For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory Only

HEALTINIB

WARNING : HEPATOTOXICITY

Hepatotoxicity has been observed in clinical trials and postmarketing experience.
Hepatotoxicity may be serere, and, and in some cases fatal.
Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.

1. **Generic Name**

Sunitinib Malate Capsules

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:
Sunitinib Malate equivalent to Sunitinib…….12.5mg/25mg/50mg
Excipients…….q.s.
Approved colours used in capsule shells.

The excipients used are Mannitol, Croscarmellose Sodium and Magnesium Stearate.

3. Dosage form and strength

Dosage form: Hard gelatin capsule

Strength : 12.5/25/50 mg

4. Clinical particulars

4.1 Therapeutic indication

Sunitinib Malate Capsules 12.5/25/50

For the treatment of G.I. Stromal tumor after disease progression on or intolerance to imatinib mesylate and advanced renal cell carcinoma.

Sunitinib Malate Capsules 12.5/25

Treatment of Unresectable or Metastatic well differentiated pancreatic neuroendocrine tumours with disease progression in adults.

4.2 Posology and method of administration

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

Posology

For GIST and MRCC, the recommended dose of Sunitinib Malate 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 Malate 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. 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. 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 Malate in patients below 18 years of age have not been established. Currently available data are described in sections 4.8, 5.2, and 5.3 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.

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.

Method of administration

Sunitinib Malate 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.

4.4 Special warnings and precautions for use

Co-administration with potent CYP3A4 inducers should be avoided because it may decrease sunitinib plasma concentration. Co-administration with potent CYP3A4 inhibitors should be avoided because it may increase the plasma concentration of sunitinib.

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.

Haemorrhage and tumour bleeding

Haemorrhagic events, some of which were fatal, reported in clinical studies with sunitinib and during postmarketing surveillance have included gastrointestinal, respiratory, urinary tract, and brain haemorrhages

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 postmarketing experience in patients treated with sunitinib for MRCC, GIST, and lung cancer. Sunitinib Malate 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. 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.

Haematological disorders

Decreased absolute neutrophil counts and decreased platelet counts were reported in association with sunitinib. 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 postmarketing 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.

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.

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.

QT interval prolongation

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 anti-arrhythmics 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.

Venous thromboembolic events

Treatment-related venous thromboembolic events were reported in patients who received sunitinib including deep venous thrombosis and pulmonary embolism. Cases of pulmonary embolism with fatal outcome have been observed in postmarketing surveillance.

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.

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.

Thrombotic microangiopathy (TMA)

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.

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.

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. 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.

Renal function

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

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 Malate. 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 Malate and intravenous bisphosphonates are used either simultaneously or sequentially. Invasive dental procedures are also an identified risk factor. Prior to treatment with Sunitinib Malate, 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.

Hypersensitivity/angioedema

If angioedema due to hypersensitivity occurs, sunitinib treatment should be interrupted and standard medical care provided.

Seizures

In clinical studies of sunitinib and from postmarketing 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**.**

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.

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. 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 antidiabetic medicinal product's dosage needs to be adjusted to minimise the risk of hypoglycaemia.

4.5 Drugs interactions

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 (Cmax) and area under the curve ($AUC0^{-\infty}$) 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 Sunitinib Malate 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. 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.

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] Cmax and $AUC0^{-\infty}$ 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 Sunitinib Malate 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.

4.6 Use in Special Populations

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 Malate.

Pregnancy

There are no studies in pregnant women using sunitinib. Studies in animals have shown reproductive toxicity including foetal malformations. Sunitinib Malate 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 Malate is used during pregnancy or if the patient becomes pregnant while on treatment with Sunitinib Malate, 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 Malate.

Fertility

Based on nonclinical findings, male and female fertility may be compromised by treatment with sunitinib.

4.7 Effects on ability to drive and use machines

Sunitinib Malate 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).

Adverse reactions reported in clinical trials

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known**

Infections and infestations		Viral infections[a] Respiratory infections[b],* Abscess[c],* Fungal infections[d] Urinary tract infection Skin infections[e] Sepsis[f],*	Necrotising fasciitis* Bacterial Infections[g]		
Blood and lymphatic disorders	Neutropoenia Thrombocytopoenia Anaemia Leukopoenia	Lymphopoenia	Pancytopenia	Thrombotic micro-angiopathy[h], *	
Immune system disorders			Hypersensitivity	Angioedema	
Endocrine disorders	Hypo-thyroidism		Hyper-thyroidism	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*	
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 Nasal congestion Nasal dryness	Pulmonary haemorrhage* Respiratory failure*		
Gastrointestinal disorders	Stomatitis[o] Abdominal pain[p] Vomiting Diarrhoea Dyspepsia Nausea	Gastro-oesophageal reflux disease Dysphagia Gastrointestinal haemorrhage* Oesophagitis*	Gastro-intestinal perforation[q],* Pancreatitis Anal fistula Colitis[r]		

	Constipation	Abdominal distension Abdominal discomfort Rectal haemorrhage Gingival bleeding Mouth ulceration Proctalgia Cheilitis Haemorrhoids Glossodynia Oral pain Dry mouth Flatulence Oral discomfort Eructation			
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 hyperpigmenta		Erythema multiforme* Stevens-Johnson syndrome Pyoderma gangrenosum Toxic epidermal necrolysis*	

		tion Skin lesion Hyperkeratosis Dermatitis Nail disorder[w]			
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 increased Alanine	Blood creatinine phosphokinase increased Blood thyroid stimulating hormone increased		

		aminotransferase increased Blood creatine increased Blood pressure increased Blood uric acid increased			

* Including fatal events.

The following terms have been combined:

[a]Nasopharyngitis and oral herpes.

Bronchitis, lower respiratory tract infection, pneumonia, and respiratory tract infection. 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.

Cellulitis and skin infection.

Sepsis and sepsis shock.

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.

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.

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

Immune system disorders

Hypersensitivity reactions, including angioedema, have been reported.

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 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 Malate is not approved for use in breast cancer. In 1 study, hypothyroidis 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 patient 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.

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.

Nervous system disorders

In clinical studies of sunitinib and from postmarketing 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.

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%) ha 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 postmarketing 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 Phas 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 postmarketing 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.

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.

Skin and subcutaneous tissue disorders

Cases of pyoderma gangrenosum, generally reversible after discontinuation of sunitinib, have been reported.

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.

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

Cases of ONJ have been reported in patients treated with Sunitinib Malate, 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.

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).

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 ½ single-arm study and from publications a 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.

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 ½ 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 side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

There is no specific antidote for overdose with Sunitinib Malate 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

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors

ATC Code: L01XE01

5.1 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 (PDGFR and PDGFR-), VEGF 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.

5.2 Pharmacodynamic Properties

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 5.2 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 below:

GIST summary of efficacy endpoints (ITT population)

Double-blind treatment[a]						
Endpoint	**Sunitinib Malate**	**Median (95% CI) Placebo**	**(95% CI)**	**Hazard ratio**	**p-value**	**Placebo cross-over group treatment[b]**
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 Malate 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 nonconsecutive 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- 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.

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-=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-. 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 nonfunctioning 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: 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 below.

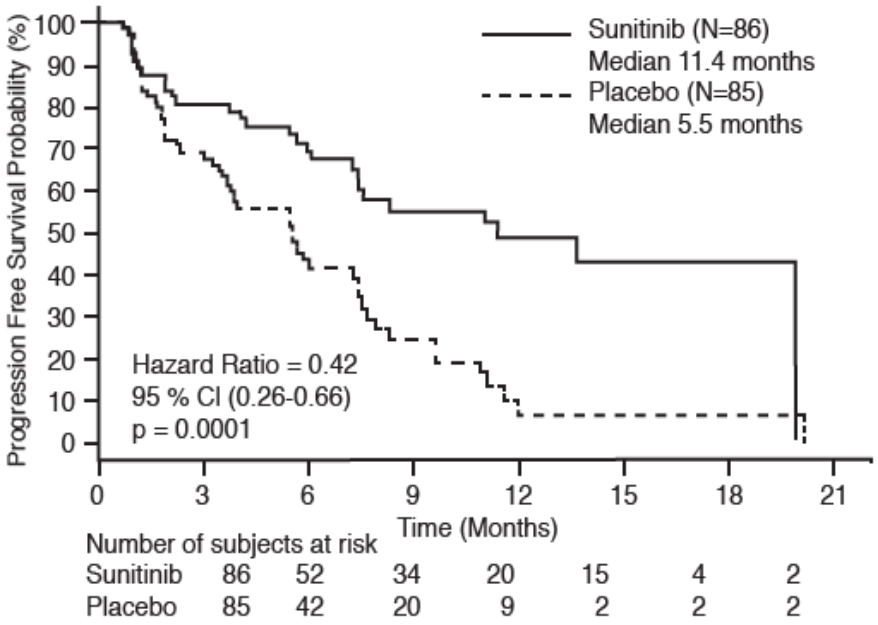
pNET efficacy results from the Phase 3 study

Efficacy parameter	**Sunitinib Malate (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	12.6 (11.1, 20.6)	5.8 (3.8, 7.2)	0.315 (0.181, 0.546)	0.000015[a]

of tumour assessments				
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]

[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).

Paediatric population

Experience on the use of sunitinib in paediatric patients is limited.

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/m2 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.

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%]).

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/m2 daily and 30 mg/m2 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 ½ 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 Sunitinib Malate 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).

The EMA has waived the obligation to submit the results of the studies with Sunitinib Malate in all subsets of the paediatric population for the treatment of gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, and phaeochromocytoma).

5.3 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 targe 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, Cmax are generally observed from 6 to 12 hours time to maximum concentration (tmax) 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 (V_d) 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 active 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.

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 Cmax 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 Malate 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 tumour 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 1.87m2, 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 doseescalation study, see section 5.2), which in paediatric patients with GIST increased to 22.5 mg/m^2 and

subsequently to 30 mg/m2 (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/m2 to 36 mg/m^2, increased to doses as high as 40.4 mg/m2 (not exceeding the total dose of 50 mg/day).

6. Nonclinical properties

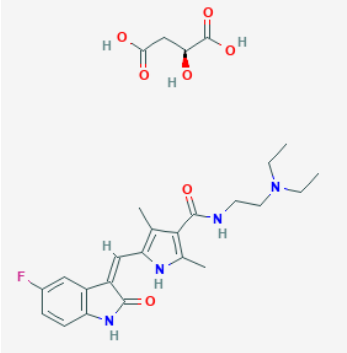
6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of sunitinib has been evaluated in 2 species: rasH2 transgenic mice and Sprague-Dawley rats. There were similar positive findings in both species. In rasH2 transgenic mice, gastroduodenal carcinomas and/or gastric mucosal hyperplasia, as well as an increased incidence of background hemangiosarcomas were observed at doses ≥25 mg/kg/day following daily dose administration of sunitinib in studies of 1 or 6 months duration. No proliferative changes were observed in rasH2 transgenic mice at 8 mg/kg/day. Similarly, in a 2-year rat carcinogenicity study, administration of sunitinib in 28-day cycles followed by 7-day dose-free periods resulted in findings of duodenal carcinoma at doses as low as 1 mg/kg/day (approximately 0.9 times the AUC in patients given the RDD of 50 mg/day). At the high dose of 3 mg/kg/day (approximately 8 times the AUC in patients at the RDD of 50 mg/day), the incidence of duodenal tumors was increased and was accompanied by findings of gastric mucous cell hyperplasia and by an increased incidence of pheochromocytoma and hyperplasia of the adrenal gland. Sunitinib did not cause genetic damage when tested in in vitro assays (bacterial mutation [Ames test], human lymphocyte chromosome aberration) and an in vivo rat bone marrow micronucleus test. In a female fertility and early embryonic development study, female rats were administered oral sunitinib (0.5, 1.5, 5 mg/kg/day) for 21 days prior to mating and for 7 days after mating. Preimplantation loss was observed in female administered 5 mg/kg/day (approximately 5 times the AUC in patients administered the RDD of 50 mg/day). No adverse effects on fertility were observed at doses ≤1.5 mg/kg/day (approximately 1 time the clinical AUC at the RDD of 50 mg/day). In addition, effects on the female reproductive system were identified in a 3-month oral repeat-dose monkey study (2,6,12 mg/kg/day). Ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (approximately 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day (approximately 0.8 times the AUC in patients administered the RDD) in a 9-month monkey study (0.3, 1.5, and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite). In a male fertility study, no reproductive effects were observed in male rats dosed with 1,3, or 10 mg/kg/day oral sunitinib for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day approximately ≥26 times the AUC in patients administered the RDD).

7. Description

Sunitinib malate

Sunitinib malate is N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide;(2S)-2-hydroxybutanedioic acid. The empirical formula is $C_{26}H_{33}FN_4O7$ and the molecular weight is 532.6 6 g/mol. The chemical structure of Sunitinib malate is:



HEALTINIB 12.5

Sunitinib malate capsules is yellow to orange free flowing granules filled in size "5" white to off white colored hard gelatin capsules. The excipients used are Mannitol, Croscarmellose Sodium and Magnesium Stearate.

HEALTINIB 25

Sunitinib malate capsules is yellow to orange free flowing granules filled in size "4" white to off white colored hard gelatin capsules. The excipients used are Mannitol, Croscarmellose Sodium and Magnesium Stearate.

HEALTINIB 50

Sunitinib malate capsules is yellow to orange free flowing granules filled in size "1" white to off white colored hard gelatin capsules. The excipients used are Mannitol, Croscarmellose Sodium and Magnesium Stearate.

8. Pharmaceutical particulars

8.1 Incompatibilities:

Not applicable

8.2 Shelf-life:

Do not use later than date of expiry.

8.3 Packaging information

HEALTINIB is available in Blister Strip of 7 Capsules.

8.4 Storage and handling instructions

- Do not store above 30°C. Protect from light and moisture.
- Keep the medicine out of the reach and sight of children.
- Any unused product or waste material should be disposed of in accordance with local requirements.

9. Patient Counselling Information

HEALTINIB

Sunitinib Malate Capsules

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- Keep all medicines out of reach of children
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What HEALTINIB is and what it is used for

9.2.What you need to know before you take HEALTINIB

9.3.How to take HEALTINIB

9.4.Possible side effects

9.5.How to store HEALTINIB

9.6.Contents of the pack and other information

9.1 What HEALTINIB is and what it is used for

HEALTINIB contains the active substance sunitinib, which is a protein kinase inhibitor. It is used to treat cancer by preventing the activity of a special group of proteins which are known to be involved in the growth and spread of cancer cells.

HEALTINIB is indicated:

Sunitinib Malate Capsules 12.5/25/50

- For the treatment of G.I. Stromal tumor after disease progression on or intolerance to imatinib mesylate and advanced renal cell carcinoma.

Sunitinib Malate Capsules 12.5/25

- Treatment of Unresectable or Metastatic well differentiated pancreatic neuroendocrine tumours with disease progression in adults.

If you have any questions about how HEALTINIB works or why this medicine has been prescribed for you, ask your doctor.

9.2 What you need to know before you take HEALTINIB

Do not take HEALTINIB

- If you are allergic to sunitinib or any of the other ingredients of HEALTINIB.

Warnings and precautions

Talk to your doctor before taking HEALTINIB:

- If you have high blood pressure. HEALTINIB can raise blood pressure. Your doctor may check your blood pressure during treatment with HEALTINIB, and you may be treated with medicines to reduce the blood pressure, if needed.
- If you have or have had blood disease, bleeding problems, or bruising. Treatment with HEALTINIB may lead to a higher risk of bleeding or lead to changes in the number of certain cells in the blood which may lead to anaemia or affect the ability of your blood to clot. If you are taking warfarin or acenocoumarole, medicines which thin the blood to prevent blood clots, there may be a greater risk of bleeding. Tell your doctor if you have any bleeding while on treatment with HEALTINIB.
- If you have heart problems. HEALTINIB can cause heart problems. Tell your doctor if you feel very tired, are short of breath, or have swollen feet and ankles.
- If you have abnormal heart rhythm changes. HEALTINIB can cause abnormality of your heart rhythm. Your doctor may obtain electrocardiograms to evaluate for these problems during your treatment with HEALTINIB. Tell your doctor if you feel dizzy, faint, or have abnormal heartbeats while taking HEALTINIB.
- If you have had a recent problem with blood clots in your veins and/or arteries (types of blood vessels), including stroke, heart attack, embolism, or thrombosis.

Call your doctor immediately if you get symptoms such as chest pain or pressure, pain in your arms, back, neck or jaw, shortness of breath, numbness or weakness on 1 side of your body, trouble talking, headache, or dizziness while on treatment with HEALTINIB.

- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- If you have or have had damage to the smallest blood vessels known as thrombotic microangiopathy (TMA). Tell your doctor if you develop fever, fatigue, tiredness, bruising, bleeding, swelling, confusion, vision loss, and seizures.
- If you have thyroid glands problems. HEALTINIB can cause thyroid gland problems. Tell your doctor if you get tired more easily, generally feel colder than other people, or your voice deepens whilst taking HEALTINIB. Your thyroid function should be checked before you take HEALTINIB and regularly while you are taking it. If your thyroid gland is not producing enough thyroid hormone, you may be treated with thyroid hormone replacement.
- If you have or have had pancreatic or gallbladder disorders. Tell your doctor if you develop any of the following signs and symptoms: pain in the area of the stomach (upper abdomen), nausea, vomiting, and fever. These may be caused by inflammation of the pancreas or gallbladder.
- If you have or have had liver problems. Tell your doctor if you develop any of the following signs and symptoms of liver problems during HEALTINIB treatment: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor

should do blood tests to check your liver function before and during treatment with HEALTINIB, and as clinically indicated.

- If you have or have had kidney problems. Your doctor will monitor your kidney function.
- If you are going to have surgery or if you had an operation recently. HEALTINIB may affect the way your wounds heal. You will usually be taken off HEALTINIB if you are having an operation. Your doctor will decide when to start HEALTINIB again.
- You may be advised to have a dental check-up before you start treatment with HEALTINIB.
- If you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth, tell your doctor and dentist immediately.
- If you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with HEALTINIB in particular when you are also receiving or have received intravenous bisphosphonates. Bisphosphonates are medicines used to prevent bone complications that may have been given for another medical condition.
- If you have or have had skin and subcutaneous tissue disorders. While you are on this medicine "pyoderma gangrenosum" (painful skin ulceration) or “necrotising fasciitis” (rapidly spreading infection of the skin/soft tissue that may be life-threatening) may occur. Contact your doctor immediately if symptoms of infection occur around a skin injury, including fever, pain, redness, swelling, or drainage of pus or blood. This event is generally reversible after HEALTINIB discontinuation. Severe skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) have been reported with the use of HEALTINIB, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. The rash may progress to widespread blistering or peeling of the skin and may be life-threatening. If you develop a rash or these skin symptoms, seek immediate advice from a doctor.
- If you have or have had seizures. Notify your doctor as soon as possible if you have high blood pressure, headache, or loss of sight.
- If you have diabetes. Blood sugar levels in diabetic patients should be checked regularly in order to assess if antidiabetic medicine’s dosage needs to be adjusted to minimise the risk of low blood sugar. Notify your doctor as soon as possible if you experience any signs and symptoms of low blood sugar (fatigue, palpitations, sweating, hunger and loss of consciousness).

HEALTINIB with food and drink

You should avoid drinking grapefruit juice while on treatment with HEALTINIB.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. If you might get pregnant, you should use a reliable method of contraception during treatment with HEALTINIB. If you

are breast-feeding, tell your doctor. You should not breast-feed during treatment with HEALTINIB.

Driving and using machines

If you experience dizziness or you feel unusually tired, take special care when driving or using machines.

HEALTINIB contains sodium

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

9.3 How to take HEALTINIB

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Your doctor will prescribe a dose that is right for you, depending on the type of cancer to be treated. If you are being treated for:

- GIST or MRCC: the usual dose is 50 mg once daily taken for 28 days (4 weeks), followed by 14 days (2 weeks) of rest (no medicine), in 6-week cycles.
- pNET: the usual dose is 37.5 mg once daily without a rest period.

Your doctor will determine the appropriate dose you need to take, as well as if and when you need to stop treatment with HEALTINIB.

HEALTINIB can be taken with or without food.

If you take more HEALTINIB than you should

If you have accidentally taken too many capsules, talk to your doctor straight away. You may require medical attention.

If you forget to take HEALTINIB

Do not take a double dose to make up for a forgotten dose.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor immediately or contact the casualty department at your nearest hospital, if you get any of the following serious side effects:

The following side effects have been reported:

<u>Infections and infestations:</u>

Common

- Viral infections
- Respiratory infections,
- Abscess,
- Fungal infections
- Urinary tract infection

- Skin infections
- Sepsis

Uncommon

- Necrotising fasciitis
- Bacterial Infections

Blood and lymphatic disorders:

Very common

- Neutropoenia
- Thrombocytopoenia
- Anaemia
- Leukopoenia

Common

- Lymphopoenia

Uncommon

- Pancytopenia

Rare

- Thrombotic micro angiopathy

Immune system disorders:

Uncommon

- Hypersensitivity

Rare

- Angioedema

Endocrine disorders

Very Common

- Hypo-thyroidism

Uncommon

- Hyper-thyroidism

Rare

- Thyroiditis

Metabolism and nutrition disorders

Very Common

- Decreased appetite

Common

- Dehydration
- Hypoglycaemia

Rare

- Tumour lysis syndrome

Psychiatric disorders

Very Common

- Insomnia

Common

- Depression

Nervous system disorders

Very Common

- Dizziness
- Headache
- Taste disturbance

Common

- Neuropathy peripheral
- Paraesthesia
- Hypoaesthesia
- Hyperaesthesia

Uncommon

- Cerebral haemorrhage
- Cerebrovascular accident
- Transient ischaemic attack

Rare

- Posterior reversible encephalopathy syndrome

Eye disorders

Common

- Periorbital oedema
- Eyelid oedema
- Lacrimation increased

Cardiac disorders

Common

- Myocardial ischemia,
- Ejection fraction decreased

Uncommon

- Cardiac failure congestive
- Myocardial infarction
- Cardiac failure
- Cardiomyopathy
- Pericardial effusion
- Electrocardiogram
- QT prolonged

Rare

- Left ventricular failure
- Torsade de pointes

Vascular disorders

Very common

- Hypertension

Common

- Deep vein thrombosis
- Hot flush
- Flushing

Uncommon

- Tumour haemorrhage

Unknown

- Aneurysms and artery dissections

Respiratory, thoracic and mediastinal disorders

Very common

- Dyspnoea
- Epistaxis
- Cough

Common

- Pulmonary embolism
- Pleural effusion
- Haemoptysis
- Dyspnoea
- exertional Oropharyngeal pain
- Nasal congestion Nasal dryness

Uncommon

- Pulmonary haemorrhage
- Respiratory failure

Gastrointestinal disorders

Very common

- Stomatitis
- Abdominal pain
- Vomiting
- Diarrhoea
- Dyspepsia
- Nausea
- Constipation

Common

- Gastro-oesophageal reflux disease
- Dysphagia
- Gastrointestinal haemorrhage
- Oesophagitis
- Abdominal distension
- Abdominal discomfort
- Rectal haemorrhage
- Gingival bleeding
- Mouth ulceration
- Proctalgia
- Cheilitis
- Haemorrhoids
- Glossodynia
- Oral pain
- Dry mouth Flatulence
- Oral discomfort Eructation

Uncommon

- Gastro-intestinal perforation
- Pancreatitis
- Anal fistula
- Colitis

Hepatobiliary disorders

Uncommon

- Hepatic failure
- Cholecystitiss,
- Hepatic function abnormal

Rare

Hepatitis

Skin and subcutaneous tissue disorders

Very common

- Skin discolouration
- Palmar-plantar erythrodysaesthesia syndrome
- Rash
- Hair colour changes
- Dry skin

Common

- Skin exfoliation
- Skin reaction
- Eczema
- Blister
- Erythema
- Alopecia
- Acne
- Pruritus
- Skin hyperpigmentation
- Skin lesion
- Hyperkeratosis
- Dermatitis
- Nail disorder

Rare

- Erythema multiform
- Stevens- Johnson syndrome
- Pyoderma gangrenosum
- Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Very common

- Pain in extremity
- Arthralgia
- Back pain

Common

- Musculoskeletal pain
- Muscle spasms Myalgia
- Muscular weakness

Uncommon

- Osteonecrosis of the jaw Fistula

Rare

- Rhabdomyolysis
- Myopathy

Renal and urinary disorders

Common

- Renal failure
- Renal failure acute
- Chromaturia
- Proteinuria

Uncommon

- Haemorrhage urinary tract

Rare

- Nephrotic syndrome

General disorders and administration site conditions

Very common

- Mucosal inflammation
- Fatigue
- Oedema
- Pyrexia

Common

- Chest pain
- Pain Influenza like illness
- Chills

Rare

- Impaired healing

Investigations

Common

- Weight decreased
- White blood cell count decreased
- Lipase increased
- Platelet count decreased
- Haemoglobin decreased
- Amylase increased
- Aspartate aminotransferase increased
- Alanine aminotransferase increased
- Blood creatine increased
- Blood pressure increased
- Blood uric acid increased

Uncommon

- Blood creatinine phosphokinase increased
- Blood thyroid stimulating hormone increased

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store HEALTINIB

Do not store above 30°C. Protect from light and moisture.

9.6 Contents of the pack and other information

HEALTINIB consists of Sunitinib malate as active ingredient in the strength of 12.5mg/25mg/50mg.

HEALTINIB 12.5: Sunitinib malate capsules is yellow to orange free flowing granules filled in size "5" white to off white colored hard gelatin capsules.

HEALTINIB 25: Sunitinib malate capsules is yellow to orange free flowing granules filled in size "4" white to off white colored hard gelatin capsules.

HEALTINIB 50: Sunitinib malate capsules is yellow to orange free flowing granules filled in size "1" white to off white colored hard gelatin capsules.

The excipients used are Mannitol, Croscarmellose Sodium and Magnesium Stearate.

HEALTINIB is available in Blister Strip of 7 Capsules.

10. Details of manufacturer

Manufactured by:

BDR Pharmaceuticals Int'l Pvt. Ltd.

R. S. No. 578, Near Effluent Channel Road,

Vill. Luna, Tal. Padra, Dist. Vadodara - 391440. Gujarat.

11. Details of permission or licence number with date

Mfg Lic No. G/25/2071 issued on 27.01.2021

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/HEALTINIB 12.5/25/50 mg/APR-21/01/PI