SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sunitinib Mylan 12,5 mg, harde capsules
Sunitinib Mylan 25 mg, harde capsules
Sunitinib Mylan 37,5 mg, harde capsules
Sunitinib Mylan 50 mg, harde capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Product name> 12.5 mg hard capsules
Each capsule contains 12.5 mg of sunitinib.

<Product name> 25 mg hard capsules
Each capsule contains 25 mg of sunitinib.

<Product name> 37.5 mg hard capsules
Each capsule contains 37.5 mg of sunitinib.

<Product name> 50 mg hard capsules
Each capsule contains 50 mg of sunitinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

<Product name> 12.5 mg hard capsules (capsules)
Gelatin capsules of 14.2 mm ± 0.5 mm size with orange cap and orange body, printed with white ink "12.5 mg" on the body and containing yellow to orange granules.

<Product name> 25 mg hard capsules (capsules)
Gelatin capsules of 15.9 mm ± 0.5 mm with caramel cap and orange body, printed with white ink "25 mg" on the body and containing yellow to orange granules.

<Product name> 37.5 mg hard capsules (capsules)
Gelatin capsules of 17.9 mm ± 0.5 mm size with yellow cap and yellow body, printed with black ink "37.5 mg" on the body and containing yellow to orange granules.

<Product name> 50 mg hard capsules (capsules)
Gelatin capsules of 19.3 mm ± 0.5 mm size with caramel cap and caramel body, printed with white ink "50 mg" on the body and containing yellow to orange granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gastrointestinal stromal tumour (GIST)

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

Metastatic renal cell carcinoma (MRCC)
<Product name> is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.

Pancreatic neuroendocrine tumours (pNET)
<Product name> 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 <Product name> 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 <Product name> is 37.5 mg taken orally once daily without a scheduled rest period.

Dose adjustments

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

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

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

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

Co-administration of sunitinib with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see sections 4.4 and 4.5). If this is not possible, the dose of sunitinib may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability.

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

Special populations

Paediatric population
The safety and efficacy of sunitinib in patients below 18 years of age have not been established.

Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

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 starting dose adjustment is recommended when administering sunitinib to patients with mild or moderate (Child-Pugh class A and B) hepatic impairment. Sunitinib has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment and therefore its use in patients with severe hepatic impairment cannot be recommended (see section 5.2).

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

Method of administration
<Product name> is for oral administration. It may be taken with or without food.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

Skin and tissue disorders
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 rash on the palms of the hands and soles of the feet.

The above reactions were not cumulative, were typically reversible and generally did not result in treatment discontinuation. Cases of pyoderma gangrenosum, generally reversible after discontinuation of sunitinib, have been reported. 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).

Haemorrhage and tumour bleeding

Haemorrhagic events, some of which were fatal, reported in clinical studies with sunitinib and during post-marketing surveillance have included gastrointestinal, respiratory, urinary tract and brain haemorrhages (see section 4.8).

Routine assessment of bleeding 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.

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

Tumour haemorrhage may occur suddenly, and in the case of pulmonary tumours, may present as severe and life- threatening haemoptysis or pulmonary haemorrhage. Cases of pulmonary haemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib for MRCC, GIST and lung cancer. Sunitinib is not approved for use in patients with lung cancer.

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

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

Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrhoeal, or antacid properties.

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

Hypertension
Hypertension has been reported in association with sunitinib including severe hypertension (>200 mmHg systolic or 110 mmHg diastolic). 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 (see section 4.8).

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. None of these events in the Phase 3 studies were fatal, but rare fatal haematological events, including haemorrhage associated with thrombocytopenia and neutropenic infections, have been reported during post-marketing surveillance.

Anaemia has been observed to occur early as well as late during treatment with sunitinib.

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, left ventricular ejection fraction decline to below the lower limit of normal, myocarditis, myocardial ischaemia and myocardial infarction, some of which were fatal, have been reported in patients treated with sunitinib. These data suggest that sunitinib increases the risk of cardiomyopathy. No specific additional risk factors for sunitinib-induced cardiomyopathy apart from the drug-specific effect have been identified in the treated patients. Use sunitinib with caution in patients who are at risk for, or who have a history of, these events (see section 4.8).

Patients who presented with cardiac events within 12 months prior to sunitinib administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischaemic attack, or pulmonary embolism were excluded from all sunitinib clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing sunitinib-related left ventricular dysfunction.

Physicians are advised to weigh this risk against the potential benefits of sunitinib. Patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib especially patients with cardiac risk factors and/or history of coronary artery disease. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

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

<u>QT interval prolongation</u>
Prolongation of QT interval and Torsade de pointes have been observed in sunitinib-exposed patients. QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes.

Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or medicinal products that can prolong QT interval, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant administration of sunitinib with potent CYP3A4 inhibitors should be limited because of the possible increase in sunitinib plasma concentrations (see sections 4.2, 4.5 and 4.8).

<u>Venous thromboembolic events</u>
Treatment-related venous thromboembolic events were reported in patients who received sunitinib including deep venous thrombosis and pulmonary embolism (see section 4.8). Cases of pulmonary embolism with fatal outcome have been observed in post-marketing surveillance.

<u>Arterial thromboembolic events</u>
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.

<u>Aneurysms and artery dissections</u>
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating <Product name>, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

<u>Thrombotic microangiopathy (TMA)</u>
The diagnosis of TMA, including thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, should be considered

in the occurrence of haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment and fever. Sunitinib therapy should be discontinued in patients who develop TMA and prompt treatment is required. Reversal of the effects of TMA has been observed after treatment discontinuation (see section 4.8).

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

Hypothyroidism has been observed to occur early as well as late during treatment with sunitinib (see section 4.8).

Pancreatitis
Increases in serum lipase and amylase activities were observed in patients with various solid tumours who received sunitinib. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours (see section 4.8).

Cases of serious pancreatic events, some with fatal outcome, have been reported. If symptoms of pancreatitis are present, patients should have sunitinib discontinued and be provided with appropriate supportive care.

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. If signs or symptoms of hepatic failure are present, sunitinib should be discontinued and appropriate supportive care should be provided (see section 4.8).

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.

Fistula
If fistula formation occurs, sunitinib treatment should be interrupted. Limited information is available on the continued use of sunitinib in patients with fistulae (see section 4.8).

Impaired wound healing

Cases of impaired wound healing have been reported during sunitinib therapy.

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

Osteonecrosis of the jaw (ONJ)
Cases of ONJ have been reported in patients treated with 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).

Hypersensitivity/angioedema
If angioedema due to hypersensitivity occurs, sunitinib treatment should be interrupted and standard medical care provided (see section 4.8).

Seizures
In clinical studies of sunitinib and from post-marketing surveillance, seizures have been reported. Patients with seizures and signs/symptoms consistent with posterior reversible leukoencephalopathy syndrome (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 (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 post-marketing 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.

Infections
Serious infections, with or without neutropenia, including some with a fatal outcome, have been reported. Uncommon cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported (see section 4.8).

Sunitinib therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Hypoglycaemia
Decreases in blood glucose, in some cases clinically symptomatic and requiring hospitalisation due to loss of consciousness, have been reported during sunitinib treatment. In case of symptomatic hypoglycaemia, sunitinib should be temporarily interrupted. Blood glucose levels in diabetic patients should be checked regularly in order to assess if antidiabetic medicinal product’s dosage needs to be adjusted to minimise the risk of hypoglycaemia (see section 4.8).

Hyperammonaemic encephalopathy

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Medicinal products that may increase sunitinib plasma concentrations

Effect of CYP3A4 inhibitors
In healthy volunteers, concomitant administration of a single dose of sunitinib with the potent CYP3A4 inhibitor ketoconazole resulted in an increase of the combined [sunitinib + primary metabolite] maximum concentration (C_{max}) and area under the curve ($AUC_{0-\infty}$) values of 49% and 51%, respectively.

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

Combination with CYP3A4 inhibitors should therefore be avoided, or the selection of an alternate concomitant medicinal product with no or minimal potential to inhibit CYP3A4 should be considered.

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

Effect of Breast Cancer Resistance Protein (BCRP) inhibitors
Limited clinical data are available on the interaction between sunitinib and BCRP inhibitors and the possibility of an interaction between sunitinib and other BCRP inhibitors cannot be excluded (see section 5.2).

Medicinal products that may decrease sunitinib plasma concentrations

Effect of CYP3A4 inducers
In healthy volunteers, concomitant administration of a single dose of sunitinib with the CYP3A4 inducer rifampicin resulted in a reduction of the combined [sunitinib + primary metabolite] C_{max} and $AUC_{0-\infty}$ values of 23% and 46%, respectively.

Administration of sunitinib with potent CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort/*Hypericum perforatum*) may decrease sunitinib concentrations. Combination with CYP3A4 inducers should therefore be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dose of <Product name> may need to be increased in 12.5 mg increments (up to 87.5 mg per day for GIST and MRCC or 62.5 mg per day for pNET), based on careful monitoring of tolerability (see section 4.2).

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with sunitinib.

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

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

<Product name> has minor influence on the ability to drive and use machines. Patients should be advised that they may experience dizziness during treatment with sunitinib.

4.8 Undesirable effects

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

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

Tabulated list of adverse reactions
Adverse reactions that were reported in GIST, MRCC, and pNET patients in a pooled dataset of 7,115 patients are listed below, by system organ class, frequency and grade of severity (NCI-CTCAE). Post-marketing adverse reactions identified in clinical studies are also included. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1. Adverse reactions reported in clinical trials

System organ class	Very common	Common	Uncommon	Rare	Not known
Infections and		Viral infections[a]	Necrotising		

infestations		Respiratory infections[b,*] Abscess[c,*] Fungal infections[d] Urinary tract infection Skin infections[e] Sepsis[f,*]	fasciitis* Bacterial infections[g]		
Blood and lymphatic system disorders	Neutropenia Thrombocytopenia Anaemia Leukopenia	Lymphopenia	Pancytopenia	Thrombotic microangiopathy[h,*]	
Immune system disorders			Hypersensitivity	Angioedema	
Endocrine disorders	Hypothyroidism		Hyperthyroidism	Thyroiditis	
Metabolism and nutrition disorders	Decreased appetite[i]	Dehydration Hypoglycaemia		Tumour lysis syndrome*	
Psychiatric disorders	Insomnia	Depression			
Nervous system disorders	Dizziness Headache Taste disturbance[j]	Neuropathy peripheral Paraesthesia Hypoaesthesia Hyperaesthesia	Cerebral haemorrhage* Cerebrovascular accident* Transient ischaemic attack	Posterior reversible encephalopathy syndrome*	Hyperammonaemic encephalopathy
Eye disorders		Periorbital oedema Eyelid oedema Lacrimation increased			
Cardiac disorders		Myocardial ischemia[k,*] Ejection fraction decreased[l]	Cardiac failure congestive Myocardial infarction[m,*] Cardiac failure* Cardiomyopathy* Pericardial effusion Electrocardiogram QT prolonged	Left ventricular failure* Torsade de pointes	
Vascular disorders	Hypertension	Deep vein thrombosis Hot flush Flushing	Tumour haemorrhage*		Aneurysms and artery dissections*
Respiratory, thoracic and mediastinal disorders	Dyspnoea Epistaxis Cough	Pulmonary embolism* Pleural effusion* Haemoptysis Dyspnoea exertional Oropharyngeal pain[n] Nasal congestion Nasal dryness	Pulmonary haemorrhage* Respiratory failure*		
Gastrointestinal disorders	Stomatitis[o] Abdominal pain[p] Vomiting Diarrhoea	Gastro-oesophageal reflux disease Dysphagia Gastrointestinal	Gastrointestinal perforation[q,*] Pancreatitis Anal fistula		

	Dyspepsia Nausea Constipation	haemorrhage* Oesophagitis* Abdominal distension Abdominal discomfort Rectal haemorrhage Gingival bleeding Mouth ulceration Proctalgia Cheilitis Haemorrhoids Glossodynia Oral pain Dry mouth Flatulence Oral discomfort Eructation	Colitis[r]		
Hepatobiliary disorders			Hepatic failure* Cholecystitis[s,]* Hepatic function abnormal	Hepatitis	
Skin and subcutaneous tissue disorders	Skin discolouration[t] Palmar-plantar erythrodysaesthesia syndrome Rash[u] Hair colour changes Dry skin	Skin exfoliation Skin reaction[v] Eczema Blister Erythema Alopecia Acne Pruritus Skin hyperpigmentation Skin lesion Hyperkeratosis Dermatitis Nail disorder[w]		Erythema multiforme* Stevens-Johnson syndrome* Pyoderma gangrenosum Toxic epidermal necrolysis*	
Musculoskeletal and connective tissue disorders	Pain in extremity Arthralgia Back pain	Musculoskeletal pain Muscle spasms Myalgia Muscular weakness	Osteonecrosis of the jaw Fistula*	Rhabdomyolysis* Myopathy	
Renal and urinary disorders		Renal failure* Renal failure acute* Chromaturia Proteinuria	Haemorrhage urinary tract	Nephrotic syndrome	
General disorders and administration site conditions	Mucosal inflammation Fatigue[x] Oedema[y] Pyrexia	Chest pain Pain Influenza like illness Chills	Impaired healing		
Investigations		Weight decreased White blood cell count decreased Lipase increased Platelet count decreased Haemoglobin decreased Amylase increased[z] Aspartate aminotransferase	Blood creatine phosphokinase increased Blood thyroid stimulating hormone increased		

		increased Alanine aminotransferase increased Blood creatinine increased Blood pressure increased Blood uric acid increased			

* Including fatal events

The following terms have been combined:

[a] Nasopharyngitis and oral herpes
[b] Bronchitis, lower respiratory tract infection, pneumonia and respiratory tract infection
[c] Abscess, abscess limb, anal abscess, gingival abscess, liver abscess, pancreatic abscess, perineal abscess, perirectal abscess, rectal abscess, subcutaneous abscess and tooth abscess
[d] Oesophageal candidiasis and oral candidiasis
[e] Cellulitis and skin infection
[f] Sepsis and sepsis shock
[g] Abdominal abscess, abdominal sepsis, diverticulitis and osteomyelitis
[h] Thrombotic microangiopathy, thrombotic thrombocytopenic purpura, and haemolytic uraemic syndrome
[I] Decreased appetite and anorexia
[j] Dysgeusia, ageusia and taste disturbance
[k] Acute coronary syndrome, angina pectoris, angina unstable, coronary artery occlusion, and myocardial ischaemia
[l] Ejection fraction decreased/abnormal
[m] Acute myocardial infarction, myocardial infarction, and silent myocardial infarction
[n] Oropharyngeal and pharyngolaryngeal pain
[o] Stomatitis and aphtous stomatitis
[p] Abdominal pain, abdominal pain lower and abdominal pain upper
[q] Gastrointestinal perforation and intestinal perforation
[r] Colitis and colitis ischaemic.
[s] Cholecystitis and acalculous cholecystitis
[t] Yellow skin, skin discolouration and pigmentation disorder
[u] Dermatitis psoriasiform, exfoliative rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic
[v] Skin reaction and skin disorder
[w] Nail disorder and discolouration
[x] Fatigue and asthenia
[y] Face oedema, oedema and oedema peripheral
[z] Amylase and amylase increased

Description of selected adverse reactions

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

Blood and lymphatic system disorders
Decreased absolute neutrophil counts of Grade 3 and 4 severities, respectively, were reported in 10% and 1.7% of patients on the Phase 3 GIST study, in 16% and 1.6% of patients on the Phase 3 MRCC study, and in 13% and 2.4% of patients on the Phase 3 pNET study. Decreased platelet counts of Grade 3 and 4 severities, respectively, were reported in 3.7% and 0.4% of patients on the Phase 3 GIST study, in 8.2% and 1.1% of patients on the Phase 3 MRCC study, and in 3.7% and 1.2% of patients on the Phase 3 pNET study (see section 4.4).

Bleeding events were reported in 18% of patients receiving sunitinib in a Phase 3 GIST study vs 17% of patients receiving placebo. In patients receiving sunitinib for treatment-naïve MRCC, 39%

had bleeding events vs 11% of patients receiving interferon-α (IFN-α). Seventeen (4.5%) patients on sunitinib versus 5 (1.7%) patients on IFN-α experienced Grade 3 or greater bleeding events. Of patients receiving sunitinib for cytokine-refractory MRCC, 26% experienced bleeding. Bleeding events, excluding epistaxis, were reported in 21.7% of patients receiving sunitinib in the Phase 3 pNET study compared to 9.85% of patients receiving placebo (see section 4.4)

In clinical trials, tumour haemorrhage was reported in approximately 2% of patients with GIST.

Immune system disorders
Hypersensitivity reactions, including angioedema, have been reported (see section 4.4).

Endocrine disorders
Hypothyroidism was reported as an adverse reaction in 7 patients (4%) receiving sunitinib across the 2 cytokine-refractory MRCC studies; in 61 patients (16%) on sunitinib and 3 patients (< 1%) in the IFN-α arm in the treatment-naïve MRCC study.

Additionally, thyroid-stimulating hormone (TSH) elevations were reported in 4 cytokine-refractory MRCC patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Acquired hypothyroidism was noted in 6.2% of GIST patients on sunitinib versus 1% on placebo. In the Phase 3 pNET study hypothyroidism was reported in 6 patients (7.2%) receiving sunitinib and in 1 patient (1.2%) on placebo.

Thyroid function was monitored prospectively in 2 studies in patients with breast cancer; Sunitinib is not approved for use in breast cancer. In 1 study, hypothyroidism was reported in 15 (13.6%) patients on sunitinib and 3 (2.9%) patients on standard of care. Blood TSH increase was reported in 1 (0.9%) patient on sunitinib and no patients on standard of care. Hyperthyroidism was reported in no sunitinib treated patients and 1 (1.0%) patient receiving standard of care. In the other study hypothyroidism was reported in a total of 31 (13%) patients on sunitinib and 2 (0.8%) patients on capecitabine. Blood TSH increase was reported in 12 (5.0%) patients on sunitinib and no patients on capecitabine.
Hyperthyroidism was reported in 4 (1.7%) patients on sunitinib and no patients on capecitabine. Blood TSH decrease was reported in 3 (1.3%) patients on sunitinib and no patients on capecitabine. T4 increase was reported in 2 (0.8%) patients on sunitinib and 1 (0.4%) patient on capecitabine. T3 increase was reported in 1 (0.8%) patient on sunitinib and no patients on capecitabine. All thyroid-related events reported were Grade 1-2 (see section 4.4).

Metabolism and nutrition disorders
A higher incidence rate of hypoglycaemia events was reported in patients with pNET in comparison to MRCC and GIST. Nevertheless most of these adverse events observed in clinical studies were not considered related to study treatment (see section 4.4).

Nervous system disorders
In clinical studies of sunitinib and from post-marketing surveillance, there have been few reports (< 1%), some fatal, of subjects presenting with seizures and radiological evidence of RPLS. Seizures have been observed in patients with or without radiological evidence of brain metastases (see section 4.4).

Cardiac disorders
In clinical trials, decreases in left ventricular ejection fraction (LVEF) of ≥ 20% and below the lower limit of normal were reported in approximately 2% of sunitinib-treated GIST patients, 4% of cytokine-refractory MRCC patients, and 2% of placebo-treated GIST patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued. In the treatment-naïve MRCC study, 27% of patients on sunitinib and 15% of patients on IFN-α had an LVEF value below the lower limit of normal. Two patients (< 1%) who received sunitinib were diagnosed with CHF.
In GIST patients ‘cardiac failure’, ‘cardiac failure congestive’, or ‘left ventricular failure’ were reported in 1.2% of patients treated with sunitinib and 1% of patients treated with placebo. In the pivotal Phase 3 GIST study (N = 312), treatment-related fatal cardiac reactions were reported in 1% of

patients on each arm of the study (i.e. sunitinib and placebo arms). In a Phase 2 study in cytokine-refractory MRCC patients, 0.9% of patients experienced treatment-related fatal myocardial infarction and in the Phase 3 study in treatment-naïve MRCC patients, 0.6% of patients on the IFN-α arm and 0% of patients on the sunitinib arm experienced fatal cardiac events. In the Phase 3 pNET study, 1 (1%) patient who received sunitinib had treatment-related fatal cardiac failure.

Vascular disorders
Hypertension
Hypertension was a very common adverse reaction reported in clinical trials. The dose of sunitinib was reduced or its administration temporarily suspended in approximately 2.7% of the patients who experienced hypertension. Sunitinib was not permanently discontinued in any of these patients. Severe hypertension (> 200 mmHg systolic or 110 mmHg diastolic) was reported in 4.7% of patients with solid tumours. Hypertension was reported in approximately 33.9% of patients receiving sunitinib for treatment-naïve MRCC compared to 3.6% of patients receiving IFN-α. Severe hypertension was reported in 12% of treatment-naïve patients on sunitinib and < 1% of patients on IFN-α. Hypertension was reported in 26.5% of patients receiving sunitinib in a Phase 3 pNET study, compared to 4.9% of patients receiving placebo. Severe hypertension was reported in 10% of pNET patients on sunitinib and 3% of patients on placebo.

Venous thromboembolic events
Treatment-related venous thromboembolic events were reported in approximately 1.0% of patients with solid tumours who received sunitinib on clinical trials, including GIST and RCC.

Seven patients (3%) on sunitinib and none on placebo in a Phase 3 GIST study experienced venous thromboembolic events; 5 of the 7 were Grade 3 deep venous thrombosis (DVT) and 2 were Grade 1 or 2. Four of these 7 GIST patients discontinued treatment following first observation of DVT.

Thirteen patients (3%) receiving sunitinib in the Phase 3 treatment-naïve MRCC study and 4 patients (2%) on the 2 cytokine-refractory MRCC studies had venous thromboembolic events reported. Nine of these patients had pulmonary embolisms; 1 was Grade 2 and 8 were Grade 4. Eight of these patients had DVT; 1 with Grade 1, 2 with Grade 2, 4 with Grade 3, and 1 with Grade 4. One patient with pulmonary embolism in the cytokine-refractory MRCC study experienced dose interruption.

In treatment-naïve MRCC patients receiving IFN-α, 6 (2%) venous thromboembolic events were reported; 1 patient (< 1%) experienced a Grade 3 DVT and 5 patients (1%) had pulmonary embolisms, all with Grade 4.

Venous thromboembolic events were reported for 1 (1.2%) patient in the sunitinib arm and 5 (6.1%) patients in the placebo arm in the Phase 3 pNET study. Two of these patients on placebo had DVT, 1 with Grade 2 and 1 with Grade 3.

No cases with fatal outcome were reported in GIST, MRCC, and pNET registrational studies. Cases with fatal outcome have been observed in the post-marketing surveillance.

Cases of pulmonary embolism were observed in approximately 3.1% of patients with GIST and in approximately 1.2% of patients with MRCC, who received sunitinib in Phase 3 studies. No pulmonary embolism was reported for patients with pNET who received sunitinib in the Phase 3 study. Rare cases with fatal outcome have been observed in the post-marketing surveillance.

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

In patients who received sunitinib in Phase 3 registrational studies, pulmonary events (i.e. dyspnoea, pleural effusion, pulmonary embolism, or pulmonary oedema) were reported in approximately 17.8% of patients with GIST, in approximately 26.7% of patients with MRCC and in 12% of patients with pNET.

Approximately 22.2% of patients with solid tumours, including GIST and MRCC, who received sunitinib in clinical trials experienced pulmonary events.

Gastrointestinal disorders
Pancreatitis has been observed uncommonly (< 1%) in patients receiving sunitinib for GIST or MRCC. No treatment-related pancreatitis was reported in the Phase 3 pNET study (see section 4.4).

Fatal gastrointestinal bleeding was reported in 0.98% of patients receiving placebo in the GIST Phase 3 study.

Hepatobiliary disorders
Hepatic dysfunction has been reported and may include Liver Function Test abnormalities, hepatitis or liver failure (see section 4.4).

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

Musculoskeletal and connective tissue disorders
Cases of myopathy and/or rhabdomyolysis, some with acute renal failure, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice (see section 4.4).

Cases of fistula formation, sometimes associated with tumour necrosis and regression, in some cases with fatal outcomes, have been reported (see section 4.4).

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

Investigations
Data from non clinical (*in vitro* and *in vivo*) studies, at doses higher than the recommended human dose, indicated that sunitinib has the potential to inhibit the cardiac action potential repolarisation process (e.g., prolongation of QT interval).

Increases in the QTc interval to over 500 msec were reported in 0.5%, and changes from baseline in excess of 60 msec were reported in 1.1% of the 450 solid tumour patients; both of these parameters are recognised as potentially significant changes. At approximately twice therapeutic concentrations, sunitinib has been shown to prolong the QTcF interval (Fridericia corrected QT interval).

QTc interval prolongation was investigated in a trial in 24 patients, ages 20-87 years, with advanced malignancies. The results of this study demonstrated that sunitinib had an effect on QTc interval (defined as a mean placebo-adjusted change of > 10 msec with a 90% confidence interval [CI] upper limit > 15 msec) at therapeutic concentration (Day 3) using the within-day baseline correction method, and at greater than therapeutic concentration (Day 9) using both baseline correction methods. No patients had a QTc interval > 500 msec. Although an effect on QTcF interval was observed on Day 3 at 24 hours postdose (i.e., at therapeutic plasma concentration expected after the recommended starting dose of 50 mg) with the within-day baseline correction method, the clinical significance of this finding is unclear.

Using comprehensive serial ECG assessments at times corresponding to either therapeutic or greater than therapeutic exposures, none of the patients in the evaluable or intent-to-treat (ITT) populations were observed to develop QTc interval prolongation considered as “severe” (i.e. equal to or greater than Grade 3 by Common Terminology Criteria for Adverse Events [CTCAE] version 3.0).

At therapeutic plasma concentrations, the maximum QTcF interval (Frederica's correction) mean change from baseline was 9 msec (90% CI: 15.1 msec). At approximately twice therapeutic concentrations, the maximum QTcF interval change from baseline was 15.4 msec (90% CI: 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF interval change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 (CTCAE version 3.0) (see section 4.4).

Long-term safety in MRCC
The long-term safety of sunitinib in patients with MRCC was analysed across 9 completed clinical studies conducted in the first-line, bevacizumab-refractory, and cytokine-refractory treatment settings in 5,739 patients, of whom 807 (14%) were treated for ≥ 2 years up to 6 years. In the 807 patients who received long-term sunitinib treatment, most treatment-related adverse events (TRAEs) occurred initially in the first 6 months–1 year and then were stable or decreased in frequency over time, with the exception of hypothyroidism, which gradually increased over time, with new cases occurring over the 6 year period. Prolonged treatment with sunitinib did not appear to be associated with new types of TRAEs.

Paediatric population
The safety profile of sunitinib has been derived from a Phase 1 dose-escalation study, a Phase 2 open-label study, a Phase 1/2 single-arm study and from publications as described below.

A Phase 1 dose-escalation study of oral sunitinib was conducted in 35 patients comprised of 30 paediatric patients (aged 3 years to 17 years) and 5 young adult patients (aged 18 to 21 years), with refractory solid tumours, the majority of whom had a primary diagnosis of brain tumour. All study participants experienced adverse drug reactions; most of these were severe (toxicity grade ≥ 3) and included cardiac toxicity. The most common adverse drug reactions were gastrointestinal (GI) toxicity, neutropenia, fatigue, and ALT elevation. The risk of cardiac adverse drug reactions appeared to be higher in paediatric patients with previous exposure to cardiac irradiation or anthracycline compared to those paediatric patients without previous exposure. In these paediatric patients without previous exposure to anthracyclines or cardiac irradiation, the maximum tolerated dose (MTD) has been identified (see section 5.1).

A phase 2 open-label study was conducted in 29 patients comprised of 27 paediatric patients (aged 3 years to 16 years) and 2 young adult patients (aged 18 years to 19 years) with recurrent/progressive/refractory high grade glioma (HGG) or ependymoma. There were no Grade 5 adverse reactions in either group. The most common (≥10%) treatment-related adverse events were neutrophil count decreased (6 [20.7%] patients) and haemorrhage intracranial (3[10.3%] patients).

A Phase 1/2 single-arm, study was conducted in 6 paediatric patients (aged 13 years to 16 years) with advanced unresectable GIST. The most frequent adverse drug reactions were diarrhoea, nausea, WBC count decreased, neutropenia, and headache in 3 (50.0%) patients each, primarily Grade 1 or 2 in severity. Four out of 6 patients (66.7%) experienced Grade 3-4 treatment-related adverse events (Grade 3 hypophosphataemia, neutropenia, and thrombocytopenia in 1 patient each and a Grade 4 neutropenia in 1 patient). There were no serious adverse events (SAEs) or Grade 5 adverse drug reactions reported in this study. In both the clinical study and the publications, the safety profile was consistent with the known safety profile in adults.

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

4.9 Overdose

There is no specific antidote for overdose with <Product name> and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed active substance may be achieved by emesis or gastric lavage. 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 RTKs that are implicated in tumour growth, neoangiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

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

Efficacy is based on time-to-tumour progression (TTP) and an increase in survival in GIST, 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 tumours
An initial open-label, dose-escalation study was conducted in patients with GIST after failure of imatinib (median maximum daily dose 800 mg) due to resistance or intolerance. Ninety-seven patients were enrolled at various doses and schedules; 55 patients received 50 mg at the recommended treatment Schedule 4 weeks on /2 weeks off (“Schedule 4/2”).

In this study, the median TTP was 34.0 weeks (95% CI: 22.0, 46.0).

A Phase 3, randomised, double-blind, placebo-controlled study of sunitinib was conducted in patients with GIST who were intolerant to, or had experienced disease progression during or following treatment with, imatinib (median maximum daily dose 800 mg). In this study, 312 patients were randomised (2:1) to receive either 50 mg sunitinib or placebo, orally once daily on Schedule 4/2 until disease progression or withdrawal from the study for another reason (207 patients received sunitinib and 105 patients received placebo). The primary efficacy endpoint of the study was TTP, defined as the time from randomisation to first documentation of objective tumour progression. At the time of the prespecified 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 on placebo 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 overall survival (OS) was statistically in favour of sunitinib [hazard ratio (HR): 0.491; (95%CI: 0.290, 0.831)]; the risk of death was 2 times higher in patients in the placebo arm compared to the sunitinib arm.

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

A total of 255 patients received sunitinib in the open-label treatment phase of the study, including 99 patients who were initially treated with placebo.

The analyses of primary and secondary endpoints in the open-label phase of the study reaffirmed the results obtained at the time of the interim analysis, as shown in 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					
PFS (weeks)[c]					
Interim	24.1 (11.1, 28.3)	6.0 (4.4, 9.9)	0.333 (0.238, 0.467)	<0.001	-
Final	22.9 (10.9, 28.0)	6.0 (4.4, 9.7)	0.347 (0.253, 0.475)	<0.001	-
ORR (%)[d]					
Interim	6.8 (3.7, 11.1)	0 (-)	NA	0.006	-
Final	6.6 (3.8, 10.5)	0 (-)	NA	0.004	10.1 (5.0, 17.8)
OS (weeks)[e]					
Interim	-	-	0.491 (0.290, 0.831)	0.007	-
Final	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 rate; OS=overall survival; PFS=progression-free survival; TTP=time-to-tumour 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 sunitinib after unblinding. Baseline was reset at cross-over and efficacy analyses were based on investigators assessment.

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

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

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

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

Treatment-naïve metastatic renal cell carcinoma

A Phase 3, randomised, multi-centre, international study evaluating the efficacy and safety of sunitinib compared with IFN-α in treatment-naïve MRCC patients was conducted. Seven hundred and fifty patients were randomised 1:1 to the treatment arms; they received treatment with either sunitinib in

repeated 6-week cycles, consisting of 4 weeks of 50 mg daily oral administration followed by 2 weeks of rest (Schedule 4/2), or IFN-α, administered as a subcutaneous injection of 3 million units (MU) the first week, 6 MU the second week, and 9 MU the third week and thereafter, on 3 non-consecutive days each week.

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

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

The overall PFS and OS, observed in the ITT population, as determined by the core radiology laboratory assessment, are summarised in Table 3.

Table 3. Treatment-naïve mRCC summary of efficacy endpoints (ITT population)

Summary of progression-free survival	**Sunitinib (N = 375)**	**IFN-α (N = 375)**
Subject did not progress or die [n (%)]	161 (42.9)	176 (46.9)
Subject observed to have progressed or died [n (%)]	214 (57.1)	199 (53.1)
PFS (weeks)		
Quartile (95% CI)		
25%	22.7 (18.0, 34.0)	10.0 (7.3, 10.3)
50%	48.3 (46.4, 58.3)	22.1 (17.1, 24.0)
75%	84.3 (72.9, 95.1)	58.1 (45.6, 82.1)
Unstratified analysis		
Hazard ratio (sunitinib versus IFN-α)	0.5268	
95% CI for hazard ratio	(0.4316, 0.6430)	
p-value[a]	<0.0001	
Summary of overall survival		
Subject not known to have died [n (%)]	185 (49.3)	175 (46.7)
Subject observed to have died [n (%)]	190 (50.7)	200 (53.3)
OS (weeks)		
Quartile (95% CI)		
25%	56.6 (48.7, 68.4)	41.7 (32.6, 51.6)
50%	114.6 (100.1, 142.9)	94.9 (77.7, 117.0)
75%	NA (NA, NA)	NA (NA, NA)
Unstratified analysis		
Hazard ratio (sunitinib versus IFN-α)	0.8209	
95% CI for hazard ratio	(0.6730, 1.0013)	
p-value[a]	0.0510	

Abbreviations: CI=confidence interval; INF-α=interferon-alfa; ITT=intent-to-treat; N=number of patients;

NA=not applicable; OS=overall survival; PFS=progression-free survival.
[a] From a 2-sided log-rank test.

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).

In this study the objective response rate was 36.5% (95% CI: 24.7%, 49.6%) and the median TTP 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. One hundred and 6 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, duration of response (DR) and OS.

In this study the ORR was 35.8% (95% CI: 26.8%, 47.5 %). The median DR and OS had not yet been reached.

Pancreatic neuroendocrine tumours
A supportive Phase 2, open-label, multi-centre study evaluated the efficacy and safety of single-agent sunitinib 50 mg daily on Schedule 4/2 in patients with unresectable pNET. In a pancreatic islet cell tumour cohort of 66 patients, the primary endpoint of response rate was 17%.

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

Patients were required to have documented progression, based on RECIST, within the prior 12 months and were randomised (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled rest period (N = 86) or placebo (N = 85).

The primary objective was to compare PFS in patients receiving sunitinib versus patients receiving placebo. Other endpoints included OS, ORR, PROs and safety.

Demographics were comparable between the sunitinib and placebo groups. Additionally, 49% of sunitinib patients had non-functioning tumours versus 52% of placebo patients and 92% of patients in both arms had liver metastases.

Use of somatostatin analogues was allowed in the study.

A total of 66% of sunitinib patients received prior systemic therapy compared with 72% of placebo patients. In addition, 24% of sunitinib patients had received somatostatin analogues compared with 22% of placebo patients.

A clinically significant advantage in investigator-assessed PFS for sunitinib over placebo was observed. The median PFS was 11.4 months for the sunitinib arm compared to 5.5 months for the placebo arm [hazard ratio: 0.418 (95% CI: 0.263, 0.662), p-value = 0.0001]; similar results were observed when derived tumour response assessments based upon application of RECIST to investigator tumour measurements were used to determine disease progression, as shown in Table 4. A hazard ratio favouring sunitinib was observed in all subgroups of baseline characteristics evaluated, including an analysis by number of prior systemic therapies. A total of 29 patients in the sunitinib arm and 24 in the placebo arm had received no prior systemic treatment; among these patients, the hazard

ratio for PFS was 0.365 (95% CI: 0.156, 0.857), p = 0.0156. Similarly, among 57 patients in the sunitinib arm (including 28 with 1 prior systemic therapy and 29 with 2 or more prior systemic therapies) and 61 patients in the placebo arm (including 25 with 1 prior systemic therapy and 36 with 2 or more prior systemic therapies), the hazard ratio for PFS was 0.456 (95% CI: 0.264, 0.787), p = 0.0036.

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

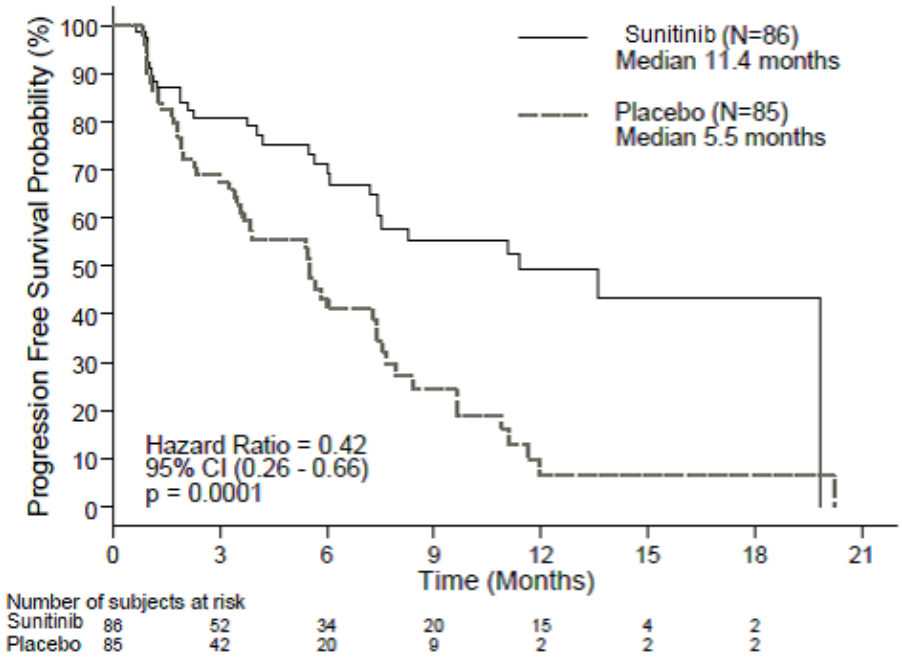
In order to rule out bias in the investigator-based assessment of PFS, a BICR of scans was performed; this review supported the investigator assessment, as shown in Table 4.

Table 4 - pNET efficacy results from the Phase 3 study

Efficacy parameter	**Sunitinib (N = 86)**	**Placebo (N = 85)**	**Hazard Ratio (95% CI)**	**p-value**
Progression-free survival [median, months (95% CI)] by Investigator Assessment	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	0.418 (0.263, 0.662)	0.0001[a]
Progression-free survival [median, months (95% CI)] by derived tumour response assessment based upon application of RECIST to investigator tumour assessments	12.6 (7.4, 16.9)	5.4 (3.5, 6.0)	0.401 (0.252, 0.640)	0.000066[a]
Progression-free survival [median, months (95% CI)] by blinded independent central review of tumour assessments	12.6 (11.1, 20.6)	5.8 (3.8, 7.2)	0.315 (0.181, 0.546)	0.000015[a]
Overall survival [5 years follow-up] [median, months (95% CI)]	38.6 (25.6, 56.4)	29.1 (16.4, 36.8)	0.730 (0.504, 1.057)	0.0940[a]
Objective response rate [%, (95% CI)]	9.3 (3.2, 15.4)	0	NA	0.0066[b]

Abbreviations: CI=confidence interval; N=number of patients; NA=not applicable; pNET=pancreatic neuroendocrine tumours; RECIST=response evaluation criteria in solid tumours.
[a] 2-sided unstratified log-rank test
[b] Fisher's Exact test

Figure 1. Kaplan-Meier plot of PFS in the pNET Phase 3 study



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

OS data were not mature at the time of the study closure [20.6 months (95% CI 20.6, NR) for the sunitinib arm compared to NR (95% CI 15.5, NR) for the placebo arm, hazard ratio: 0.409 (95% CI: 0.187, 0.894), p-value = 0.0204]. There were 9 deaths in the sunitinib arm and 21 deaths in the placebo arm.

Upon disease progression, patients were unblinded and placebo patients were offered access to open-label sunitinib in a separate extension study. As a result of the early study closure, remaining patients were unblinded and offered access to open-label sunitinib in an extension study. A total of 59 out of 85 patients (69.4%) from the placebo arm crossed over to open-label sunitinib following disease progression or unblinding at study closure. OS observed after 5 years of follow-up in the extension study showed a hazard ratio of 0.730 (95% CI 0.504, 1.057).

Results from the European Organisation 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 5 functioning domains (physical, role, cognitive, emotional and social) were maintained for patients on sunitinib treatment as compared to placebo with limited adverse symptomatic effects.

A Phase 4 multinational, multi-centre, single-arm, open-label study evaluating the efficacy and safety of sunitinib was conducted in patients with progressive, advanced/metastatic, well-differentiated, unresectable pNET.

One hundred six patients (61 patients in the treatment-naïve cohort and 45 patients in the later-line cohort) received treatment with sunitinib orally at 37.5 mg once a day on a continuous daily dosing (CDD) schedule.

The investigator-assessed median PFS was 13.2 months, both in the overall population (95% CI: 10.9, 16.7) and in the treatment-naïve cohort (95% CI: 7.4, 16.8).

<u>Paediatric population</u>

Experience on the use of sunitinib in paediatric patients is limited (see section 4.2).

A Phase 1 dose-escalation study of oral sunitinib was conducted in 35 patients comprised of 30 paediatric patients (aged 3 years to 17 years) and 5 young adult patients (aged: 18 years to 21 years), with refractory solid tumours, the majority of whom were enrolled with a primary diagnosis of brain tumour. Dose-limiting cardiotoxicity was observed in the first part of the study which was therefore amended to exclude patients with previous exposure to potentially cardiotoxic therapies (including anthracyclines) or cardiac radiation. In the second part of the study, including patients with prior anticancer therapy but without risk factors for cardiac toxicity, sunitinib was generally tolerable and clinically manageable at the dose of 15 mg/m^2 daily (MTD) on Schedule 4/2. None of the subjects achieved complete response or partial response. Stable disease was observed in 6 patients (17%). One patient with GIST was enrolled at the 15 mg/m^2 dose level with no evidence of benefit. The observed adverse drug reactions were similar overall to those seen in adults (see section 4.8).

A Phase 2 open-label study was conducted in 29 patients comprised of 27 paediatric patients (aged 3 years to 16 years) and 2 young adult patients (aged 18 years to 19 years) with HGG or ependymoma. The study was closed at the time of planned interim analysis due to the lack of disease control. Median PFS was 2.3 months in the HGG group and 2.7 months in the ependymoma group. Median overall OS was 5.1 months in the HGG group and 12.3 months in the ependymoma group. The most common (≥10%) reported treatment- related adverse events in patients in both groups combined were neutrophil count decreased (6 patients [20.7%]) and haemorrhage intracranial (3 patients [10.3%]) (see section 4.8).

Evidence from a Phase 1/2 study of oral sunitinib conducted in 6 paediatric patients with GIST aged 13 years to 16 years who received sunitinib on Schedule 4/2, at doses ranging between 15 mg/m^2 daily and 30 mg/m^2 daily, and available published data (20 paediatric or young adult patients with GIST) indicated that sunitinib treatment resulted in disease stabilization in 18 of 26 (69.2%) patients, either after imatinib failure or intolerance (16 patients with stable disease out of 21), or de novo/after surgery (2 patients with stable disease out of 5). In the Phase 1/2 study, stable disease and disease progression was observed in 3 out of 6 patients each (1 patient received neo adjuvant and 1 patient received adjuvant imatinib, respectively). In the same study, 4 out of 6 patients (66.7%) experienced Grade 3-4 treatment-related adverse events (Grade 3 hypophosphataemia, neutropenia, and thrombocytopenia in 1 patient each and a Grade 4 neutropenia in 1 patient). In addition, the publications reported the following Grade 3 adverse drug reactions experienced by 5 patients: fatigue (2), gastrointestinal adverse drug reactions (including diarrhoea) (2), haematologic adverse drug reactions (including anaemia) (2), cholecystitis (1), hyperthyroidism (1), and mucositis (1).

A population pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) analysis was conducted with the scope to extrapolate the PK and key safety and efficacy endpoints of sunitinib in paediatric patients with GIST (aged: 6 years to 17 years). This analysis was based on data collected from adults with GIST or solid tumours and from paediatric patients with solid tumours. Based on the modelling analyses, the younger age and lower body size did not appear to affect negatively the safety and efficacy responses to sunitinib plasma exposures. Sunitinib benefit/risk did not appear to be negatively affected by younger age or lower body size, and was mainly driven by its plasma exposure.

The EMA has waived the obligation to submit the results of studies with the reference medicinal product containing sunitinib in all subsets of the paediatric population for the treatment of kidney or renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma, and rhabdoid tumour of the kidney) (see section 4.2).

The EMA has waived the obligation to submit the results of the studies with the reference medicinal product containing sunitinib in all subsets of the paediatric population for the treatment of gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, and phaeochromocytoma) (see section 4.2).

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.

In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3 to 4-fold and its primary active metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite are 62.9 - 101 ng/ml which are target concentrations predicted from preclinical data to inhibit receptor phosphorylation *in vitro* and result in tumour stasis/growth reduction *in vivo*. The primary active metabolite comprises 23% to 37% of the total exposure. No significant changes in the PK of sunitinib or the primary active metabolite are observed with repeated daily administration or with repeated cycles in the dosing schedules tested.

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

Food has no effect on the bioavailability of sunitinib.

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

Metabolic interactions
The calculated *in vitro* Ki values for all cytochrome P450 (CYP) isoforms tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11) indicated that sunitinib and its primary active metabolite are unlikely to induce metabolism, to any clinically relevant extent, of other actives substances that may be metabolised by these enzymes.

Biotransformation
Sunitinib is metabolised primarily by CYP3A4, the CYP isoform which produces its primary active metabolite, desethyl sunitinib, which is then further metabolised by the same isoenzyme.

Co-administration of sunitinib with potent CYP3A4 inducers or inhibitors should be avoided because the plasma levels of sunitinib may be altered (see sections 4.4 and 4.5).

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

Co-administration with medicinal products that are BCRP inhibitors
In vitro, sunitinib is a substrate of the efflux transporter BCRP. In study A6181038 the co-administration of gefitinib, a BCRP inhibitor, did not result in a clinically relevant effect on the C_{max} and AUC for sunitinib or total drug (sunitinib + metabolite) (see section 4.5). This study was a multi-centre, open-label, Phase 1/2 study examining the safety/tolerability, the maximum tolerated dose, and the antitumour activity of sunitinib in combination with gefitinib in subjects with MRCC. The PK of gefitinib (250 mg daily) and sunitinib (37.5 mg [Cohort 1, n=4] or 50 mg [Cohort 2,

n=7] daily on a 4-weeks on followed by 2 weeks-off schedule) when co-administered was evaluated as a secondary study objective. Changes in sunitinib PK parameters were of no clinical significance and did not indicate any drug-drug interactions; however, considering the relatively low number of subjects (i.e. N=7+4) and the moderate-large interpatient variability in the pharmacokinetic parameters, caution needs to be taken when interpreting the PK drug-drug interaction findings from this study.

Special populations

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

Studies in cancer patients have excluded patients with ALT or AST > 2.5 x ULN (upper limit of normal) or > 5.0 x ULN if due to liver metastasis.

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

Weight, performance status
Population 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.

Paediatric population
Experience on the use of sunitinib in paediatric patients is limited (see section 4.2). Population PK analyses of a pooled dataset from adult patients with GIST and solid tumours and paediatric patients with solid tumours were completed. Stepwise covariate modelling analyses were performed to evaluate the effect of age and body size (total body weight or body surface area) as well as other covariates on important PK parameters for sunitinib and its active metabolite. Among age and body-size related covariates tested, age was a significant covariate on apparent clearance of sunitinib (the younger the age of the paediatric patient, the lower the apparent clearance). Similarly, body surface area was a significant covariate on the apparent clearance of the active metabolite (the lower the body surface area, the lower the apparent clearance).

Furthermore, based on an integrated population PK analysis of pooled data from the 3 paediatric studies (2 paediatric solid tumor studies and 1 paediatric GIST study; ages: 6 years to 11 years and 12 years to 17 years), baseline body surface area (BSA) was a significant covariate on apparent clearance of sunitinib and its active metabolite. Based on this analysis, a dose of approximately 20 mg/m^2 daily in paediatric patients, with BSA values between 1.10 and 1.87 m^2, is expected to provide plasma exposures to sunitinib and its active metabolite comparable (between 75 and 125% of the AUC) to those in adults with GIST administered sunitinib 50 mg daily on Schedule 4/2 (AUC 1233 ng.hr/mL). In paediatric studies, the starting dose of sunitinib was 15 mg/m^2 (based on the MTD identified in the Phase 1 dose-escalation study, see section 5.1), which in paediatric patients with GIST increased to 22.5 mg/m^2 and subsequently to 30 mg/m^2 (not to exceed the total dose of 50 mg/day) based on

individual patient safety/tolerability. Furthermore, according to the published literatures in paediatric patients with GIST, the calculated starting dose ranged from 16.6 mg/m^2 to 36 mg/m^2, increased to doses as high as 40.4 mg/m^2 (not exceeding the total dose of 50 mg/day).

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 male or female fertility were observed in reproductive toxicity studies. However, in repeated-dose toxicity studies performed in rats and monkeys, effects on female fertility were observed in the form of follicular atresia, degeneration of corpora lutea, endometrial changes in the uterus and decreased uterine and ovarian weights at clinically relevant systemic exposure levels. Effects on male fertility in rat were observed in the form of tubular atrophy in the testes, reduction of

spermatozoa in epididymides and colloid depletion in prostate and seminal vesicles at plasma exposure levels 25 times the systemic exposure in humans.

In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions, increased post implantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5 times the systemic exposure in humans. In rabbits, reductions in gravid uterine weights and number of live foetuses were due to increases in the number of resorptions, increases in post implantation loss and complete litter loss in 4 of 6 pregnant females at plasma exposure levels 3 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 foetal skeletal malformations, predominantly characterised as retarded ossification of thoracic/lumbar vertebrae and occurred at plasma exposure levels 5.5 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Cellulose, microcrystalline (E460)
Mannitol (E421)
Croscarmellose sodium
Povidone (E1201)
Magnesium stearate (E470b)

<u><Product name> 12.5 mg hard capsules</u>
Capsule shell
Red iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Printing ink, white
Shellac
Titanium dioxide (E171)
Propylene glycol (E1520)

<u><Product name> 25 mg hard capsules</u>
Capsule shell
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Printing ink, white

Shellac
Titanium dioxide (E171)
Propylene glycol (E1520)

<Product name> 37.5 mg hard capsules
Capsule shell
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Printing ink, black
Shellac
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonium hydroxide (E527)

<Product name> 50 mg hard capsules
Capsule shell
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Printing ink, white
Shellac
Titanium dioxide (E171)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Carton box with Aluminium-OPA/Alu/PVC blisters containing 28 hard capsules.
Carton box with Aluminium-OPA/Alu/PVC perforated unit-dose blisters containing 28 x 1 hard capsules.
Carton box with Aluminium-OPA/Alu/PVC perforated unit-dose blisters containing 30 x 1 hard capsules.
Carton box with High Density Polyethylene (HDPE) bottles with a polypropylene (PP) child resistant closure (screw cap) containing 30 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Ltd
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ierland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 123584 Sunitinib Mylan 12,5 mg, harde capsules
RVG 123597 Sunitinib Mylan 25 mg, harde capsules
RVG 123598 Sunitinib Mylan 37,5 mg, harde capsules
RVG 123599 Sunitinib Mylan 50 mg, harde capsules

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 15 maart 2019
Datum van laatste verlenging van de vergunning: 27 februari 2024

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 4.4, 4.8: 12 september 2024