NIBSUTIB (Sunitinib Hard Capsules 12.5mg)

1. NAME OF THE MEDICINAL PRODUCT
NIBSUTIB (Sunitinib Hard Capsules 12.5mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
NIBSUTIB (Sunitinib Hard Capsules 12.5mg)
Each capsule contains sunitinib malate equivalent to 12.5 mg of sunitinib.

For the full list of excipients, see section "List of Excipients"

3. PHARMACEUTICAL FORM
Hard Capsule

Yellow to Orange colored granules filled in hard gelatin capsules with Reddish Orange colored cap and Reddish Orange colored body imprinted 'SC' on cap and '12.5' on body with black imprinting ink.

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
4.1.1 Gastrointestinal Stromal Tumor (GIST)
NIBSUTIB is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

4.1.2 Advanced Renal Cell Carcinoma (RCC)
NIBSUTIB is indicated for the treatment of advanced renal cell carcinoma.

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

4.2 Posology and method of administration
4.2.1 Recommended Dose
For *GIST* and Advanced *RCC*, the recommended dose of sunitinib is 50 mg taken orally once daily for 4 consecutive weeks, followed by a 2-week off period (Schedule 4/2) to comprise a complete cycle of 6 weeks.

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

Sunitinib 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.

4.2.2 Dose Modifications
Safety and Tolerability
For GIST and Advanced RCC, dose modifications in 12.5 mg increments or decrements may be applied based on individual safety and tolerability up to 75 mg or down to 25 mg.

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

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

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

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

Selection of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP3A4 is recommended.

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

Use in the Elderly
Dose adjustments are not required in elderly patients. Approximately 34% of the subjects in clinical studies of sunitinib were 65 years of age or over. No significant differences in safety or efficacy were observed between younger and older patients.

Hepatic Insufficiency
No dose adjustment is necessary when administering sunitinib to patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Sunitinib was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment (***see Section 5.2***).

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

4.3 Contraindications
Use of sunitinib is contraindicated in patients with hypersensitivity to sunitinib or to any of the excipients.

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

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

Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM) and cases suggestive of Stevens-Johnson syndrome (SJS), some of which were fatal. If signs or symptoms of SJS or EM (e.g., progressive skin rash often with blisters or mucosal lesions) are present, sunitinib treatment should be discontinued. If the diagnosis of SJS is confirmed, treatment must not be re-started. In some cases of suspected EM, patients tolerated the reintroduction of sunitinib therapy at a lower dose after

resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines.

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

Treatment-emergent bleeding events occurred in 18% of subjects receiving sunitinib in the double- blind treatment phase of GIST Study compared to 17% of subjects receiving placebo. In subjects receiving sunitinib for treatment-naïve advanced RCC, 39% of patients had bleeding events compared with 11% of subjects receiving interferon-α (IFN-α). Seventeen (4.5%) subjects on sunitinib versus 5 (1.7%) of subjects on IFN-α experienced Grade 3 or greater bleeding events. Of subjects receiving sunitinib for cytokine-refractory advanced RCC, 26% experienced bleeding. Bleeding events, excluding epistaxis, occurred in 21.7% of subjects receiving sunitinib in the phase 3 pNET study compared to 9.85% of subjects receiving placebo. Routine assessment of these events should include complete blood counts and physical examination.

Gastrointestinal Tract
Serious, sometimes fatal GI complications including GI perforation, have occurred in subjects with intra-abdominal malignancies treated with sunitinib.

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

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

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 tumor patients treated with sunitinib. Monitor liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) before initiation of treatment, during each cycle of treatment, and as clinically indicated. Sunitinib should be interrupted for Grade 3 or 4 hepatic-related adverse events and discontinued if there is no resolution.

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

Complete blood counts should be performed at the beginning of each treatment cycle for patients

receiving treatment with sunitinib.

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

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

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

Subjects who presented with cardiac events, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism within 12 months prior to sunitinib administration, were excluded from sunitinib clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

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

QT Interval Prolongation
At approximately twice the therapeutic concentrations, sunitinib has been shown to prolong the QTcF (Fridericia's correction) interval (***see Section 5.2***). There were no patients with greater than Grade 2 Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) QT/QTc interval prolongation. QT interval prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. Torsade de pointes has been observed in <0.1% of sunitinib-exposed patients. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of sunitinib reduced (***see Sections 4.2 and 4.5***).

Hypertension
Hypertension was a very common adverse reaction reported in clinical trials in subjects with solid tumors, including primarily GIST and cytokine-refractory RCC†. Sunitinib dosing was reduced or temporarily delayed in approximately 2.7% of this patient population. None of these subjects were discontinued from treatment with sunitinib. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 4.7% of this patient population. Hypertension was reported in approximately 33.9% of subjects receiving sunitinib for treatment-naïve advanced RCC compared to 3.6% of subjects receiving IFN-α. Severe hypertension occurred in 12% of treatment-naïve subjects on

sunitinib and <1% of patients on IFN-α. Hypertension was reported in 26.5% of subjects receiving sunitinib in a phase 3 pNET study, compared to 4.9% of subjects receiving placebo. Severe hypertension occurred in 10% of pNET subjects on sunitinib and 3% of subjects on placebo. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

Aneurysms and Artery Dissections
The use of vascular endothelial growth factor (VEGF) pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating sunitinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Thyroid Dysfunction
Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on sunitinib treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

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

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

Seizures
In clinical studies of sunitinib, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been rare (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Surgical Procedures
Cases of impaired wound healing have been reported during sunitinib therapy. Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of 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)
ONJ has been uncommonly observed in clinical trials and has been reported in post-marketing experience in patients treated with sunitinib. The majority of cases occurred in patients who had received prior or concomitant treatment with intravenous (IV) bisphosphonates, for which ONJ is an

identified risk. Caution should therefore be exercised when sunitinib and IV bisphosphonates are used either simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor for ONJ. Prior to treatment with sunitinib, a dental examination and appropriate preventive dentistry should be considered. In patients being treated with sunitinib, who have previously received or are receiving IV bisphosphonates, invasive dental procedures should be avoided, if possible.

Tumor Lysis Syndrome (TLS)
Cases of TLS, some fatal, have been rarely observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

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

Thrombotic Microangiopathy
Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of sunitinib as monotherapy and in combination with bevacizumab. Discontinue sunitinib in patients developing TMA. Reversal of the effects of TMA has been observed after treatment discontinuation.

Proteinuria
Cases of proteinuria and nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue sunitinib in patients with nephrotic syndrome.

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

4.5 Interaction with other medicinal products and other forms of interactions

*Drugs that may **increase** sunitinib plasma concentrations*:
Concomitant administration of sunitinib with the strong CYP3A4 inhibitor ketoconazole resulted in a 49% and 51% increase of the complex [sunitinib + primary active metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib in healthy volunteers.

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

*Drugs that may **decrease** sunitinib plasma concentrations*:
Concomitant use of sunitinib with the CYP3A4 inducer rifampin resulted in a 23% and 46% reduction of the complex [sunitinib + primary active metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib in healthy volunteers.

Administration of sunitinib with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or *Hypericum perforatum* also known as St. John's wort) may decrease sunitinib concentrations. Concomitant administration with inducers should therefore be avoided, or selection of an alternate concomitant medication with no, or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dosage of sunitinib may need to be increased (***see Section 4.2***).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no studies in pregnant women using sunitinib.

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

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and post-natal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at ≥1 mg/kg/day but no maternal reproductive toxicity was observed up to 3 mg/kg/day (estimate exposure ≥2.3 times the AUC in patients administered the recommended daily dose [RDD]). Reduced offspring body weights were observed during the pre-weaning and post-weaning periods at 3 mg/kg/day. No development toxicity was observed at 1 mg/kg/day (approximate exposure ≥0.9 times the AUC in patients administered the RDD).

Fertility

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

Lactation

Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should not breastfeed while taking sunitinib.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Table 1 presents the adverse drug reactions (ADRs) by system organ class (SOC) from single-agent studies (N=7527) in advanced RCC, GIST, pNET of RCC, and from the post-marketing experience. A dataset that pooled the 12 single-agent studies in the marketed indications was used to calculate causality. ADRs are listed within each SOC by decreasing medical seriousness or clinical importance.

Table 1: ADRs by System Organ Class and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
Infections and infestations	Infections*			
Blood and lymphatic system disorders	Anaemia Thrombocytopenia Neutropenia Leukopenia	Lymphopenia		Thrombotic microangiopathy[a,]**
Immune system disorders			Hypersensitivity	Angioedema
Endocrine disorders	Hypothyroidism		Hyperthyroidism	Thyroiditis
Metabolism and nutrition disorders	Decreased appetite	Dehydration** Hypoglycaemia		Tumour lysis syndrome**
Psychiatric disorders	Insomnia	Depression		
Nervous system disorders	Headache Dysgeusia	Dizziness Paraesthesia Ageusia	Cerebral haemorrhage** Cerebrovascular accident** Transient ischaemic attack	Cerebral infarction Posterior reversible encephalopathy syndrome
Eye disorders		Periorbital oedema Eyelid oedema Lacrimation increased		
Cardiac disorders		Myocardial ischaemia[b,]**	Myocardial infarction[c,]** Cardiac failure** Cardiomyopathy** Cardiac failure congestive	Left ventricular failure** Torsade de pointes
Vascular disorders	Hypertension	Deep vein thrombosis	Aneurysms and artery dissections[d,]** Tumour haemorrhage**	
Respiratory, thoracic and mediastinal disorders	Dyspnoea Epistaxis	Pulmonary embolism** Haemoptysis[e,]** Pleural effusion Oropharyngeal pain[f]		

Gastrointestinal disorders	Abdominal pain[g] Diarrhoea Vomiting Nausea Dyspepsia Stomatitis[h] Constipation	Gastrointestinal haemorrhage** Oesophagitis Abdominal distension Gastro-oesophageal reflux disease Oral pain Glossodynia Gingival bleeding Dry mouth Flatulence	Gastrointestinal perforation[i,]** Pancreatitis	
Hepatobiliary disorders			Hepatic failure** Cholecystitis[j]	
Skin and subcutaneous tissue disorders	Rash[k] Palmar-plantar erythrodysaesthesia syndrome Skin discolouration[l] Hair colour changes Dry skin	Skin reaction Skin lesion Erythema Pruritus Skin exfoliation Blister Alopecia Nail disorder	Dermatitis exfoliative	Stevens-Johnson syndrome** Erythema multiforme** Pyoderma gangrenosum
Musculoskeletal and connective tissue disorders	Arthralgia Pain in extremity	Myalgia	Fistula** Osteonecrosis of Jaw	Rhabdomyolysis** Myopathy
Renal and urinary disorders		Renal failure** Proteinuria Chromaturia	Nephrotic syndrome Renal impairment Haemorrhage urinary tract	
General disorders and administration site conditions	Fatigue[m] Mucosal inflammation Oedema[n] Pyrexia	Chills Influenza like illness		
Investigations		Ejection fraction decreased[o] Haemoglobin decreased Platelet count decreased White blood cell	Electrocardiogram QT Prolonged Blood thyroid stimulating hormone increased	

Infections and infestations are described in the subsection Description of Selected Adverse Reactions.
** Event may be fatal.
Abbreviations: ADRs=adverse drug reactions; CIOMS=Council for International Organizations of Medical Sciences.
[a] Thrombotic microangiopathy: The following terms have been combined: Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura, and Hemolytic uremic syndrome.
[b] Myocardial ischaemia: The following terms have been combined: Acute coronary syndrome, Angina pectoris, Angina

unstable, Coronary artery occlusion, and Myocardial ischaemia.
[c] Myocardial infarction: The following terms have been combined: Acute myocardial infarction, Myocardial infarction, and Silent myocardial infarction.
[d] Aneurysms and artery dissections: The following terms have been combined: Aneurysm ruptured, Aortic aneurysm, Aortic aneurysm rupture, and Aortic dissection.
[e] Haemoptysis: The following terms have been combined: Haemoptysis and Pulmonary haemorrhage.
[f] Oropharyngeal pain: The following terms have been combined: Laryngeal pain and Oropharyngeal pain.
[g] Abdominal pain: The following terms have been combined: Abdominal pain, Abdominal pain lower, and Abdominal pain upper.
[h] Stomatitis: The following terms have been combined: Stomatitis and Aphthous ulcer.
[i] Gastrointestinal perforation: The following terms have been combined: Gastrointestinal perforation and Intestinal perforation.
[j] Cholecystitis: The following terms have been combined: Cholecystitis and Acalculous cholecystitis.
[k] Rash: The following terms have been combined: Dermatitis psoriasiform, Exfoliative rash, Rash, Rash erythematous, Rash follicular, Rash generalised, Rash macular, Rash maculopapular, Rash papular, and Rash pruritic.
[l] Skin discolouration: The following terms have been combined: Skin discolouration, Yellow skin, and Pigmentation disorder.
[m] Fatigue: The following terms have been combined: Fatigue and Asthenia.
[n] Oedema: The following terms have been combined: Face oedema, Oedema, and Oedema peripheral.
[o] Ejection fraction decreased: The following terms have been combined: Ejection fraction decreased and Ejection fraction abnormal.
[p] Amylase increased: The following terms have been combined: Amylase and Amylase increased.

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

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

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

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

In clinical studies of sunitinib, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of RPLS (***see Section 4.4***).

Description of Selected Adverse Reactions

Infections and Infestations

Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported. The infections observed with sunitinib treatment are infections typically seen in cancer patients, e.g., respiratory infections (e.g., pneumonia, bronchitis), urinary tract infections, skin infections (e.g., cellulitis), sepsis/septic shock, and abscess (e.g., oral, genital, anorectal, skin, limb, visceral). Infections may be bacterial, viral, or fungal. Rare cases of necrotizing fasciitis, including of the perineum, sometimes fatal, have been reported.

Blood and Lymphatic System Disorders

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

Vascular Disorders

Arterial Thromboembolic Events (ATE)

Cases of arterial thromboembolic events (ATE), sometimes fatal, have been reported in patients treated with sunitinib. The most frequent events included cerebrovascular accident, transient 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.

Venous Thromboembolic Events (VTE)

In the double-blind treatment phase of GIST study, 7 patients (3%) on sunitinib and none on placebo experienced VTE; 5 of the 7 were Grade 3 deep vein 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 for treatment-naïve advanced RCC and 4 (2%) patients in the 2 cytokine-refractory advanced RCC studies had VTE reported. Nine of these patients had pulmonary embolism: 1 was Grade 2 and 8 were Grade 4. Eight 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 advanced RCC study experienced dose interruption. In treatment-naïve advanced RCC patients receiving IFN-α, 6 (2%) VTE occurred; 1 (<1%) patient experienced a Grade 3 DVT and 5 (1%) patients had pulmonary embolism, all Grade 4.

Pulmonary embolism was reported in approximately 2.2% of patients with solid tumors‡ who received sunitinib. None of these events resulted in a patient discontinuing treatment with sunitinib; however, a dose reduction or temporary delay in treatment occurred in a few cases. There were no further occurrences of pulmonary embolism in these patients after treatment was resumed.

Musculoskeletal and Connective Tissue Disorders

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

Long-term Safety in RCC

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sunitinib inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), VEGF receptors (VEGFR1, VEGFR2, and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets *in vivo* and demonstrated inhibition of tumor growth or tumor regression, and/or inhibited in metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) *in vitro* and to inhibit PDGFRβ- and VEGFR2-dependent tumor angiogenesis *in vivo.*

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

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

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

5.2 Pharmacokinetic properties

The pharmacokinetics of sunitinib and sunitinib malate were evaluated in 135 healthy volunteers and 266 subjects with solid tumors.

Absorption

Maximum plasma concentrations (C_{max}) are generally observed between 6 – 12 hours (T_{max}) following oral administration. Food has no effect on the bioavailability of sunitinib.

Distribution

Binding of sunitinib and its primary active metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no apparent concentration dependence in the range of 100 – 4000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was large (2230 L), indicating distribution into the tissues. In the dosing range of 25 – 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increased proportionately with dose.

Metabolism

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

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

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

Elimination

Excretion is primarily via feces (61%) with renal elimination of drug and metabolites accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug- related compounds identified in plasma, urine and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces, but generally were not found in plasma. Total oral clearance (CL/F) ranged from 34-62 L/hr with an inter-patient variability of 40%. Following administration of a single-oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active desethyl metabolite were approximately 40–60 hours, and 80–110 hours,

respectively.

Pharmacokinetics in special patient groups

Hepatic Insufficiency

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

Renal Insufficiency

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

Cardiac Electrophysiology

QT interval prolongation was investigated in a Phase 1 trial with 24 evaluable subjects, aged 20-87 years, with advanced malignancies. At therapeutic plasma concentrations, the maximum QTcF mean change from baseline was 9.6 msec (90% CI upper limit of 15.1 msec). At approximately twice the therapeutic concentrations, the maximum QTcF mean change from baseline was 15.4 msec (90% CI upper limit of 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 (CTCAE version 3.0). No patient presented with a cardiac arrhythmia (***see Section 4.4***).

Plasma Pharmacokinetics

Following administration of a single-oral dose in healthy volunteers, the elimination half-lives of sunitinib and its primary active metabolite are approximately 40 - 60 hours, and 80 - 110 hours, respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary active metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite are 62.9 - 101 ng/mL which are target concentrations predicted from preclinical data to inhibit receptor phosphorylation *in vitro* and result in tumor stasis/growth reduction *in vivo*. No significant changes in the pharmacokinetics of sunitinib or the primary, active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

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

Population Pharmacokinetics

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

Weight, performance status: Population pharmacokinetic analyses of demographic data indicate that no starting dose adjustments are necessary for weight or 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Mannitol (E421)
Croscarmellose sodium
Povidone (K-25)
Magnesium stearate

Capsule shell
Gelatin,
Purified Water,
SLS,
Titanium Dioxide,
Red Iron Oxide.

Printing ink
Shellac,
Dehydrated Alcohol,
Isopropyl Alcohol,
Butyl Alcohol,
Propylene Glycol,
Ammonia,
Black Iron Oxide,
Potassium Hydroxide,
Purified Water

6.2 Shelf-life
24 months

6.3 Special precautions for storage
Store at or below 30°C

6.4 Nature and contents of container
Blister of Hard tempered Aluminum foil with Clear, transparent, polyvinylchloride (PVC) film laminated with Aclar containing 7 capsules. Such 4 blisters are packed into an outer carton with a pack insert.

7. MANUFACTURER
Dr. Reddy’s Laboratories Ltd,
FTO 7, Plot No. P1 to P9,
Phase III, VSEZ, Duvvada,
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8. Product Registration Holder
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