophosphataemia (9% sunitinib vs. 0% placebo). Grade 3 hypophosphataemia were reported in three sunitinib patients (1.5%) and acquired hypothyroidism was reported in eight patients (4%) versus 1 (1%) on sunitinib and placebo, respectively.

RCC studies adverse events

The interim safety analysis of the as-treated patient population for the Phase 3 RCC trial involved 250 patients, randomized to 129 sunitinib and 121 interferon-α. A reduction in dosage occurred in 42 (33%) and 15 (12%) patients for sunitinib and interferon-α, respectively. Interruptions of dosage occurred in 45 (35%) and 44 (36%) patients for sunitinib and interferon-α, respectively. The rates of permanent discontinuation due to non-fatal treatment-emergent adverse events were 9% for sunitinib and 13% for interferon-α. In both study arms, the majority of treatment-emergent adverse events (TEAE) were considered Grade 1 or 2 severity. Grade 3 or 4 TEAE were reported in 67% of patients on sunitinib versus 49% of patients on interferon-α. In patients given sunitinib, altered taste, bleeding, diarrhoea, hypertension, mucositis and skin abnormalities were more common. Table 3 shows the comparison of the incidence of common (≥10%) TEAE in patients taking sunitinib versus patients taking interferon-α.

Sunitinib treatment information recorded for the 169 patients registered in the pivotal and supportive trials in cytokine-refractory mRCC are also incorporated in Table 3. For the pivotal trial, the median duration of treatment was 5.5 months (range: 0.8-11.2) and for the supportive trial it was 7.7 months (range: 0.2-16.1). Dosage interruptions appeared in 48 patients (45%) and 45 patients (71%) in the pivotal trial and supportive trial, respectively. One or more dosage reduction appeared in 23 patients (22%) and 22 patients (35%) in the pivotal trial versus the supportive trial, respectively.

Table 3. Reports of Treatment-Emergent Adverse Events of Patients (≥10%) with mRCC who were given sunitinib or Interferon-α*

	Treatment-naïve n (%)				**Cytokine-refractory n (%)**	
	Sunitinib (n=129)		**Interferon-α (n=121)**		**Sunitinib (N=169)**	
Adverse Event	**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)
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)

Constitutional						
• Asthenia	20 (16)	6 (5)	26 (22)	7 (6)	16 (9)	4 (2)
• Chills	12 (9)	0 (0)	45 (37)	0 (0)	18 (11)	0 (0)
• Fatigue	81 (63)	12 (9)	77 (64)	21(17)	125 (74)	19 (11)
• 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)
Dermatology						
• Alopecia	8 (6)	0 (0)	15 (12)	0 (0)	20 (12)	0 (0)
• Dry skin	30 (23)	0 (0)	10 (8)	0 (0)	29 (17)	0 (0)
• 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)
• Rash	29 (23)	1 (1)	15 (12)	1 (1)	64 (38)	1 (1)
Gastrointestinal						
• 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)
• Diarrhoea	78 (60)	9 (7)	24 (20)	0 (0)	93 (55)	8 (5)
• Dry mouth	14 (11)	0 (0)	9 (7)	1 (1)	10 (6)	0 (0)
• Dyspepsia	35 (27)	1 (1)	7 (6)	0 (0)	77 (46)	1 (1)
• Flatulence	19 (15)	0 (0)	5 (4)	0 (0)	24 (14)	0 (0)
• Glossodynia	14 (11)	0 (0)	1 (1)	0 (0)	25 (15)	0 (0)
• 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)
Haemorrhage/ bleeding						
• Bleeding, all sites	43 (33)	2 (2)	7 (6)	0 (0)	44 (26)	1 (1)
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)
Musculoskeletal						
• Arthralgia	25 (19)	0 (0)	22 (18)	0 (0)	48 (28)	2 (1)
• 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)
Neurology						
• Altered taste[e]	60 (47)	0 (0)	22 (18)	0 (0)	73 (43)	0 (0)
• Dizziness	9 (7)	0 (0)	22 (18)	1 (1)	27 (16)	3 (2)
• Headache	27 (21)	1 (1)	22 (18)	0 (0)	43 (25)	2 (1)

Psychiatric						
• Depression	6 (5)	0 (0)	16 (13)	3 (3)	14 (8)	1 (1)
• Insomnia	14 (11)	0 (0)	10 (8)	0 (0)	22 (13)	1 (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)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.
[a] Grade 4 Adverse Events in patients on sunitinib included back pain (2%) and rash (1%).
[b] Grade 4 Adverse Events in patients on interferon-α included depression (1%), dyspnoea (2%), and fatigue (1%).
[c] No Grade 4 Adverse Events were reported amongst the events with a ≥10% incidence in the cytokine-refractory mRCC group.
[d] Includes flank pain.
[e] Includes ageusia, dysgeusia and hypogeusia.
[f] Includes a reduction in appetite.

In the cytokine-refractory mRCC patients given sunitinib, other significant adverse events that occurred included appetite disturbance (9)%, increased lacrimation (6%), periorbital oedema (7%), peripheral neuropathy (10%), and skin blistering (7%).

In the Phase 3 trial, Grade 4 treatment-emergent chemistry laboratory abnormalities were reported in 20 patients (16%) and 14 patients (12%) for sunitinib vs. interferon-α, respectively. The most frequently observed Grade 4 chemistry abnormalities were elevated hyperuricaemia levels (10% in both treatment groups) and increased lipase levels (4% vs. 2% for sunitinib and n interferon-α, respectively). The most common chemistry abnormalities (Grade 3) observed for both study arms was hyperglycemia (4% on each arm) and an increase in lipase (15% vs. 5% for sunitinib and interferon-α, respectively). Other common laboratory abnormalities (Grade 3) were increased amylase (5%) and hyponatraemia (5%) for sunitinib, and for interferon-α were AST (3%) and hypophosphataemia (5%). Common treatment-emergent chemistry laboratory abnormalities (Grade 3 and 4) in the cytokine-refractory mRCC studies for patients on sunitinib included hyperuricaemia (10%), hypophosphataemia (10%), increased amylase (5%) and increased lipase (16%).

Table 4 presents the haematology laboratory abnormalities.

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

	Treatment-naïve n (%)				**Cytokine-refractory n (%)**	
	Sunitinib (n=129)		**Interferon-α (n=121)**		**(n=169)**	
Laboratory Test	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Haematology						
• Anaemia	4 (3)	0 (0)	3 (3)	0 (0)	9 (5)	3 (2)
• Leukopenia	8 (6)	0 (0)	2 (2)	0 (0)	12 (7)	0 (0)
• Lymphopenia	19 (14)	0 (0)	26 (21)	0 (0)	33 (20)	2 (1)
• Neutropenia	15 (12)	2 (2)	7 (6)	1 (1)	21 (12)	1 (1)
• Thrombocytopenia	9 (7)	0 (0)	0 (0)	0 (0)	5 (3)	0 (0)

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

mRCC long-term safety

The safety for patients long-term with mRCC taking sunitinib was examined across nine clinical studies operated in the first-line, bevacizumab-refractory and cytokine-refractory treatment settings. The evaluation included 5739 patients, where 807 (14%) were treated between ≥2 years to 6 years. Prolonged sunitinib treatment was not related with new types of treatment-related adverse events or increased severity and excluding hypothyroidism, toxicity did not become cumulative.

Phase 3 pancreatic NET study adverse events

For patients on sunitinib, the median number of treatment days was 139 days (range 13 - 532 days) and for patients on placebo 113 days (range 1 - 614 days). Patients that were studied for >1 year included nineteen patients (23%) and 3 patients (4%) for sunitinib vs. placebo, respectively. Interruptions to dosage occurred in 25 patients (30%) and 10 patients (12%) on sunitinib and placebo, respectively. Reductions of dose occurred in 26 (31%) and 9 patients (11%) on sunitinib and placebo, respectively. Discontinuation rates were 22% for sunitinib and 17% for placebo due to adverse events.

The majority of treatment-emergent adverse events (TEAE) in both sunitinib and placebo were considered Grade 1 or 2 in severity. Grade 3 or 4 TEAE were reported in 54% of patients on sunitinib versus 50% of patients on placebo. Table 5 compares the incidence of common (≥10%) TEAE for patients receiving sunitinib and reported more commonly in patients receiving sunitinib than in patients receiving placebo.

Table 5. Reports of Adverse Events in the Phase 3 Pancreatic NET Study in Patients (≥10%) who Received Sunitinib and More Frequently than in Patients Assigned Placebo*

Adverse event	Pancreatic NET n (%)			
	Sunitinib (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)
Cardiac				
• Hypertension	22 (27)	8 (10)	4 (5)	1 (1)
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)
Dermatology				
• Dry skin	12 (15)	0 (0)	9 (11)	0 (0)
• 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)

Gastrointestinal				
• Abdominal pain - upper	11 (13)	1 (1)	6 (7)	0 (0)
• Diarrhoea	49 (59)	4 (5)	32 (39)	2 (2)
• Dyspepsia	12 (15)	0 (0)	5 (6)	0 (0)
• Nausea	37 (45)	1 (1)	24 (29)	1 (1)
• Stomatitis/Oral Syndromes[b]	40 (48)	5 (6)	15 (18)	0 (0)
• Vomiting	28 (34)	0 (0)	25 (31)	2 (2)
Haemorrhage/Bleeding				
• Bleeding events[c]	18 (22)	0 (0)	8 (10)	3 (4)
• Epistaxis	17 (21)	1 (1)	4 (5)	0 (0)
Musculoskeletal				
• Arthralgia	12 (15)	0 (0)	5 (6)	0 (0)
Neurology				
• Dysgeusia	17 (21)	0 (0)	4 (5)	0 (0)
• Headache	15 (18)	0 (0)	11 (13)	1 (1)
Psychiatric				
• Insomnia	15 (18)	0 (0)	10 (12)	0 (0)

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

a Grade 4 Adverse Events in patients on sunitinib included fatigue (1%).

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

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

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

Table 6. Reports of Laboratory Abnormalities in Patients (≥10%) Who Received Sunitinib in the Phase 3 Pancreatic NET Study

Laboratory Parameter	Pancreatic NET n (%)					
	Sunitinib			Placebo		
	N	All Grades*	Grade 3/4*[a]	N	All Grades*	Grade 3/4*[b]
Gastrointestinal						
• Alkaline phosphatase	82	52 (63)	8 (10)	80	56 (70)	9 (11)
• ALT	82	50 (61)	3 (4)	80	44 (55)	2 (3)
• Amylase	74	15 (20)	3 (4)	74	7 (10)	1 (1)
• AST	82	59 (72)	4 (5)	80	56 (70)	2 (3)
• Lipase	75	13 (17)	4 (5)	72	8 (11)	3 (4)
• Total bilirubin	82	30 (37)	1 (1)	80	22 (28)	3 (4)
Haematology						
• Hemoglobin	82	53 (65)	0 (0)	80	44 (55)	1 (1)
• Lymphocytes	82	46 (56)	6 (7)	80	28 (35)	3 (4)
• Neutrophils	82	58 (71)	13 (16)	80	13 (16)	0 (0)
• Platelets	82	49 (60)	4 (5)	80	12 (15)	0 (0)
Renal/Metabolic						
• Albumin	81	33 (41)	1 (1)	79	29 (37)	1 (1)
• Calcium decreased	82	28 (34)	0 (0)	80	15 (19)	0 (0)
• Creatinine	82	22 (27)	4 (5)	80	22 (28)	4 (5)
• Glucose decreased	82	18 (22)	2 (2)	80	12 (15)	3 (4)
• Glucose increased	82	58 (71)	10 (12)	80	62 (78)	14 (18)
• Magnesium decreased	52	10 (19)	0 (0)	39	4 (10)	0 (0)
• Phosphorus	81	29 (36)	6 (7)	77	17 (22)	4 (5)
• Potassium decreased	82	17 (21)	3 (4)	80	11 (14)	0 (0)
• Potassium increased	82	15 (18)	1 (1)	80	9 (11)	1 (1)
• Sodium decreased	82	24 (29)	2 (2)	80	27 (34)	2 (3)

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

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

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

Post-marketing experience

The adverse events below have been discovered during the post-approval sunitinib use (refer also to section 4.4 Special warnings and precautions of use). As these effects are reported from an unknown population size voluntarily, it is not always achievable to estimate the reliability of frequency or find a causal relationship to pharmaceutical exposure.

Blood and lymphatic system disorders

There are reports of rare cases of thrombotic microangiopathy, in some instances with a fatal outcome. It is recommended that sunitinib use be temporarily suspended. After resolution, medication may be restarted at the treating physician's discretion (refer to section 4.4 Special warnings and precaution of use - Thrombotic microangiopathy).

Cardiac disorders
There are reports of cardiac failure, cardiomyopathy, left ventricular failure, myocardial infarction and myocardial ischaemia, in some instances with a fatal outcome. There are also reports of congestive cardiac failure, prolonged QT interval and torsade de pointes.

Connective tissue and musculoskeletal disorders
There are reports of myopathy and/or rhabdomyolysis (with or without acute renal failure) and in some cases fatal. The majority of these patients had known pre-existing risk factors and/or were taking concomitant treatments known to be related to these adverse reactions. Patients showing symptoms or signs of muscle toxicity must be managed as per standard medical practice.

There are reports of fistula formation, in some cases related to tumour necrosis and/or regression with fatal outcome.

In some reports, there are cases of osteonecrosis of the jaw (ONJ) in patients on sunitinib treatment. The majority occurred in patients who had ONJ identified risk factors, specifically a history of dental disease (requiring serious dental procedures) and/or exposure to IV bisphosphonates (refer to section 4.4 Special warnings and precautions of use).

Endocrine disorders
There are reports of hyperthyroidism, in some cases followed by hypothyroidism in clinical studies and through post-marketing experience (refer to section 4.4 Special warnings and precautions of use - Thyroid dysfunction). There are also reports of thyroiditis.

Gastrointestinal disorders
There are reports of gastrointestinal perforation, oesophagitis and pancreatitis.

Haemorrhagic events
There are reports of brain, GI, pulmonary, tumour and urinary tract haemorrhages, in some cases fatal. There have been reports of fatal haemorrhage associated with thrombocytopenia.

Hepatobiliary disorders
There are reports of cholecystitis (mainly acalculous cholecystitis) and hepatic failure.

Immune system disorders
There are reports of hypersensitivity reactions, including angioedema.

Infections and infestations
There are reports of serious infection with or without neutropenia and in some cases fatal. The most commonly reported infections with sunitinib use are typically seen in cancer patients, which include respiratory infections (for example; bronchitis and pneumonia), septic shock/sepsis and abscess (for example; anorectal, genital, limb, oral, skin and visceral), skin infections (for example; cellulitis) and urinary tract infections. Infections may be bacterial (for example; intra-abdominal or osteomyelitis), fungal (for example; candidiasis - oral or oesophageal) and viral (for example; nasopharyngitis or oral herpes). There are rare reports of necrotising fasciitis, including of the perineum in some cases fatal (refer to section 4.4 Special warnings and precautions of use).

Investigations
There are reports of increased TSH and blood uric acid.

Nervous system disorders
There are reports of taste disturbances, including ageusia.
Hyperammonaemic encephalopathy has also been reported.

Nutrition disorders and metabolism
There are reports of tumour lysis syndrome (TLS), in some cases fatal.

Blood glucose decreases, in some cases clinically symptomatic, have also been reported (refer to section 4.4 Special warnings and precautions of use - Hypoglycaemia).

Respiratory, thoracic and mediastinal disorders
There are reports of pulmonary embolism, with some cases of fatal outcome. Cases of pleural effusion have also been reported.

Skin and subcutaneous tissue disorders
There are reports of erythema multiforme, pyoderma gangrenosum and Stevens-Johnson syndrome.

Urinary and renal disorders
There are reports of renal impairment and/or failure. In some cases, with a fatal outcome. Rare cases of nephrotic syndrome and cases of proteinuria have also been reported (refer to section 4.4 Special warnings and precautions of use).

Vascular disorders
There are reports of arterial thromboembolic events (ATE), in some cases fatal. The most common events include cerebral infarction, cerebrovascular accident and transient ischaemic attack. ATE risk factors, in addition to the primary malignant disease and age ≥65 years, includes diabetes mellitus, hypertension, and previous thromboembolic disease.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after approval 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

There are known reports of sunitinib overdose. In some cases adverse reactions that are consistent with the known sunitinib safety profile were recorded.

In the event of overdose, there is no particular antidote for sunitinib and overdose treatment should include general supportive measures.

Sunitinib is not eliminated from the blood by dialysis.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX01.

Mechanism of action

Sunitinib is a small compound that inhibits simultaneously multiple receptor tyrosine kinases (RTKs) that are associated with, pathologic angiogenesis, tumour growth and the metastatic advancement of cancer. In various kinase inhibition assays, sunitinib demonstrated significant inhibitory effects, particularly targeting platelet-derived growth factor receptor β (PDGFRβ), stem cell factor receptor (KIT), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), colony stimulating factor receptor Type 1 (CSF-1R), Fms-like tyrosine kinase-3 (FLT3) and the glial cell-line derived neurotrophic factor receptor (RET).

Sunitinib has been shown to inhibit tyrosine kinase activity of these RTKs in both biochemical and cellular assays. The function of inhibition was shown in cell proliferation assays in where PDGFRα activity was inhibited. The primary metabolite displays comparable potency to sunitinib in both biochemical and cellular assays, specifically inhibiting PDGFRβ, VEGFR2 and KIT tyrosine kinase activities.

In vivo, sunitinib effectively suppressed the phosphorylation of various RTKs (PDGFRα, VEGFR2, KIT) in tumour xenografts expressing these RTK targets. This inhibition was associated with either a reduction in tumour growth, tumour regression, or the inhibition of metastases in certain experimental cancer models. Reflecting its multi-targeted nature, sunitinib displays the capability to directly impede the growth of tumour cells expressing dysregulated RTK targets (PDGFR, RET, FLT3 or KIT) and hindered tumour angiogenesis.

Clinical efficacy and safety

Advanced renal cell carcinoma (RCC)
An ongoing Phase 3 study involved a 1:1 randomised, multi-centre, comparison of sunitinib with interferon-α in more than 700 treatment-naïve patients diagnosed with metastatic RCC (mRCC). The prescribed regimen for sunitinib was 50 mg orally once per day, administered as a single agent for four consecutive weeks, followed by a two-week break (Schedule 4/2). Simultaneously, interferon-α2a (IFN-α) was administered subcutaneously at a dosage of 9 MIU three times per week.

Progression Free Survival (PFS) was the primary endpoint and the research was adequately driven to identify enhancements in Overall Survival (OS). The statistical strategy incorporated an interim analysis of the Objective Response Rate (ORR) of the two treatments, set to occur after at least 250 patients had completed three cycles. Table 7 presents the results of the preplanned interim analysis, where ORR serves as the primary endpoint.

Table 7. Interim results for Objective Response Rate and Progression in First-Line Treatment of Metastatic Renal Cell Carcinoma: Sunitinib vs. IFN- α

Core Imaging Laboratory Measurements (n= 235)		
	Sunitinib n=129	**IFN-α n=124**
Individuals with baseline assessment, n (%)	115 (89.1)	106 (85.5)
Best Overall Response, n (%)		
Complete Response (CR)	0 (0)	0 (0)
Partial Response (PR)	33 (25.6)	9 (7.3)
Stable Disease (SD)	53 (41.1)	54 (43.5)
Progressive Disease (PD)	25 (19.4)	29 (23.4)
Not evaluable (< 6 weeks on study)	4 (3.1)	14 (11.3)
Scans still to evaluate	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] Includes a 28-day follow up period following the last dose of medicine.
NA = Unable to be calculated due to information not complete.

Two studies were conducted to explore the effectiveness of single agent sunitinib in treating advanced cytokine-refractory RCC; a Phase 2 pivotal study and a supportive Phase 2 study. Both investigations adopted a single-arm, multi-centre, non-randomised, open-label approach, enrolling patients with mRCC who had proven refractoriness to previous cytokine treatments (interferon-α, interleukin-2, or interferon-α plus interleukin-2). ORR was the primary endpoint for both studies, with secondary endpoints encompassing the evaluation of Time to Tumour Progression (TTP), Duration of Response (DR), PFS, and OS.

The pivotal study comprised of 106 individuals, while the supportive study involved 63 individuals. The initial dosage was sunitinib 50 mg per on a Schedule 4/2 for both studies. Treatment continued until patients met the withdrawal criteria or experienced progressive disease. Baseline characteristics included age, race, gender, baseline malignancy, ECOG performance status, and previous treatment history demonstrated comparability between the two studies. The majority of patients (97% of the combined population) had undergone nephrectomy; a prerequisite for enrollment in the pivotal study. All individuals had received one prior cytokine regimen, with 9.5% (n=16) achieving an objective disease response. At study entry, 81% of patients had lung metastases. Liver metastases was more prevalent in the pivotal study (27% vs. 16% in the supportive study), while bone metastases were more frequent in the supportive study (51% vs. 25% in the pivotal study). Approximately 52% of patients in the combined population exhibited at least three metastatic sites.

Table 8 presents the results of the two studies.

Table 8. mRCC Efficacy Results in second-line treatment

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, DR=Duration of Response, PFS= Progression Free Survival, PR=Partial response, TTP=Time To Progression.

[a] Evaluated by blinded core radiology laboratory.

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

* Information not complete to determine upper confidence limit.

** Median DR has not yet been achieved.

In both studies, the primary endpoint was the Objective Response Rate (ORR). The core imaging laboratory documented 38 partial responses (PRs) in the pivotal study yielding an ORR of 35.8% (95% CI: 26.8, 45.7). Similarly, the supportive study showed consistent results with a demonstrated ORR of 25.4%.

The majority of objective disease responses occurred during Cycles 2 to 4, with responses continuing as late as Cycle 11. Regarding the duration of tumour response (DR) information from the pivotal study, it is currently premature as only a relatively small number of individuals who responded to treatment have experienced disease progression (Median DR not yet reached [95% CI: 42.0 weeks*] based on core-laboratory assessment). In the supportive study, the median DR as assessed by investigators, was 54 weeks (95% CI: 34.3, 70.1). These findings suggest that the disease responses stimulated by sunitinib in individuals with cytokine-refractory RCC were enduring.

Gastrointestinal stromal tumours (GIST)

A preliminary open-label, dose-escalation trial was carried out in individuals with GIST who experienced imatinib failure (median maximum daily dose 800 mg) due to intolerance or resistance. Ninety-seven individuals were included in the study, receiving varying doses and schedules; among them, 55 patients were administered a daily dose of 50 mg following the recommended treatment schedule of 4 weeks on followed by 2 weeks off (Schedule 4/2). In this examination, the median TTP, as assessed by the investigator was 34.0 weeks (95% CI = 22.0–46.0 weeks).

A Phase 3 study of sunitinib was carried out in patients with GIST who exhibited intolerance to, or had undergone disease progression during or after imatinib treatment (median maximum daily dose 800 mg). This randomized, double-blind, placebo-controlled trial involved 312 patients, with a 2:1 allocation to either receive sunitinib 50 mg or placebo orally once per day on Schedule 4/2 until progression of the disease or withdrawal from the study for other reasons (207 patients received sunitinib and 105 patients received placebo).

Table 9 presents the outcomes of both dose escalation and Phase 3 studies.

Table 9. GIST Efficacy Results[a]

Efficacy Parameter	Phase 3 Study[b]		Dose escalating study[c]
	Sunitinib n = 207	Placebo n = 105	Sunitinib n= 55
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)
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

CI=Confidence interval, CR=Complete response, PR=Partial response, SD=Stable disease.
a Information 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 determine due to the low number of deaths in the ongoing study.

In the Phase 3 trial, a statistically significant extension in the primary endpoint TTP, was identified between the treatment groups, demonstrating clinical significance (refer to Figure 1). As assessed by the core imaging laboratory the median TTP was 27.3 weeks for the sunitinib arm compared to 6.4 weeks for the placebo arm (Hazard Ratio 0.329, 95% CI 0.222, 0.466, p-value <0.0001). Patients in the placebo group were three times more likely to experience disease progression.

In comparison to the sunitinib arm (signifying a 67% decrease in the risk of increasing progressive disease for individuals receiving sunitinib treatment), the median TTP for the cohort treated with sunitinib exceeded four times the duration observed in patients receiving placebo. The findings from the dose escalation study, which indicated a median TTP of 34.0 weeks based on investigator assessment, align with the outcomes of the Phase 3 study.

In the Phase 3 trial, sunitinib treatment resulted in 14 Partial Responses, equivalent to 6.8% ORR, determined by the Response Evaluation Criteria In Solid Tumours (RECIST) using core laboratory assessment. In contrast, no PRs were noted in the placebo arm. The dose escalation study yielded consistent findings, reporting 5 PRs (9.1% ORR) according to investigator assessment.

When assessed for clinical benefit response (defined as the percentage of patients with CR, PR or stable disease [SD] lasting ≥22 weeks), 50 patients (24.2%) treated with sunitinib in the Phase 3 study experienced clinical benefit, whereas only 2 patients (1.9%) in the placebo group achieved clinical benefit. In the dose escalation study, the clinical benefit rate was 60%. The variance in clinical benefit response rates between the studies is attributable to the longer follow-up period in the dose escalation study, leading to more patients receiving treatment for at least 22 weeks in comparison to the Phase 3 study. These findings underscore the capacity of sunitinib to achieve and sustain disease control in patients with

GIST following imatinib failure.

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

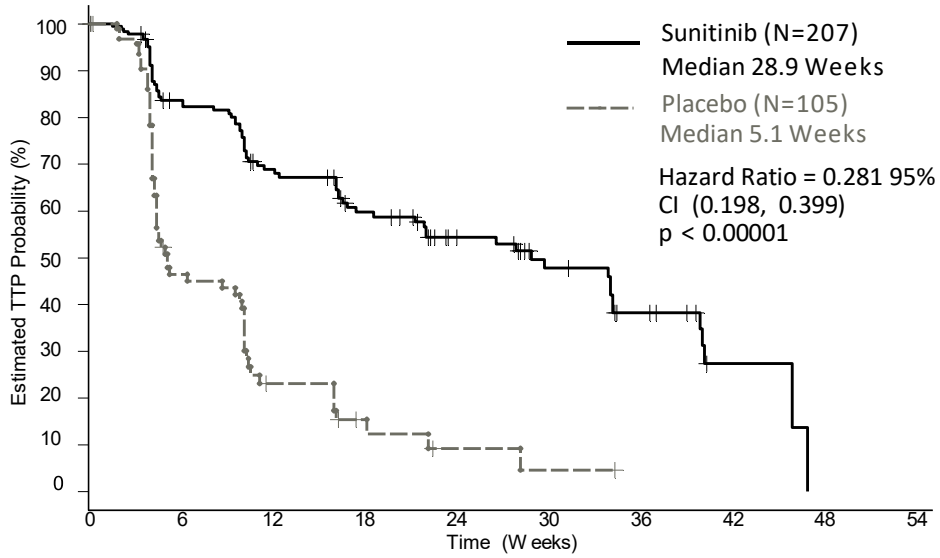
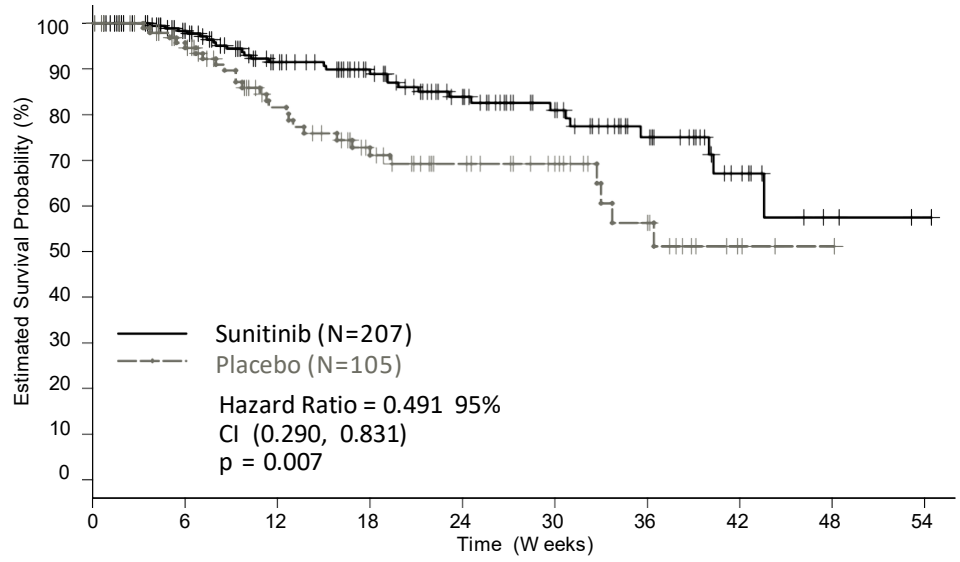


Figure 2. (Intent-to-Treat Population) - Kaplan-Meier Curve of OS



A statistically significant distinction in OS was observed in the Phase 3 study (refer to Figure 2) with a Hazard Ratio of 0.491 (95% CI: 0.290, 0.831, p = 0.007). The risk of death was twice as high in patients assigned to the placebo arm compared to those receiving sunitinib. At the time of analysis, the median OS had not yet been reached in either treatment group. The recorded percentages of deaths were 14% and 25% for sunitinib and placebo, respectively.

Pancreatic neuroendocrine tumours (pancreatic NET)
In a supportive Phase 2 study, which was open-label and multi-centered the effectiveness and safety of a single-agent sunitinib at a daily dose of 50 mg on Schedule 4/2 (4 weeks on treatment followed by a 2-week rest period) was assessed in patients with unresectable pancreatic NET. Among a cohort of 66 patients with pancreatic islet cell tumours, the primary endpoint of response rate was 17% with all responses characterised as partial responses.

A pivotal Phase 3 study, conducted as a randomised, multi-centre, international, double-blind placebo-controlled design to assess the efficacy of single agent sunitinib in patients with unresectable, well-differentiated pancreatic NET where eligible patients had documented progression within the prior 12 months based on RECIST criteria. The study involved randomising patients (1:1) to receive either 37.5 mg sunitinib once per day without a scheduled rest period (n=86) or placebo (n=85). The primary objective aimed to compare PFS between patients receiving sunitinib and those receiving placebo. Additional endpoints encompassed OS, ORR, Patient-reported Outcomes (PRO) and safety. The use of somatostatin analogs were permitted during the study.

Demographic characteristics were similar between the sunitinib and placebo cohorts. Furthermore, non-functioning tumours were present in 49% of sunitinib patients compared to 52% of placebo patients, and both treatment groups exhibited a high prevalence of liver metastases, with 92% of patients in each arm having this condition. Regarding prior systemic therapy, 66% of sunitinib patients had previously received treatment, slightly less than the 72% observed in the placebo group. Additionally, 24% of sunitinib patients had a history of somatostatin analog use, while 22% of placebo patients reported similar prior treatment.

A substantial clinical advantage in PFS was evident for sunitinib compared to placebo. The median PFS was 11.4 months in the sunitinib arm, contrasting with 5.5 months for the placebo arm [hazard ratio: 0.418 (95% CI 0.263, 0.662) p-value =0.0001]. The hazard ratio favouring sunitinib was consistent across all subgroups of baseline characteristics evaluated, as detailed in Table 10.

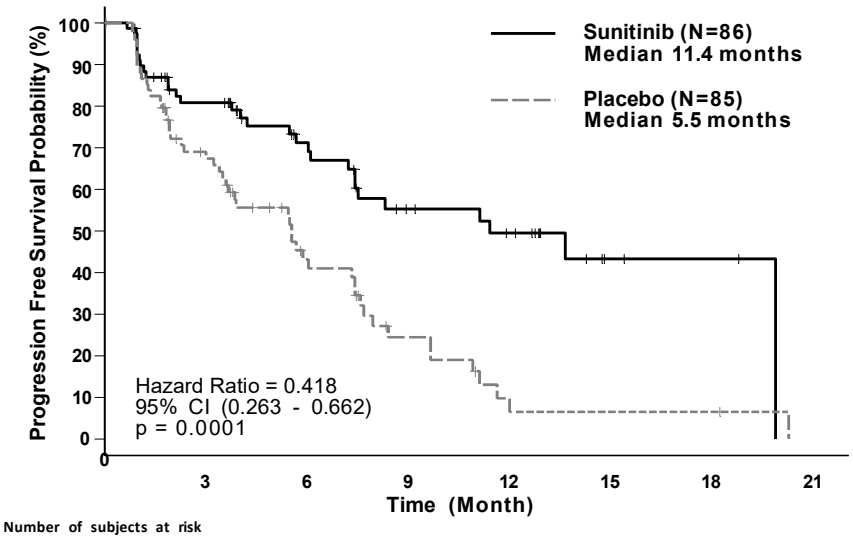
This study was prematurely ended based on the recommendation of an independent Drug Monitoring Committee, with patients subsequently provided the option of open-label sunitinib in extension studies.

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

Efficacy Parameter	Sunitinib (n = 86)	Placebo (n = 85)	P-Value	HR (95% CI)
Objective Response Rate [%] (95% CI)	9.3 (3.2, 15.4)	0	0.0066[c]	NA
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)

CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached.
[a] All patients originally randomised were included and analysed under the original randomised treatment arm.
[b] 2-sided unstratified log-rank test.
[c] Fisher's Exact test.

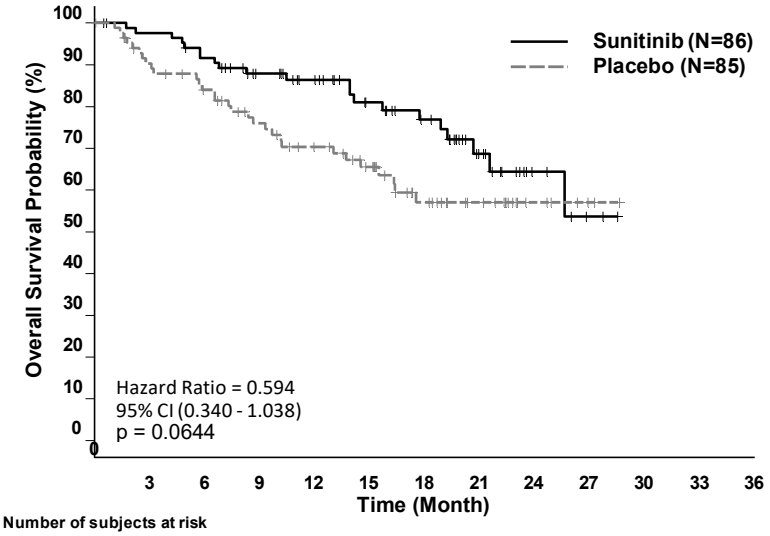
Figure 3. Phase 3 Pancreatic NET Study - Kaplan-Meier Curve of PFS



Number of subjects at risk

Sunitinib	86	52	34	20	15	4	2
Placebo	85	42	20	9	2	2	2

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



Number of subjects at risk

Sunitinib	86	82	76	64	54	42	34	18	7	2
Placebo	85	73	65	55	46	38	24	16	6	2

Overall Survival data was not fully developed at the time of the analysis, with 21 and 30 deaths reported in the sunitinib arm versus the placebo arm, respectively. Notably, patients in the placebo arm had the option to receive sunitinib after disease progression, which could potentially complicate the survival analysis. Despite this, a statistically significant difference in ORR favored sunitinib over placebo.

Findings from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC-30) revealed that patients on sunitinib treatment maintained their overall global health-related quality of life, as well as the five functioning domains (cognitive, emotional, physical, role and social) with minimal adverse symptomatic effects compared to the placebo group.

5.2 Pharmacokinetic properties

Pharmacokinetics of sunitinib malate and sunitinib have been assessed in 135 healthy individuals and 266 patients presenting with solid tumours.

Absorption

The absolute bioavailability is yet to be determined.

Maximum plasma concentrations (Cmax) are normally detected between 6 - 12 hours (Tmax) after oral administration. In numerous studies on dosage within the dose range of 25 to 100 mg, the area below the plasma concentration-time curve (AUC) and Cmax expand respectively with the dose. During recurrent daily administration, sunitinib accrues 3 to 4 fold and its primary metabolite accrues 7 to 10 fold. Steady-state concentrations are attained within 10 to 14 days for sunitinib and its primary active metabolite. By approximately day 14, the combined plasma concentrations of sunitinib and its primary metabolite are 62.9 - 101 ng/mL which are the level of concentrations expected from preclinical information to inhibit receptor phosphorylation in vitro and therefore result in a reduction of tumour stasis/growth *in vivo*. The bioavailability of sunitinib is not affected by food.

Distribution

Binding to human plasma protein *in vitro* occurs in 95% of sunitinib and 90% for its primary active metabolite. There is no obvious concentration dependence within the range of 100 - 4000 ng/mL. The evident distribution volume (Vd/F) for sunitinib was large at 2230 L, representing distribution into the tissues.

Biotransformation

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

Elimination

In healthy individuals, following oral administration, the elimination half-live of sunitinib was 40 to 60 hours and for its primary active metabolite was 80 to 110 hours.

Excretion is principally via faeces (61%) with renal elimination of sunitinib and its metabolites occurring for 16% of the dose administered. Sunitinib and its primary active metabolite were the major medicine-related compounds eliminated in faeces (73.8%), plasma (91.5%) and

urine (86.4%) of radioactivity in pooled samples. Minor metabolites were identified in faeces and urine, but usually were not located in plasma. Total oral clearance (Cl/F) was 34-62 L/hr with an inter-patient variability of 40%.

Recurring daily administration or repeated cycles of the dosage schedules tested showed no significant changes in sunitinib pharmacokinetics for the primary, active metabolite.

Special populations

In healthy individuals and populations with solid tumours, the pharmacokinetics were similar.

Hepatic impairment
Sunitinib and its primary metabolite are mostly metabolised by the liver. Following a single dose of sunitinib, systemic exposures were comparable in individuals with mild or moderate (Child-Pugh Class A and B) hepatic impairment in contrast to individuals with normal hepatic function. Sunitinib has not been studied in patients with severe (Child-Pugh class C) hepatic impairment.

Renal impairment
Following a single dose of sunitinib, systemic exposures were comparable in individuals with severe renal impairment (CLcr<30 mL/min) in contrast to individuals with normal renal function (CLcr>80 mL/min). While sunitinib and its primary metabolite were not eliminated through haemodialysis in individuals with end-stage renal disease (ESRD), the total systemic exposures were lesser by 47% for sunitinib and 31% for its primary metabolite in comparison to individuals with normal renal function.

Population pharmacokinetics

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

Paediatric population
For paediatric subjects, there is no pharmacokinetic information available.

5.3 Preclinical safety data

Carcinogenicity

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

An oral gavage carcinogenicity trial was conducted in rasH2 transgenic mice over 6-months (0, 8, 25, or 75 [reduced to 50] mg/kg per day) with daily administration. A heightened incidence of background hemangiosarcoma, gastroduodenal carcinomas, and/or gastric mucosal hyperplasia were detected at doses of ≥25 mg/kg per day after 1 or 6 months duration (≥7.3 times the AUC in individuals given the RDD).

In a rat carcinogenicity trial (0, 0.33, 1, or 3 mg/kg per day) conducted over two years, sunitinib administration occurred in 28 day cycles pursued by dose-free periods of 7 days which resulted in the incidence of hyperplasia and pheochromocytomas in the adrenal

medulla of male rats administered 3 mg/kg per day following >1 year of treatment (≥7.8 times the AUC in individuals given the RDD) to increase. Brunner's glands carcinoma was observed in the duodenum of females at ≥1 mg/kg per day and in males at 3 mg/kg per day. Mucous cell hyperplasia was apparent in the glandular stomach for males at 3 mg/kg per day, which happened at ≥0.9, 7.8 and 7.8 times the AUC in subjects administered the RDD, respectively. The significance of the neoplastic results to humans observed in the mouse (rasH2 transgenic) and rat carcinogenicity studies with treatment of sunitinib is uncertain.

Genotoxicity

In vitro tests for bacterial gene mutation and human lymphocyte structural chromosomal aberrations revealed that sunitinib was not genotoxic. This outcome was also observed in rats in an *in vivo* micronucleus test. *In vitro* human lymphocytes showed that at high sunitinib concentrations polyploidy (numerical chromosome aberrations) were induced. In these tests, the major active metabolite was evaluated indirectly.

Reproductive and developmental toxicity

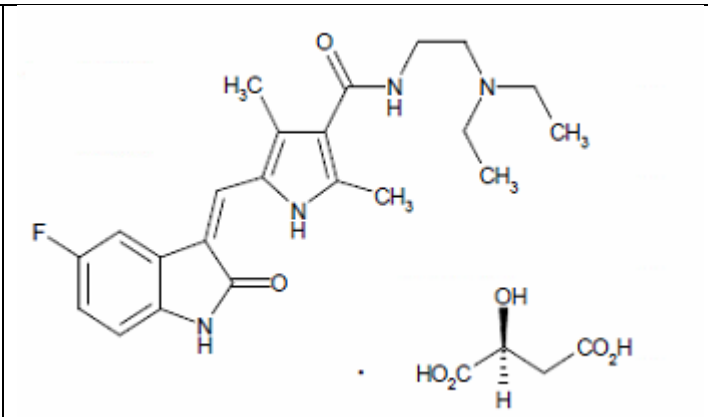
In sunitinib administration in rats of doses up to 10 mg/kg per day in males or 5 mg/kg per day in females, fertility was unchanged, which resulted in AUC exposures to sunitinib and its primary metabolite that were approximately 26 times and 5 times the human rate with the recommended daily dose of 50 mg, respectively. In treated females, embryolethality was observed at 5 mg/kg per day, but not at 1.5 mg/kg per day.

In toxicity studies, the adverse effects on the female reproductive system were observed in cynomolgus monkeys (which included uterine endometrial atrophy, impaired ovarian follicular development, and vaginal epithelial atrophy) and rats (uterine atrophy and corpora lutea degeneration). On the male reproductive system, adverse effects were also observed in toxicity studies in rats (which included testicular tubular atrophy). In both monkeys and rats, these adverse effects predominantly occurred at dosages that stimulated major toxicity.

When sunitinib was given to pregnant rabbits and rats it was indicated to be embryotoxic and teratogenic. In rats, increased fetal resorptions, reduced fetal weights and skeletal malformations were seen with a dosage of 5 mg/kg per day, while fetal variations were increased at 3 mg/kg per day. These dosages resulted in sunitinib plus its primary metabolite (AUC) exposures that were approximately 6 times and 2 times the human rate with the recommended daily dosage of 50 mg, respectively. There are limited studies in rabbits that have revealed the occurrence of cleft lip at doses of 1 and 5 mg/kg per day, which resulted in sunitinib plus its primary metabolite exposures that were approximately 0.3 times and 3 times the human rate, respectively. Increased fetal resorptions were seen at 5 mg/kg per day.

6 PHARMACEUTICAL PARTICULARS

CAS Registry Number	341031-54-7
Molecular Formula	$C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$
Chemical Name	(Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro- 3H indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate
Molecular Weight	532.57

Molecular Diagram	

6.1 List of excipients

12.5 mg strength:
Capsule: Mannitol, Croscarmellose sodium, Povidone and Magnesium stearate.
Capsule Shell: Gelatin, Titanium dioxide, Red iron oxide and Purified water.

25 mg strength:
Capsule: Mannitol, Croscarmellose sodium, Povidone and Magnesium stearate.
Capsule Shell: Gelatin, Titanium dioxide, Red iron oxide, Yellow iron oxide and Purified water.

50 mg strength:
Capsule: Mannitol, Croscarmellose sodium, Povidone and Magnesium stearate.
Capsule Shell: Gelatin, Titanium dioxide, Red iron oxide, Yellow iron oxide and Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months when stored at or below 30°C.

6.4 Special precautions for storage

Store at or below 30°C.
The product should be stored in the original packaging and protected from moisture.

6.5 Nature and contents of container

12.5 mg and 25 mg are blister packs containing 28 capsules.
50 mg are blister packs containing either 28 or 30 capsules.

Some strengths or pack sizes may not be marketed.

6.6 Special precautions for disposal

Disposal of any unused sunitinib or waste material should be completed as per local requirements.

7 MEDICINE SCHEDULE

Prescription Only Medicine.

8 SPONSOR

REX Medical Ltd
P O Box 18-119
Glen Innes
Auckland 1743
New Zealand

Ph (09) 574 6060
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9 DATE OF FIRST APPROVAL

1 June 2023

10 DATE OF REVISION OF THE TEXT

23 June 2025

Summary table of changes

Section changed	Summary of new information
All	Rewrite including editorial updates
4.4	Hyperammonaemic encephalopy addition of adverse event
4.8	Post Marketing adverse event hyperammonaemic encephalopy addition
8	Update sponsor details