1. NAME OF THE MEDICINAL PRODUCT

Alsuni 12.5 mg hard capsules
Alsuni 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

12.5 mg hard capsules
Each capsule contains sunitinib malate, equivalent to 12.5 mg of sunitinib.

50 mg hard capsules
Each capsule contains sunitinib malate, equivalent to 50 mg of sunitinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Alsuni 12.5 mg hard capsules
Hard capsules with dark brown opaque cap and dark brown opaque body, 13.8-14.8 mm, printed with white ink "LP" on the cap, "650" on the body, and containing yellow to orange granular powder.

Alsuni 50 mg hard capsules
Hard capsules with light brown opaque cap and light brown opaque body, 17.5-18.5 mm, printed with white ink "LP" on the cap, "653" on the body, and containing yellow to orange granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gastrointestinal stromal tumour (GIST)
Sunitinib is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib mesylate treatment due to resistance or intolerance (see section 5.1).

Metastatic renal cell carcinoma (MRCC)
Sunitinib is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) in adults (see section 5.1).

Pancreatic neuroendocrine tumours (pNET)
Sunitinib is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

4.2 Posology and method of administration

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

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

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

Dose adjustments

Safety and tolerability

For GIST and MRCC, dose modifications in 12.5 mg increments or decrements may be applied based on individual safety and tolerability. Daily dose should not exceed 75 mg or down to 25 mg..

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

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

CYP3A4 inhibitors/inducers

Co-administration of sunitinib with potent CYP3A4 inducers, such as rifampicin, should be avoided (see section 4.5). If this is not possible, the dose of sunitinib may need to be increased in 12.5 mg increments to a maximum of 87.5 mg (GIST and RCC) or 62.5 mg (pNET) daily, based on careful monitoring of tolerability.

Co-administration of sunitinib with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see section 4.5). If this is not possible, the dose of sunitinib may need to be reduced in 12.5 mg decrements to a minimum of 37.5 mg (GIST and RCC) or 25 mg (pNET) daily, based on careful monitoring of tolerability.

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

Special populations

Paediatric population

The safety and efficacy of sunitinib in pediatric patients have not been established.

Sunitinib should not be used in pediatric population until further data become available.

Elderly

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

Hepatic impairment

No dose adjustment is recommended when administering sunitinib to patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Sunitinib has not been studied in subjects with severe (Child-Pugh Class C) hepatic impairment (see section 5.2).

Renal impairment

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

Method of administration

Sunitinib is for oral administration. It may be taken with or without food.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

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

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

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

Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), cases suggestive of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of SJS, TEN, or EM (e.g., progressive skin rash often with blisters or mucosal lesions) are present, sunitinib treatment should be discontinued. If the diagnosis of SJS or TEN is confirmed, treatment must not be restarted. In some cases of suspected EM, patients tolerated the reintroduction of sunitinib therapy at a lower dose after resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines (see section 4.8).

Gastrointestinal Events
Nausea, diarrhea, stomatitis, dyspepsia, and vomiting were the most commonly reported treatment-related gastrointestinal (GI) events. Supportive care for GI adverse events requiring treatment may include medication with an anti-emetic or anti-diarrheal medication.

Haemorrhage and tumour bleeding
Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. In clinical trials, tumor hemorrhage occurred in approximately 2% of subjects with GIST. These events may occur suddenly, and in the case of pulmonary tumors, may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Cases of pulmonary hemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib for MRCC, GIST and metastatic non-small cell lung cancer (NSCLC). Sunitinib is not approved for use in patients with NSCLC.

Treatment emergent bleeding events occurred in 18% of subjects receiving sunitinib in the double-blind treatment phase of GIST Study compared to 17% of subjects receiving placebo. In subjects receiving sunitinib for treatment-naïve MRCC, 39% of patients had bleeding events compared with 11% of subjects receiving interferon-α (IFN-α). Seventeen (4.5%) subjects on sunitinib versus 5 (1.7%) of subjects on IFN-α experienced Grade 3 or greater bleeding events. Of subjects receiving sunitinib for cytokine-refractory MRCC, 26% experienced bleeding. Bleeding events, excluding epistaxis, occurred in 21.7% of subjects receiving sunitinib in the 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.

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

Gastrointestinal disorders
Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation were reported in patients with intra-abdominal malignancies treated with sunitinib.

Hypertension
Hypertension was a very common adverse reaction reported in clinical trials in subjects with solid tumors. Sunitinib dosing was reduced or temporarily delayed in approximately 2.7% of this patient population. None of these subjects were discontinued from treatment with sunitinib. 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 subjects receiving sunitinib for treatment-naïve MRCC compared to 3.6% of subjects receiving IFN-α. Severe hypertension occurred in 12% of treatment-naïve subjects on sunitinib and <1% of patients on IFN-α. Hypertension was reported in 26.5% of subjects receiving sunitinib in a Phase 3 pNET study, compared to 4.9% of subjects receiving placebo. Severe hypertension occurred in 10% of pNET subjects on sunitinib and 3% of subjects on placebo. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

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 sunitinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Haematological disorders
Decreased absolute neutrophil counts and decreased platelet counts were reported in association with sunitinib (see section 4.8). The above events were not cumulative, were typically reversible, and generally did not result in treatment discontinuation. In addition, some cases of fatal hemorrhage 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 sunitinib (see section 4.8).

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

In the treatment-naïve MRCC study, 27% of patients on sunitinib and 15% of subjects on IFN-α, had an LVEF value below the LLN. Two (<1%) subjects who received sunitinib were diagnosed with congestive heart failure (CHF).

Cardiac failure, cardiac failure congestive or left ventricular failure were reported in 0.8% of subjects with solid tumors* and 1% of subjects treated with placebo. In the Phase 3 pNET study, 1 (1.2%) subject who received sunitinib had treatment-related fatal cardiac failure.

Subjects who presented with cardiac events, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or

transient ischemic attack, or pulmonary embolism within 12 months prior to sunitinib administration, were excluded from sunitinib clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

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

* From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.

QT interval prolongation

At approximately twice therapeutic concentrations, sunitinib has been shown to prolong the QTcF interval (Fridericia's Correction) (see section 5.2). There were no patients with greater than Grade 2 Common Terminology Criteria for Adverse Events (CTCAE v3.0) QT/QTc interval prolongation. QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. Torsade de pointes has been observed in <0.1% of sunitinib-exposed patients. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of sunitinib reduced (see sections 4.2 and 4.5).

Venous thromboembolic events

Seven patients (3%) on sunitinib and none on placebo in the double-blind treatment phase of GIST study experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT), and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Thirteen patients (3%) receiving sunitinib for treatment-naïve MRCC and four (2%) patients on the two cytokine-refractory MRCC studies had venous thromboembolic events reported. Nine of these patients had pulmonary embolism, one was Grade 2 and eight were Grade 4. Eight patients had DVT, one with Grade 1, two with Grade 2, four with Grade 3, and 1 with Grade 4. Dose interruption occurred in one of these cases. In treatment-naïve MRCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolism, all Grade 4.

Arterial thromboembolic events

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

Respiratory Events

Patients who presented with pulmonary embolism within the previous 12 months were excluded from sunitinib clinical studies.

In patients who received sunitinib in Phase 3 registrational studies, treatment-related pulmonary events (i.e. dyspnea, pleural effusion, pulmonary embolism or pulmonary edema) were reported in approximately 5% of patients with GIST, in approximately 14% of patients with MRCC and in 7.2% of patients with pNET.

Approximately 8% of patients with solid tumors, including GIST and MRCC, who received sunitinib in clinical trials experienced treatment-related pulmonary events. Cases of pulmonary embolism were observed in approximately 1.3% of patients with GIST and in approximately 0.8% of patients with MRCC, who received sunitinib in Phase 3 studies. No treatment-related pulmonary embolism was reported for patients with pNET who received sunitinib in the Phase 3 study. Rare cases with fatal outcome have been observed in post-marketing setting.

Thyroid dysfunction
Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. During sunitinib treatment, routine monitoring of thyroid function should be performed every 3 months. In addition, patients should be observed closely for signs and symptoms of thyroid dysfunction during treatment, and patients who develop any signs and/or symptoms suggestive of thyroid dysfunction should have laboratory testing of thyroid function performed as clinically indicated. Patients who develop thyroid dysfunction should be treated as per standard medical practice.

Acquired hypothyroidism was noted in 6.2% of GIST subjects on sunitinib versus 1% on placebo. Hypothyroidism was reported as an adverse event in 16% of subjects on sunitinib in the treatment-naïve MRCC study and 3 subjects (<1%) in the IFN-α arm, and in 4% of subjects across the 2 cytokine-refractory MRCC studies. Additionally, thyroid stimulating hormone (TSH) elevations were reported in 2% of cytokine-refractory MRCC subjects. Overall, 7% of the cytokine-refractory MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. In the Phase 3 pNET study, hypothyroidism was reported in 6 (7.2%) subjects receiving sunitinib and in 1 (1.2%) subject on placebo.

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

Pancreatitis
Pancreatitis has been reported in clinical trials of sunitinib. Increases in serum lipase and amylase were observed in subjects with various solid tumors who received sunitinib. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumors. If symptoms of pancreatitis are present, patients should have sunitinib discontinued and be provided with appropriate supportive care.

Seizures
In clinical studies of sunitinib, 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 sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

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

Renal function
Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported (see section 4.8).

Risk factors associated with renal impairment/failure in patients receiving sunitinib included, in addition to underlying RCC, older age, diabetes mellitus, underlying renal impairment, cardiac failure, hypertension, sepsis, dehydration/hypovolaemia, and rhabdomyolysis.

The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. Discontinue sunitinib in patients with nephrotic syndrome.

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

Osteonecrosis of the jaw (ONJ)
Cases of ONJ have been reported in patients treated with sunitinib. The majority of cases were reported in patients who had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when sunitinib and intravenous bisphosphonates are used either simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor. Prior to treatment with sunitinib, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 4.8).

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

Necrotizing Fasciitis
Rare cases of necrotizing fasciitis, including of the perineum, sometimes fatal, have been reported. Sunitinib therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated.

Thrombotic microangiopathy (TMA)
Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of sunitinib as monotherapy and in combination with bevacizumab. Discontinue sunitinib in patients developing TMA. Reversal of the effects of TMA has been observed after treatment discontinuation.
Proteinuria
Cases of proteinuria and nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue sunitinib in patients with nephrotic syndrome.

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

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

*Drugs that may **increase** sunitinib plasma concentrations*
Concomitant administration of sunitinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 49% and 51% increase of the complex [sunitinib + primary active metabolite] Cmax and AUC0-∞ values, respectively, after a single dose of sunitinib in healthy volunteers.

Administration of sunitinib with strong inhibitors of the CYP3A4 family (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations.

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

*Drugs that may **decrease** sunitinib plasma concentrations*
Concomitant use of sunitinib with the CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction of the complex [sunitinib + primary active metabolite] Cmax and AUC0-∞ values, respectively, after a single dose of sunitinib in healthy volunteers.

Administration of sunitinib with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or *Hypericum perforatum* also known as St. John's Wort) may decrease sunitinib concentrations. Concomitant administration with inducers should therefore, be avoided, or selection of an alternate concomitant medication with no or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dosage of sunitinib may need to be increased in 12.5 mg increments (up to 87.5 mg/day for GIST and MRCC or 62.5 mg/day for pNET) based on careful monitoring of tolerability (see section 4.2).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no studies in pregnant women using sunitinib.

Studies in animals have shown reproductive toxicity including fetal malformations (see section 5.3). Sunitinib should not be used during pregnancy or in any woman not employing adequate contraception unless the potential benefit justifies the potential risk to the fetus. If sunitinib is used during pregnancy or if the patient becomes pregnant while receiving sunitinib, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with sunitinib.

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

mg/kg/day. No development toxicity was observed at 1 mg/kg/day (approximate exposure ⩾0.9 times the AUC in patients administered the RDD).

Sunitinib did not cause genetic damage when tested in in vitro assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an in vivo rat bone marrow micronucleus test.

Breast-feeding
Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite is excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should not breast feed while taking sunitinib.
Fertility
Based on nonclinical findings, male and female fertility may be compromised by treatment with sunitinib (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Table 1 presents the adverse drug reactions (ADRs) from single-agent studies in advanced RCC, GIST, pNET, and from post-marketing experience. A dataset that pooled the 10 singleagent studies in the marketed indications was used to calculate the treatment-emergent, all-causality frequencies. Frequencies are defined as: very common (⩾1/10), common (⩾ 1/100 to <1/10), uncommon (⩾ 1/1,000 to <1/100), rare (⩾1/10,000 to <1/1,000), very rare (<1/10,000), not known.

Table 1. ADR Frequency and Category Overview Table for Advanced RCC, GIST and pNET and from Postmarketing Experience (10 Study Pool)

System Organ Class	ADR Term	Sunitinib (N=7115) Frequency			Category
		All Grades (%)	Grade 3 (%)	Grade 4 (%)	
Infections and infestations	Infections*	2956 (41.5)	528 (7.4)	83 (1.2)	Very common
Blood and lymphatic system disorders	Neutropenia	1224 (17.2)	484 (6.8)	46 (0.6)	Very common
	Leukopenia	725 (10.2)	141 (2.0)	9 (0.1)	
	Thrombocytopenia	1563 (22.0)	460 (6.5)	115 (1.6)	
	Anaemia	1697 (23.9)	462 (6.5)	103 (1.4)	
	Lymphopenia	155 (2.2)	49 (0.7)	2 (0.028)	Common
	Thrombotic microangiopathy[a].**	4 (0.06)	3 (0.04)	1 (0.01)	Rare
Immune system disorders	Hypersensitivity	45 (0.6)	7 (0.098)	0 (0.0)	Uncommon
	Angioedema	7 (0.098)	3 (0.042)	0 (0.0)	Rare
Endocrine disorders	Hypothyroidism	890 (12.5)	52 (0.7)	6 (0.084)	Very common
	Hyperthyroidism	52 (0.7)	5 (0.07)	0 (0.0)	Uncommon
	Thyroiditis	6 (0.084)	0 (0.0)	0 (0.0)	Rare
Metabolism and nutrition disorders	Decreased appetite	2644 (37.2)	218 (3.1)	3 (0.0042)	Very common
	Dehydration**	501 (7.0)	192 (2.7)	15 (0.2)	Common
	Hypoglycaemia	106 (1.5)	28 (0.4)	16 (0.2)	
	Tumour lysis syndrome**	4 (0.056)	3 (0.042)	0 (0.0)	Rare
Psychiatric disorders	Insomnia	759 (10.7)	12 (0.2)	0 (0.0)	Very common
	Depression	379 (5.3)	18 (0.3)	3 (0.042)	Common
Nervous system disorders	Dysgeusia	2048 (28.8)	32 (0.4)	0 (0.0)	Very common
	Headache	1406 (19.8)	85 (1.2)	5 (0.070)	
	Dizziness	684 (9.6)	34 (0.5)	3 (0.042)	Common
	Paraesthesia	382 (5.4)	13 (0.2)	1 (0.014)	

	Cerebral haemorrhage**	23 (0.3)	2 (0.028)	4 (0.056)	Uncommon
	Cerebrovascular accident**	32 (0.4)	8 (0.1)	11 (0.2)	
	Transient ischaemic attack	21 (0.3)	8 (0.1)	3 (0.042)	
	Cerebral infarction	6 (0.084)	2 (0.028)	2 (0.028)	Rare
	Posterior reversible encephalopathy syndrome	5 (0.070)	3 (0.042)	1 (0.014)	
	Ageusia	3 (0.042)	-	-	
Eye disorders	Periorbital oedema	333 (4.7)	3 (0.042)	0 (0.0)	Common
	Eyelid oedema	276 (3.9)	9 (0.1)	0 (0.0)	
	Lacrimation increased	394 (5.5)	1 (0.01)	0 (0.0)	
Cardiac disorders	Myocardial ischaemia[b,**]	87 (1.2)	27 (0.4)	3 (0.0)	Common
	Ejection fraction decreased[c]	152 (2.1)	27 (0.4)	0 (0.0)	
	Myocardial infarction[d,**]	62 (0.9)	10 (0.1)	33 (0.5)	Uncommon
	Cardiac failure**	51 (0.7)	22 (0.3)	8 (0.1)	
	Cardiac failure congestive	32 (0.4)	22 (0.3)	4 (0.056)	
	Electrocardiogram QT Prolonged	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)	Rare
Vascular disorders	Hypertension	1991 (28.0)	505 (7.1)	15 (0.2)	Very common
	Deep vein thrombosis	91 (1.3)	50 (0.7)	6 (<0.1)	Common
	Tumour haemorrhage**	49 (0.7)	26 (0.4)	3 (0.042)	Uncommon
	Aneurysms and artery dissections[e,**]	9 (0.1)	4 (0.056)	2 (0.028)	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1443 (20.3)	322 (4.5)	75 (1.1)	Very common
	Epistaxis	1080 (15.2)	43 (0.6)	4 (0.056)	
	Oropharyngeal pain[f]	455 (6.4)	6 (0.1)	0 (0.0)	Common
	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	Diarrhoea	3729 (52.4)	430 (6.0)	13 (0.2)	Very common
	Nausea	3035 (42.7)	246 (3.5)	4 (0.056)	
	Vomiting	2416 (34.0)	287 (4.0)	17 (0.2)	
	Abdominal pain[h]	2162 (30.4)	406 (5.7)	38 (0.5)	
	Stomatitis[i]	2011 (28.3)	189 (2.7)	2 (0.028)	
	Constipation	1653 (23.2)	67 (0.9)	3 (0.042)	
	Dyspepsia	1564 (22.0)	36 (0.5)	1 (0.014)	
	Gastrointestinal haemorrhage**	121 (1.7)	56 (0.8)	20 (0.3)	Common
	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)	
	Pancreatitis	17 (0.2)	6 (0.084)	1 (0.014)	Uncommon
	Gastrointestinal perforation**	15 (0.2)	7 (0.098)	4 (0.056)	
Hepatobiliary disorders	Cholecystitis[j]	33 (0.5)	16 (0.2)	4 (0.056)	Uncommon
	Hepatic failure**	23 (0.3)	4 (0.056)	8 (0.1)	
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome	1984 (27.9)	551 (7.7)	3 (0.042)	Very common
	Skin discolouration[k]	1761 (24.8)	13 (0.2)	0 (0.0)	
	Rash[l]	1595 (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)	
	Alopecia	564 (7.9)	1 (0.014)	0 (0.0)	Common
	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)	
	Dermatitis exfoliative	21 (0.3)	2 (0.028)	0 (0.0)	Uncommon
	Erythema multiforme**	5 (0.070)	0 (0.0)	0 (0.0)	Rare
	Stevens-Johnson syndrome**	2 (0.028)	1 (0.014)	1 (0.014)	
	Pyoderma gangrenosum	1 (0.014)	0 (0.0)	0 (0.0)	
Musculoskeletal, connective tissue and bone disorders	Pain in extremity	1237 (17.4)	125 (1.8)	13 (0.2)	Very common
	Arthralgia	1023 (14.4)	97 (1.4)	5 (0.070)	
	Myalgia	650 (9.1)	34 (0.5)	0 (0.0)	Common
	Osteonecrosis of Jaw	31 (0.4)	12 (0.2)	0 (0.0)	Uncommon
	Fistula formation**	13 (0.2)	3 (0.042)	2 (0.028)	
	Rhabdomyolysis**	7 (0.098)	2 (0.028)	1 (0.014)	Rare
	Myopathy	7 (0.098)	0 (0.0)	0 (0.0)	
Renal and urinary disorders	Renal failure**	153 (2.2)	66 (0.9)	18 (0.3)	Common
	Chromaturia	197 (2.8)	0 (0.0)	0 (0.0)	
	Proteinuria	105 (1.5)	39 (0.5)	4 (0.056)	
	Renal impairment	29 (0.4)	9 (0.1)	1 (0.0)	Uncommon
	Haemorrhage urinary tract	8 (0.1)	2 (0.028)	0 (0.0)	
	Nephrotic syndrome	7 (0.098)	1 (0.014)	4 (0.056)	Rare
General disorders and administration site conditions	Fatigue[m]	4746 (66.7)	1211 (17.0)	87 (1.2)	Very common
	Mucosal inflammation	1928 (27.1)	180 (2.5)	10 (0.1)	
	Oedema[n]	1723 (24.2)	87 (1.2)	2 (0.028)	
	Pyrexia	1252 (17.6)	72 (1.0)	8 (0.1)	
	Chills	430 (6.0)	11 (0.2)	1 (0.014)	Common
	Influenza like illness	155 (2.2)	4 (0.056)	0 (0.0)	
Investigations	Lipase increased	105 (1.5)	46 (0.6)	26 (0.4)	Common
	Amylase increased[o]	76 (1.1)	31 (0.4)	4 (0.056)	
	Blood uric acid increased	98 (1.4)	4 (0.056)	22 (0.3)	
	White blood cell count decreased	274 (3.9)	95 (1.3)	7 (0.098)	
	Platelet count decreased	307 (4.3)	94 (1.3)	15 (0.2)	
	Haemoglobin decreased	269 (3.8)	62 (0.9)	12 (0.2)	
	Weight decreased	701 (9.9)	29 (0.4)	1 (0.014)	
	Blood creatine phosphokinase increased	60 (0.8)	12 (0.2)	5 (0.07)	Uncommon
	Blood thyroid stimulating hormone increased	45 (0.6)	7 (0.098)	0 (0.0)	

* Infections and infestations are described in the subsection Description of Selected Adverse Reactions.

** Event may be fatal.

Abbreviations: ADR=adverse drug reaction, GIST=gastrointestinal stromal tumor; n=number of subjects; pNET=pancreatic neuroendocrine tumors; RCC=renal cell carcinoma.

[a] Thrombotic microangiopathy: The following terms have been combined: Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura, and Hemolytic uremic syndrome.

[b] Myocardial ischaemia: The following terms have been combined: Acute coronary syndrome, Angina pectoris, Angina unstable, Coronary artery occlusion, and Myocardial ischaemia.

[c] Ejection fraction decreased: The following terms have been combined: Ejection fraction decreased and Ejection fraction abnormal.

[d] Myocardial infarction: The following terms have been combined: Acute myocardial infarction, Myocardial infarction, and 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: Haemoptysis and Pulmonary haemorrhage.

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

[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, and Pigmentation disorder.

[l] Rash: The following terms have been combined: Dermatitis psoriasiform, Exfoliative rash, Rash, Rash erythematous, Rash follicular, Rash generalised, Rash macular, Rash maculopapular, Rash papular, and Rash pruritic.

[m] Fatigue: The following terms have been combined: Fatigue and Asthenia.

[n] Oedema: The following terms have been combined: Face oedema, Oedema, and Oedema peripheral.

[o] Amylase increased: The following terms have been combined: Amylase and Amylase increased.

ADR frequencies presented in this section represent the frequencies of the events that occurred in sunitinib-treated subjects regardless of causality assessment.

The most important serious adverse reactions associated with sunitinib treatment of patients with solid tumors* were pulmonary embolism, thrombocytopenia, tumor hemorrhage, febrile neutropenia, and hypertension (see section 4.4).

The most common ADRs of any grade included: fatigue; gastrointestinal disorders, such as diarrhea, nausea, stomatitis, dyspepsia and vomiting; skin discoloration; rash; palmar-plantar erythrodysesthesia; dry skin; hair color changes; mucosal inflammation; asthenia; dysgeusia; anorexia and hypertension. Fatigue, hypertension, and neutropenia were the most common ADRs of Grade 3 maximum severity, and increased lipase was the most frequently occurring ADR of Grade 4 maximum severity in subjects with solid tumors.

Epistaxis, was the most frequent hemorrhagic ADR, having been reported for approximately half of the subjects with solid tumors* who experienced hemorrhagic events (see section 4.4).

* From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.

Description of selected adverse reactions

Infections and infestations
Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported. The infections observed with sunitinib treatment are infections typically seen in cancer patients, e.g., 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, viral, or fungal. Rare cases of necrotizing fasciitis, including of the perineum, sometimes fatal, have been reported.

Blood and lymphatic system disorders
Rare cases of thrombotic microangiopathy, in some cases with fatal outcome, have been reported. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

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

Venous Thromboembolic Events (VTE)
In the double-blind treatment phase of GIST study, 7 subjects (3%) on sunitinib and none on placebo experienced VTE; 5 of the 7 were Grade 3 DVT, and 2 were Grade 1 or 2. Four of these 7 GIST subjects discontinued treatment following first observation of DVT.

Thirteen subjects (3%) receiving sunitinib for treatment-naïve MRCC and 4 (2%) subjects in the 2 cytokine-refractory MRCC studies had VTE reported. Nine of these subjects had pulmonary embolism: 1 was Grade 2 and 8 were Grade 4. Eight subjects had DVT, 1 with Grade 1, 2 with Grade 2, 4 with Grade 3, and 1 with Grade 4. One subject with pulmonary embolism in the cytokine-refractory MRCC study experienced dose interruption. In treatment-naïve MRCC subjects receiving IFN-α, 6 (2%) VTE occurred; 1(<1%) patient experienced a Grade 3 DVT and 5 (1%) subjects had pulmonary embolism, all Grade 4.

Pulmonary embolism was reported in approximately 2.2% of patients with solid tumors* who received sunitinib. None of these events resulted in a subject discontinuing treatment with sunitinib; however a

dose reduction or temporary delay in treatment occurred in a few cases. There were no further occurrences of pulmonary embolism in these subjects after treatment was resumed.

* From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.

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

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

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

4.9 Overdose

There is no experience of acute overdosage with sunitinib. There is no specific antidote for overdose with sunitinib and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed drug may be achieved by emesis or gastric lavage. Cases of overdose have been reported; some cases were associated with adverse reactions consistent with the known safety profile of sunitinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Sunitinib inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs 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 inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets in vivo and demonstrated inhibition of tumor growth or tumor regression, and/or inhibited in metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) in vitro and to inhibit PDGFRβ- and VEGFR2-dependent tumor angiogenesis in vivo.

Clinical efficacy and safety

The clinical safety and efficacy of sunitinib has been studied in subjects with malignant GIST who were resistant to imatinib (i.e. those who experienced disease progression during or following treatment with imatinib); or intolerant to imatinib (i.e. those who experienced significant toxicity during treatment with imatinib that precluded further treatment); in subjects with MRCC; and in subjects with unresectable pNET.

Efficacy is based on time to tumor progression (TTP) and an increase in survival in GIST.

Efficacy is based on progression free survival (PFS) and objective response rates (ORR) for treatment-naïve and cytokine-refractory MRCC respectively, and on PFS for pNET.

Gastrointestinal Stromal Tumors
An initial open-label, dose-escalation study was conducted in subjects with GIST after failure of imatinib (median maximum daily dose 800 mg) due to resistance or intolerance. Ninety-seven subjects were enrolled at various doses and schedules; 55 subjects received 50 mg at the recommended treatment schedule of 4 weeks on/2 weeks off (Schedule 4/2). In this study the median TTP and PFS was 34.0 weeks (95% confidence interval [CI]: 22.0. 46.0).

A Phase 3, randomized, double-blind, placebo-controlled study of sunitinib was conducted in subjects with GIST who were intolerant to, or had experienced disease progression during or following treatment with imatinib (Median maximum daily dose 800 mg). In this study, 312 subjects were randomized (2:1) to receive either 50 mg sunitinib or placebo, orally once daily on Schedule 4/2 until disease progression or withdrawal from the study for another reason (207 subjects received sunitinib and 105 subjects received placebo). The primary efficacy endpoint of the study was TTP (as assessed by the Independent Review), defined as the time from randomization to first documentation of objective tumor progression. Secondary objectives included PFS, ORR, and overall survival (OS).

At the time of the pre-specified interim analysis, the median TTP on sunitinib was 28.9 weeks (95% CI: 21.3, 34.1) as assessed by the Investigator and 27.3 weeks (95% CI: 16.0, 32.1) as assessed by the Independent Review and was statistically significantly longer than the TTP of 5.1 weeks (95% CI: 4.4, 10.1) as assessed by the Investigator and 6.4 weeks (95% CI: 4.4, 10.0) as assessed by the Independent Review. The difference in OS was statistically in favor of sunitinib (hazard ratio [HR]: 0.491 [95% CI: 0.290, 0.831]); the risk of death was 2 times higher in subjects in the placebo arm compared to the sunitinib arm. Additional efficacy information is presented below in Table 2.

After the positive interim analysis of efficacy and safety, at the recommendation of the independent Data and Safety Monitoring Board (DSMB), the study was unblinded and subjects on the placebo arm were offered open-label sunitinib treatment.

A total of 255 subjects received sunitinib in the open-label treatment phase of the study, including 99 subjects who were initially treated with placebo. In this final analysis, the placebo arm included those subjects randomized to placebo who subsequently received open-label sunitinib treatment.

The final analyses of primary and secondary endpoints in the open-label phase of the study reaffirmed the results obtained at the time of the interim analysis, as shown in Table 2:

Table 2. GIST summary of efficacy endpoints (ITT population)

	Double-blind treatment[a]				
	Median (95% CI)		**Hazard ratio**		**Placebo cross-over group treatment[b]**
Endpoint	**Sunitinib**	**Placebo**	**(95% CI)**	**p-value**	
Primary TTP (weeks)					
Interim	27.3 (16.0, 32,1)	6.4 (4.4, 10.0)	0.329 (0.233, 0.466)	<0.001	-
Final	26.6 (16.0, 32.1)	6.4 (4.4, 10.0)	0.339 (0.244, 0.472)	<0.001	10.4(4.3, 22.0)

Secondary					
Interim					
PFS (weeks)[c]	24.1 (11.1, 28.3)	6.0 (4.4, 9.9)	0.333 (0.238, 0.467)	<0.001	-
ORR (%)[d]	6.8 (3.7, 11.1)	0 (-)	NA	0.006	-
OS (weeks)[e]	-	-	0.491 (0.290, 0.831)	0.007	
Final					
PFS (weeks)	22.9 (10.9, 28.0)	6.0 (4.4, 9.7)	0.347 (0.253, 0.475)	<0.001	-
ORR (%)[d]	6.6 (3.8, 10.5)	0 (-)	NA	0.004	10.1 (5.0, 17.8)
OS (weeks)	72.7 (61.3, 83.0)	64.9 (45.7, 96.0)	0.876 (0.679, 1.129)	0.306	-

Abbreviations: CI=confidence interval; ITT=intent to treat; NA=Not Applicable; ORR=objective response; OS=overall survival; PFS=progression-free-survival; TTP=time-to-tumor progression

[a] Results of double-blind treatment are from the ITT population and using central radiologist measurement, as appropriate.

[b] Efficacy results for the 99 subjects who crossed over from placebo to after unblinding. Baseline was reset at cross-over and efficacy analyses were based on investigators assessment.

[c] The interim PFS numbers have been updated based on a recalculation of the original data.

[d] Results for ORR are given as percent of subjects with confirmed response with the 95% CI.

[e] Median not achieved because the data were not yet mature.

Of those subjects randomized to the sunitinib arm, 62.7% survived longer than 1 year, 35.5% survived longer than 2-years, and 22.3% survived longer than 3 years.

Overall, the study demonstrated a statistically significant and clinically meaningful improvement in TTP, the primary endpoint, for sunitinib plus best supportive care compared with placebo plus best supportive care.

Pancreatic Neuroendocrine Tumors

A Phase 2, open-label, multi-center study evaluated the efficacy and safety of single-agent sunitinib 50 mg daily on Schedule 4/2 in subjects with advanced unresectable pNET. In a pancreatic islet cell tumor cohort of 66 subjects, a 17% ORR was observed.

A pivotal Phase 3, multi-center, international, randomized, double-blind placebo-controlled study of single-agent sunitinib was conducted in subjects with unresectable pNET.

Subjects were required to have documented progression, based on Response Evaluation Criteria in Solid Tumors (RECIST), within the prior 12 months and were randomized (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled off-treatment period (n=86) or placebo (n=85).

The primary objective was to compare PFS in subjects receiving sunitinib versus subjects receiving placebo. Other endpoints included OS, ORR, patient-reported outcomes (PRO) and safety. Demographics were comparable between the sunitinib and placebo groups. Additionally, 49% of sunitinib subjects had non-functioning tumors versus 52% of placebo subjects and 92% of subjects in both arms had liver metastases. Use of somatostatin analogs was allowed in the study. A total of 66% of sunitinib subjects received prior systemic therapy compared with 72% of placebo subjects. In addition, 24% of sunitinib subjects had received somatostatin analogs compared with 22% of placebo subjects.

A clinically significant advantage in investigator-assessed PFS for sunitinib over placebo was observed. The median PFS was 11.4 months for the sunitinib arm compared to 5.5 months for the placebo arm [HR: 0.418 (95% CI: 0.263, 0.662), p-value=0.0001]. Similar results were observed when derived tumor response assessments based upon application of RECIST to investigator tumor measurements were used to determine disease progression, as shown in Table 3. A hazard ratio favoring sunitinib was observed in all subgroups of baseline characteristics evaluated, including an analysis by number of prior systemic therapies. A total of 29 subjects in the sunitinib arm and 24 in the placebo arm had received no prior systemic treatment; among these subjects, the hazard ratio for PFS was 0.365 (95% CI: 0.156, 0.857), p=0.0156. Similarly, among 57 subjects in the sunitinib arm (including 28 with 1 prior systemic therapy and 29 with 2 or more prior systemic therapies), and 61 subjects in the placebo arm (including 25 with 1 prior systemic therapy and 36 with 2 or more prior systemic therapies), the hazard ratio for PFS was 0.456 (95% CI: 0.264, 0.787), p=0.0036.

A sensitivity analysis of PFS was conducted in which progression was based upon investigator-reported tumor measurements and in which all subjects censored for reasons other than study termination were treated as having PFS events. This analysis provided a conservative estimate of the treatment effect of sunitinib and supported the primary analysis, demonstrating a hazard ratio of 0.507 (95% CI: 0.350, 0.733), p=0.000193. The pivotal study in pNET was terminated prematurely at the recommendation of an independent Drug Monitoring Committee, and the primary endpoint was based upon investigator assessment, both of which may have affected the estimates of the treatment effect.

In order to rule out bias in the investigator-based assessment of PFS, a blinded independent central review (BICR) of scans was performed; this review supported the investigator assessment, as shown in Table 3. The Kaplan-Meier curve for PFS is in Figure 1.

Table 3: pNET Efficacy Results from the Phase 3 Study

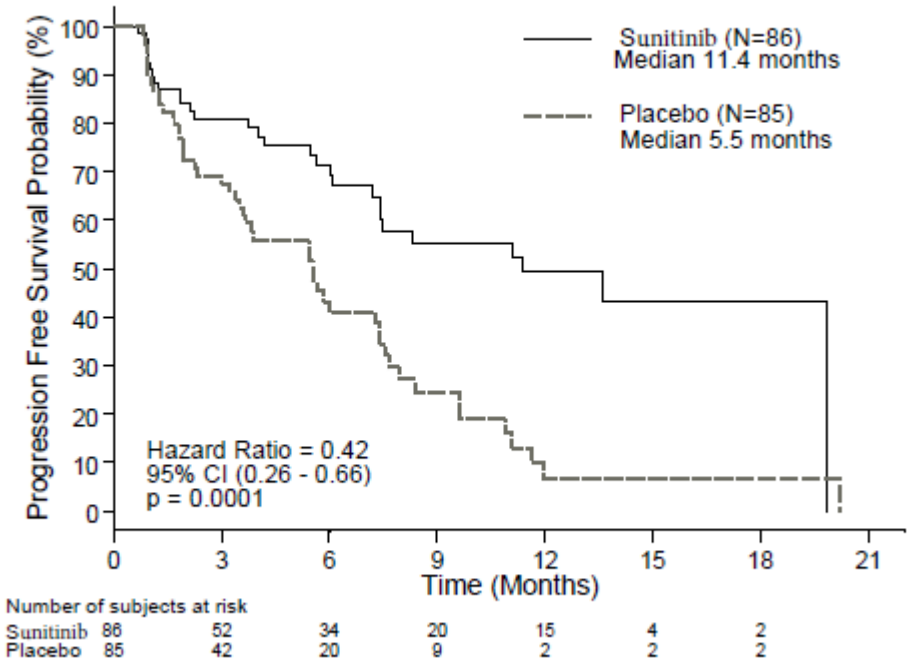
Efficacy Parameter	Sunitinib	Placebo (n=85)	HR (95% CI)	p-value
PFS [median, months (95% CI)] by Investigator Assessment	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	0.418 (0.263, 0.662)	0.0001[a]
PFS [median, months (95% CI)] by derived response assessment based upon application of RECIST to investigator tumor assessments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

Abbreviations: CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; pNET=pancreatic neuroendocrine tumors; RECIST=Response Evaluation Criteria in Solid Tumors.

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

[b] Fisher's Exact test.

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



Abbreviations: CI=confidence interval; N=number of subjects; PFS=progression-free survival; pNET=pancreatic neuroendocrine tumors.

OS data were not mature at the time of the analysis. There were 9 deaths in the sunitinib arm and 21 deaths in the placebo arm. A statistically significant difference in ORR favoring sunitinib over placebo was observed.

Upon disease progression, subjects were unblinded and placebo subjects could have been offered access to open-label sunitinib in a separate extension study. As a result of the early study closure, remaining subjects were unblinded and offered access to open-label sunitinib in an extension study. A total of 59 subjects from the placebo arm received sunitinib in an extension study.

Results from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) showed that the overall global health-related quality of life and the five functioning domains (physical, role, cognitive, emotional and social) were maintained for subjects on sunitinib treatment as compared to placebo with limited adverse symptomatic effects.

Renal Cell Carcinoma
Treatment-naïve MRCC
A Phase 3 randomized, multicenter, international, study evaluating the efficacy and safety of sunitinib compared with IFN-α in subjects with treatment-naïve metastatic RCC was conducted. The primary objective was to compare PFS in subjects receiving sunitinib versus subjects receiving IFN-α. Secondary objectives included TTP, ORR, OS, safety and PROs. Seven hundred fifty (750) subjects were randomized (1:1) to receive either 50 mg sunitinib once daily on Schedule 4/2 or to receive IFN-α administered subcutaneously at 9 MIU three times a week. Subjects were treated until disease progression or withdrawal from the study for another reason.

The ITT population included 750 subjects, 375 randomized to sunitinib and 375 randomized to IFN-α. Baseline age, gender, race and Eastern Cooperative Oncology Group (ECOG) performance status were comparable and balanced between the sunitinib and IFN-α groups. Demographics and patient characteristics are shown in Table4. The most common site of metastases present at screening was the lung (78% versus 80%, respectively), followed by the lymph nodes (58% versus 53%, respectively),

and bone (30% each arm). The majority of the subjects had multiple (2 or more) metastatic sites at baseline (80% versus 77%, respectively).

Table 4: Baseline Demographics in Treatment-naïve MRCC Study

	Treatment-naïve MRCC	
	Sunitinib (n=375)	**IFN-α (n=375)**
Gender [n (%)]		
Male	267 (71)	269 (72)
Female	108 (29)	106 (28)
Self-identified Race [n (%)]		
White	354 (94)	340 (91)
Asian	7 (2)	12 (3)
Black	4 (1)	9 (2)
Not reported	10 (3)	14 (4)
Age Group [n (%)]		
<65 years	223 (59)	252 (67)
≥65 years	152 (41)	123 (33)
Performance Status [n (%)]		
0	231 (62)	229 (61)
1	144 (38)	142 (38)
2	0 (0)	4 (1)[a]
Prior Treatment [n (%)]		
Nephrectomy	340 (91)	335 (89)
Radiotherapy	53 (14)	54 (14)

Abbreviations: ECOG= Eastern Cooperative Oncology Group; IFN-α =interferon-α; MRCC=metastatic renal cell carcinoma; n=number of subjects.

[a] Subjects had ECOG performance status of 1 at screening which changed to 2 at baseline

The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for sunitinib treatment and 4.1 months (range: 0.1 – 45.6) for IFN-α treatment. Dose interruptions occurred in 202 (54%) subjects on sunitinib and 141 (39%) subjects on IFN-α. Dose reductions occurred in 194 (52%) subjects on sunitinib and 98 (27%) subjects on IFN-α. Discontinuation rates due to adverse reactions were 20% for sunitinib and 23% for IFN-α. Subjects were treated until disease progression or withdrawal from the study. The primary efficacy endpoint was PFS. A planned interim analysis showed a statistically significant advantage for sunitinib over IFN-α in the primary endpoint of PFS, with PFS for sunitinib more than double that of IFN-α (47.3 weeks and 22.0 weeks, respectively). The secondary endpoint of ORR was more than four times higher for sunitinib than IFN-α (27.5% and 5.3%, respectively). Data were not mature enough to determine the overall survival benefit; at the time of the interim analysis, 374 of 750 (50%) subjects enrolled continued on study, 248 of 375 (66%) on the sunitinib arm and 126 of 375 (34%) on the IFN-α arm.

At the time of the final analysis there was a statistically significant advantage for sunitinib over IFN-α in the endpoint of PFS (see Table 5 and Figure 2). In the pre-specified stratification factors of lactate dehydrogenase (LDH) (>1.5 ULN versus. ⩽1.5 ULN), ECOG performance status (0 versus. 1), and prior nephrectomy (yes versus. no), the HR favored sunitinib over IFN- α. Core radiology assessment was discontinued after the primary endpoint had been met. The ORR as determined by the investigators' assessment was 46% (95% CI: 41, 51) for the sunitinib arm and 12% (95% CI: 9, 16) for the IFN-α arm ($p<0.001$) (see Table 5).

The results were similar in the supportive analyses and they were robust when controlling for demographic (age, gender, race and performance status) and known risk factors. For 262 of 750 subjects (35%) with no known risk factors, median PFS was 64.1 weeks in the sunitinib arm and 34.1 weeks in the IFN-α arm (HR: 0.447; 95% CI: 0.313, 0.640); for the 424 subjects (56%) with 1 or 2 risk factors, median PFS was 46.6 weeks in the sunitinib arm and 16.1 weeks in the IFN-α arm (HR:

0.547; 95% CI: 0.423, 0.707); and for the 47 subjects (6%) with ⩾3 risk factors, median PFS was 12.1 weeks in the sunitinib arm and 5.7 weeks in the IFN-α arm (HR: 0.679; 95% CI: 0.330, 1.398).

As shown in Figure 3, sunitinib treatment was associated with longer survival compared to IFN-α. The median OS was 114.6 weeks for the sunitinib arm (95% CI: 100.1, 142.9) and 94.9 weeks for the IFN-α arm (95% CI: 77.7, 117.0) [HR: 0.821; (95% CI: 0.673, 1.001); p=0.0510 by log-rank test, p=0.013 by Wilcoxon test]. In the stratified analysis (LDH > versus. ⩽1.5 x ULN, ECOG performance status 0 versus. ⩾1, and absence or presence of prior nephrectomy), the HR was 0.818 (95% CI: 0.669, 0.999; p=0.049 by log-rank test). The median OS for the IFN-α arm included 25 subjects who discontinued IFN-α treatment because of disease progression and crossed over to treatment with sunitinib. Following discontinuation from the study, 213 subjects on the IFN-α arm received post-study cancer treatment, including 32% who received sunitinib; 182 subjects on the sunitinib arm received post-study cancer treatment, including 11% who received sunitinib. In post-hoc analyses censoring subjects who crossed over from IFN-α treatment to sunitinib treatment, median OS at the time of crossover was 114.6 versus. 86.7 weeks (unstratified hazard ratio: 0.808; p=0.0361 by log-rank test; p=0.0081 by Wilcoxon test). When excluding subjects who received post-study anticancer therapy, median OS was 121.9 versus. 61.3 weeks on sunitinib versus. IFN-α (HR: 0.647; 95% CI: 0.482, 0.867; p=0.0033 by log-rank test; p=0.0013 by Wilcoxon test).

Table 5: MRCC Efficacy Results

Efficacy Parameter	**Treatment-naïve MRCC**			
	Sunitinib (n=375)	**IFN-α (n=375)**	**p-value (log-rank test)**	**HR (95% CI)**
PFS[a][median, weeks (95% CI)]	48.3 (46.4, 58.3)	22.1 (17.1, 24.0)	<0.000001	0.516 (0.419, 0.635)
TTP[a] [median, weeks (95% CI)]	49.1 (46.6, 59.1)	22.4 (21.9, 31.3)	<0.0001	0.516 (0.419, 0.635)
ORR[a] [%, (95% CI)]	38.7 (33.7, 43.8)	7.7 (5.2, 10.9)	<0.0001	NA
Efficacy Parameter	**Cytokine-refractory MRCC**			
	Study 1 (n=106)		**Study 2 (n=63)**	
Objective Response Rate [%, (95% CI)]	34.0[a] (25.0, 43.8)		36.5[b] (24.7, 49.6)	
Duration of Response [median, weeks (95% CI)]	* (42.0, **)		54[b] (34.3, 70.1)	

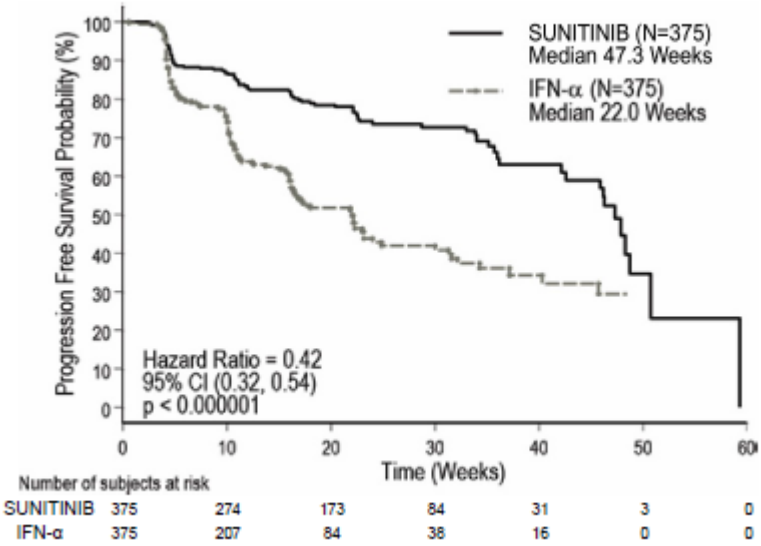
Abbreviations: CI=Confidence interval; DR=duration of response; HR=hazard ratio; IFN-α=interferon-α; MRCC=metastatic renal cell carcinoma; n=number of subjects; NA=not applicable; ORR=objective response rate; PFS=progression-free survival; RCC=renal cell carcinoma; TTP=time to tumor progression. [a] Assessed by blinded core radiology laboratory: 90 subjects' scans had not been read at time of analysis.

[b] Assessed by investigators.

* Median DR has not yet been reached.

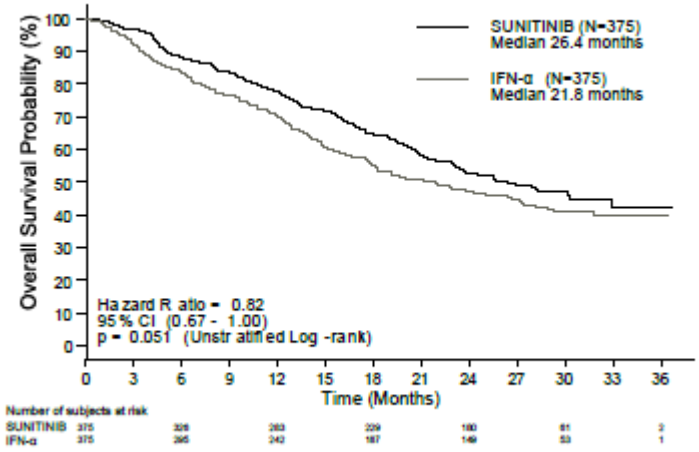
** Data not mature enough to determine upper confidence limit.

Figure 2: Kaplan-Meier Curve of PFS in Treatment-naïve MRCC Study (Intent-to-Treat Population)



Abbreviations: CI=confidence interval; IFN-α-interferon-α; MRCC=metastatic renal cell carcinoma; PFS=progression-free survival.

Figure 3: Kaplan-Meier Curve of OS in Treatment-naïve RCC Study (Intent-to-Treat Population)



Abbreviations: CI=confidence interval; IFN-α-interferon-α; OS=overall survival; RCC=renal cell carcinoma

PRO were measured using the Functional Assessment of Cancer Therapy-Advanced Kidney Cancer Symptom Index (FKSI) and the Functional Assessment of Cancer Therapy-General (FACT-G). PRO endpoints include the FKSI score, its Disease Related Symptoms subscale (FKSI-DRS) score, the FACT-G total score and its four subscale scores (Physical Well-Being [PWB], Social/Family Well-Being [SWB], Emotional Well-Being [EWB] and Functional Well-Being [FWB]. The FKSI-DRS was pre-specified as the primary PRO endpoint and used to assess patient-reported kidney cancer related symptoms (lack of energy/fatigue, pain/bone pain, weight loss, shortness of breath, cough, fever, and hematuria) in 719 subjects. Subjects treated with sunitinib reported statistically significant better FKSI-DRS index scores ($p \leq 0.0071$), FKSI scores ($p \leq 0.0133$), FACT-G total scores ($p \leq 0.0244$), PWB ($p \leq 0.0208$), and FWB ($p \leq 0.0044$) than subjects treated with IFN-α at all post-baseline assessment time points up to 20 cycles of treatment. For PWB, SWB, and EWB, the statistical significance level increased above the 0.05 level after cycle 13, cycle-15-day 1, and cycle 10 respectively. Compared to the pre-established minimum clinically important differences for these

endpoints, the between treatment differences for kidney cancer related symptoms (FKSI at all post-baseline timepoints and FKSI-DRS after cycle 3, day 1) and overall quality of life (FACT-G) at all post-baseline time points were considered clinically meaningful.

Cytokine-refractory metastatic renal cell carcinoma
A Phase 2 study of sunitinib was conducted in patients who were refractory to prior cytokine therapy with interleukin-2 or IFN-α. Sixty-three patients received a starting dose of 50 mg sunitinib orally, once daily for 4 consecutive weeks followed by a 2-week rest period, to comprise a complete cycle of 6 weeks (Schedule 4/2). The primary efficacy endpoint was ORR, based on Response Evaluation Criteria in Solid Tumours (RECIST). Secondary endpoints included TTP, PFS, duration of response (DR), and OS.

In this study, the objective response rate was 36.5% (95% CI: 24.7%, 49.6%) and the median TTP/PFS was 37.7 weeks (95% CI: 24.0, 46.4).

A confirmatory, open-label, single-arm, multi-centre study evaluating the efficacy and safety of sunitinib was conducted in patients with MRCC who were refractory to prior cytokine therapy. 106 patients received at least one 50 mg dose of sunitinib on Schedule 4/2.

The primary efficacy endpoint of this study was ORR. Secondary endpoints included TTP, PFS, duration of response (DR) and OS.
In this study the ORR was 34.0% (95% CI: 25.0%-3.8%) The median TTP, PFS, DR and OS had not yet been reached.

5.2 Pharmacokinetic properties

The PK of sunitinib were evaluated in 135 healthy volunteers and 266 patients with solid tumours. The PK were similar in all solid tumours populations tested and in healthy volunteers.

Absorption
After oral administration of sunitinib, C_{max} are generally observed from 6 to 12 hours time to maximum concentration (t_{max}) post administration.

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 in the range of 100-4,000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was large (2,230 L), indicating distribution into the tissues. In the dosing range of 25–100 mg, the area under the plasma concentration-time curve (AUC) and Cmax increased proportionately with dose.

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 drug-drug interactions with drugs that may be metabolized by these enzymes.

In vitro studies also indicate that sunitinib neither induces nor inhibits major CYP enzymes, including CYP3A4 (see section 4.5).

Sunitinib is metabolized primarily by CYP3A4, the cytochrome P450 enzyme, to produce its primary active metabolite, which is then further metabolized by CYP3A4. The primary active metabolite comprises 23% to 37% of the total exposure.

Elimination

Excretion is primarily via faeces (61%), with renal elimination of unchanged active substance and metabolites accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major compounds identified in plasma, urine, and faeces, representing 91.5%, 86.4%, and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and faeces, but generally were not found in plasma. Total oral clearance (CL/F) was 34-62 L/h. Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40-60 hours and 80-110 hours, respectively.

Special populations

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

Renal impairment
Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in subjects with calculated creatinine clearances in the range of 42-347 mL/min. Systemic exposures after a single dose of sunitinib were similar in subjects with severe renal impairment (CLcr<30 mL/min) compared to subjects with normal renal function (CLcr>80 mL/min). Although sunitinib and its primary metabolite were not eliminated through hemodialysis in subjects with ESRD, the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function

Plasma Pharmacokinetics
Following administration of a single oral dose 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 Cmax increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its primary active metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite are 62.9 - 101 ng/mL which are target concentrations predicted from preclinical data to inhibit receptor phosphorylation in vitro and result in tumor stasis/growth reduction in vivo. No significant changes in the pharmacokinetics of sunitinib or the primary, active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

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

Population Pharmacokinetics
Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, gender, race or ECOG score on the pharmacokinetics of sunitinib or the primary active metabolite.

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

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

Cardiac Electrophysiology
QT interval prolongation was investigated in a Phase 1 trial with 24 evaluable subjects, aged 20-87 years, with advanced malignancies. At therapeutic plasma concentrations, the maximum QTcF mean change from baseline was 9.6 msec (90% CI upper limit of 15.1 msec). At approximately twice the

therapeutic concentrations, the maximum QTcF mean change from baseline was 15.4 msec (90% CI upper limit of 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 (CTCAE version 3.0). No patient presented with a cardiac arrhythmia (see section 4.4).

5.3 Preclinical safety data

In rat and monkey repeated-dose toxicity studies up to 9-months duration, the primary target organ effects were identified in the gastrointestinal tract (emesis and diarrhoea in monkeys); adrenal gland (cortical congestion and/or haemorrhage in rats and monkeys, with necrosis followed by fibrosis in rats); haemolymphopoietic system (bone morrow hypocellularity and lymphoid depletion of thymus, spleen, and lymph node); exocrine pancreas (acinar cell degranulation with single cell necrosis); salivary gland (acinar hypertrophy); bone joint (growth plate thickening); uterus (atrophy); and ovaries (decreased follicular development). All findings occurred at clinically relevant sunitinib plasma exposure levels. Additional effects observed in other studies included: QTc interval prolongation, LVEF reduction and testicular tubular atrophy, increased mesangial cells in kidney, haemorrhage in gastrointestinal tract and oral mucosa, and hypertrophy of anterior pituitary cells. Changes in the uterus (endometrial atrophy) and bone growth plate (physeal thickening or dysplasia of cartilage) are thought to be related to the pharmacological action of sunitinib. Most of these findings were reversible after 2 to 6 weeks without treatment.

Genotoxicity
The genotoxic potential of sunitinib was assessed *in vitro* and *in vivo*. Sunitinib was not mutagenic in bacteria using metabolic activation provided by rat liver. Sunitinib did not induce structural chromosome aberrations in human peripheral blood lymphocyte cells *in vitro.* Polyploidy (numerical chromosome aberrations) was observed in human peripheral blood lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Sunitinib was not clastogenic in rat bone marrow *in vivo.* The major active metabolite was not evaluated for genotoxic potential.

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

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

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

Reproductive and developmental toxicity
No effects on fertility were observed in male rats dosed for 58 days prior to mating with untreated females. No reproductive effects were observed in female rats treated for 14 days prior to mating with untreated males, at doses resulting in systemic exposures approximately 5 times the systemic exposure in humans. However, in repeated-dose toxicity studies performed in rats and monkeys, effects on female fertility were observed in the form of follicular atresia, degeneration of corpora lutea,

endometrial changes in the uterus and decreased uterine and ovarian weights at clinically relevant systemic exposure levels. Moreover, in repeat-dose toxicity studies conducted in rats, effects on male fertility were observed in the form of tubular atrophy in the testes, reduction of spermatozoa in epididymides and colloid depletion in prostate and seminal vesicles at plasma exposure levels 25 times the systemic exposure in humans. Not all the effects observed in male rats were reversible at the end of the recovery period (6 weeks)

In rats, treatment-related embryo-fetal mortality was evident as significant reductions in the number of live fetuses, increased numbers of resorptions (early and total), corresponding increased post-implantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5 times the systemic exposure in humans. In rabbits, reductions in gravid uterine weights and number of live fetuses were due to increases in the number of resorptions (early and total), increases in post-implantation loss and complete litter loss in 4 of 6 pregnant females at plasma exposure levels 3 times the systemic exposure in humans.

Sunitinib treatment in rats during organogenesis resulted in developmental effects at ≥5 mg/kg/day consisting of increased incidence of fetal skeletal malformations, predominantly characterized as retarded ossification of thoracic/lumbar vertebrae. Developmental effects in rats occurred at plasma exposure levels 6 times the systemic exposure in humans. In rabbits, developmental effects consisted of increased incidence of cleft lip at plasma exposure levels approximately equal to that observed in clinic, and cleft lip and cleft palate at plasma exposure levels 2.7 times the systemic exposure in humans.

A definitive rabbit embryo-fetal development toxicity study was not conducted as embryo-fetal effects were clearly demonstrated in the rat and reported in the preliminary study conducted in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

12.5 mg hard capsules
Capsule content
Povidone (K-25)
Mannitol (E421) (Ph. Eur.)
Croscamellose sodium
Magnesium stearate (Ph. Eur.) [vegetable]

Capsule shell
Gelatin
Red Iron Oxide (E172)
Titanium Dioxide (E171)
Black Iron Oxide (E172)

Printing ink
Shellac
Propylene Glycol
Sodium Hydroxide
Povidone
Titanium Dioxide (E171)

50 mg hard capsules
Capsule content
Povidone
Mannitol (E421)
Croscamellose sodium
Magnesium stearate

Capsule shell
Gelatin
Titanium Dioxide (E171)
Yellow Iron Oxide (E172)
Red Iron Oxide (E172)
Black Iron Oxide (E172)

Printing ink
Shellac
Propylene Glycol
Sodium Hydroxide
Povidone
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to outer carton.

6.4 Special precautions for storage

Please refer to outer carton.

6.5 Nature and contents of container

Capsules are packed in:
White Polyvinylchloride (PVC)/Polychlorotrifluoroethylene (PCTFE)-Aluminum blisters:
28 hard capsules.
30 hard capsules.

HDPE bottles with PP caps containing 30 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Unused medicinal product or waste material should be eliminated in accordance with the national requirements.

7. PRODUCT OWNER

LOTUS INTERNATIONAL PTE. LTD.
80 Robinson Road
#02-00
Singapore 068898

8. DATE OF REVISION OF THE TEXT

01/2022