Sutinib

Sunitinib Malate INN 50 mg Capsule

DRUG INTERNATIONAL LTD.

Composition: Sutinib: Each capsule contains Sunitinib 50 mg as Sunitinib Malate INN.

Mechanism of Action: Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Pharmacokinetics: Maximum plasma concentrations (Cmax) of Sunitinib are generally observed between 6 and 12 hours (time to maximum plasma concentration [Tmax]) following oral administration. Food has no effect on the bioavailability of Sunitinib. Sutinib may be taken with or without food. Binding of Sunitinib and its primary active metabolite to human plasma protein in vitro was 95% and 90%, respectively, with no concentration dependence in the range of 100–4000 ng/mL. The apparent volume of distribution (Vd/F) for Sunitinib was 2230 L. In the dosing range of 25-100 mg, the AUC and Cmax increase proportionately with dose. Following administration of a single oral dose in healthy volunteers, the terminal half-lives of Sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively. With repeated daily administration, Sunitinib accumulates 3-to 4-fold while the primary 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 ranged from 62.9–101 ng/mL. 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.

Pharmacokinetics in Special Populations: Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, race, gender, or Eastern Cooperative Oncology Group (ECOG) score on the pharmacokinetics of Sutinib or the primary active metabolite. **Pediatric Use:** The pharmacokinetics of Sutinib have not been evaluated in pediatric patients. **Renal Insufficiency:** Sunitinib systemic exposure after a single dose of Sutinib was similar in patients with severe renal impairment (CLcr <30 mL/min) compared to patients with normal renal function (CLcr >80 mL/min). Although Sunitinib was not eliminated through hemodialysis, the Sunitinib systemic exposure was 47% lower in patients with ESRD on hemodialysis compared to patients with normal renal function. **Hepatic Insufficiency:** Systemic exposures after a single dose of Sutinib were similar in patients with mild exocrine (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment compared to patients with normal hepatic function. **Cardiac Electrophysiology:** Sutinib can cause QT interval prolongation in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes.

Indications: Gastrointestinal Stromal Tumor (GIST): It is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to Imatinib Mesylate. **Advanced Renal Cell Carcinoma (RCC):** It is indicated for the treatment of advanced renal cell carcinoma. **Adjuvant Treatment of Renal Cell Carcinoma (RCC):** It is indicated for the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy. **Advanced Pancreatic Neuroendocrine Tumors (pNET):** It is indicated for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease.

Dosage and Administration: Recommended Dose for GIST and Advanced RCC: The recommended dose of Sutinib for gastrointestinal stromal tumor (GIST) and advanced renal cell carcinoma (RCC) is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). It may be taken with or without food. **Recommended Dose for Adjuvant Treatment of RCC:** The recommended dose of Sutinib for the adjuvant treatment of RCC is 50 mg taken orally once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2), for nine 6-week cycles. It may be taken with or without food. **Recommended Dose for pNET:** The recommended dose of Sutinib for pancreatic neuroendocrine tumors (pNET) is 37.5 mg taken orally once daily continuously without a scheduled off-treatment period. It may be taken with or without food.

Dose Modification: Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability. The maximum dose administered in the pNET study was 50 mg daily. In the adjuvant RCC study, the minimum dose administered was 37.5 mg. Strong CYP3A4 inhibitors such as Ketoconazole may increase Sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for Sutinib to a minimum of 37.5 mg (GIST and RCC) or 25 mg (pNET) daily should be considered if Sutinib must be coadministered with a strong CYP3A4 inhibitor. CYP3A4 inducers such as Rifampin may decrease Sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. A dose increase for Sutinib to a maximum of 87.5 mg (GIST and RCC) or 62.5 mg (pNET) daily should be considered if Sutinib must be coadministered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity. Or, as directed by the registered physician.

Side Effects: The most common side effects are • Hepatotoxicity • Cardiovascular Events • QT Interval Prolongation and Torsade de Pointes • Hypertension • Hemorrhagic Events • Tumor Lysis Syndrome (TLS) • Thrombotic Microangiopathy • Proteinuria • Dermatologic Toxicities • Thyroid Dysfunction • Hypoglycemia • Osteonecrosis of the Jaw (ONJ) • Wound Healing **Contraindications:** It is contraindicated in patients with known hypersensitivity to Sunitinib or any other components of this product.

Use in pregnancy and lactation: It can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform a drug-associated risk. If it is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. **Lactation:** There is no information regarding the presence of Sunitinib and its metabolites in human milk. Because of the potential for serious adverse reactions in breastfed infants from Sutinib, a lactating woman should be advised not to breastfeed during treatment with Sutinib and for at least 4 weeks after the last dose. **Females and Males of Reproductive Potential:** It can cause fetal harm when administered to a pregnant woman. **Pregnancy Testing:** Females of reproductive potential should have a pregnancy test before treatment with Sutinib is started. **Contraception: Females:** Females of reproductive potential should be advised to use effective contraception during treatment with Sutinib and for at least 4 weeks after the last dose. **Males:** Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Sutinib and for 7 weeks after the last dose. **Infertility:** Male and female fertility may be compromised by treatment with Sutinib. **Pediatric Use:** The safety and efficacy of Sutinib in pediatric patients have not been established. **Geriatric Use:** Of 825 patients with GIST or metastatic RCC who received Sutinib on clinical studies, 277 (34%) were 65 and over. In the pNET study, 22 patients (27%) who received Sutinib were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients. **Hepatic Impairment:** No dose adjustment to the starting dose is required when administering Sutinib to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of Sutinib were similar in patients with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to patients with normal hepatic function. Sutinib was not studied in patients with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN. **Renal Impairment:** No adjustment to the starting dose is required when administering Stinib to patients with mild (CLcr 50. 80 mL/min), moderate (CLcr 30.<50 mL/min), or severe (CLcr <30 mL/min) renal impairment who are not on dialysis. In patients with end-stage renal disease (ESRD) on hemodialysis, no adjustment to the starting dose is required. However, compared to patients with normal renal function, the Sunitinib exposure is 47% lower in patients with ESRD on hemodialysis.

Drug Interactions: CYP3A4 Inhibitors: Strong CYP3A4 inhibitors such as Ketoconazole may increase Sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of Sutinib with the strong CYP3A4 inhibitor, Ketoconazole, resulted in 49% and 51% increases in the combined (Sunitinib + primary active metabolite) Cmax and AUC0-∞ values, respectively, after a single dose of Sutinib in healthy volunteers. Coadministration of Sutinib with strong inhibitors of the CYP3A4 family (e.g., Ketoconazole, Itraconazole, Clarithromycin, Atazanavir, Indinavir, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Voriconazole) may increase Sunitinib concentrations. Grapefruit may also increase plasma s of Sunitinib. A dose reduction for Sutinib should be considered when it must be coadministered with strong CYP3A4 inhibitors. CYP3A4 Inducers: CYP3A4 inducers such as Rifampin may decrease Sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of Sutinib with the strong CYP3A4 inducer, Rifampin, resulted in a 23% and 46% reduction in the combined (Sunitinib + primary active metabolite) Cmax and AUC0-∞ values, respectively, after a single dose of Sutinib in healthy volunteers. Coadministration of Sutinib with inducers of the CYP3A4 family (e.g., Dexamethasone, Phenytoin, Carbamazepine, Rifampin, Rifabutin, Rifapentin, Phenobarbital, St. John's Wort) may decrease Sunitinib concentrations. St. John's Wort may decrease Sunitinib plasma concentrations unpredictably. Patients receiving Sutinib should not take St. John's Wort concomitantly. A dose increase for Sutinib should be considered when it must be coadministered with CYP3A4 inducers. **In Vitro Studies of CYP Inhibition and Induction:** In vitro studies indicated that Sunitinib does not induce or inhibit major CYP enzymes. The in vitro studies in human liver microsomes and hepatocytes of the activity of CYP isoforms 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.

Precautions: Hepatotoxicity: Sutinib can cause severe hepatotoxicity, resulting in liver failure or death. Liver failure occurred at an incidence of <1% in clinical trials. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Liver function tests should be monitored (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. Sutinib should be interrupted for Grade 3 or 4 drug-related hepatic adverse reactions and discontinue if there is no resolution. Sutinib should not be restarted if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure. Safety in patients with ALT or AST >2.5 x upper limit of normal (ULN) or, if due to liver metastases, >5.0 x ULN has not been established. **Cardiovascular Events:** Sutinib should be discontinued in the presence of clinical manifestations of congestive heart failure (CHF). Sutinib should be interrupted and/or reduced the dose in patients without clinical evidence of CHF who have an ejection fraction of >20% but <50% below baseline or below the lower limit of normal if baseline ejection fraction is not obtained. In patients without cardiac risk factors a baseline evaluation of ejection fraction should be considered. Patients should be monitored carefully for clinical signs and symptoms of CHF while receiving Sutinib. Baseline and periodic evaluations of left ventricular ejection fraction (LVEF) should also be considered while these patients are receiving Sutinib. Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. In patients treated with Sutinib (N=7527) for GIST, advanced RCC, adjuvant treatment of RCC and pNET, 3% of patients experienced heart failure; 71% of the patients with heart failure were reported as recovered. Fatal cardiac failure was reported in <1% of patients. In the adjuvant treatment of RCC study, 11 patients in each arm experienced a decreased ejection fraction meeting Grade 2 CTCAE criteria (LVEF 40-50% and a 10-19% decrease from baseline). No patients had a Grade 3-4 decrease in ejection fraction. The ejection fractions of three patients in the Sutinib arm and 2 patients in the placebo arm did not return to ≥50% or baseline by the time of last measurement. No patients who received Sutinib were diagnosed with CHF. Patients who presented with cardiac events within 12 months prior to Sutinib administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from Sutinib clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. **QT Interval Prolongation and Torsade De Pointes:** Sutinib can cause QT interval prolongation in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of Sutinib- exposed patients. Patients should be monitored with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using Sutinib, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors may increase Sunitinib plasma concentrations and dose reduction of Sutinib should be considered. Hypertension: Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of Sutinib is recommended until hypertension is controlled. In patients treated with Sutinib (N=7527) in GIST, advanced RCC, adjuvant treatment of RCC and pNET, 29% of patients experienced hypertension. Grade 3 hypertension was reported in 7% of patients, and Grade 4 hypertension was reported in 0.2% of patients. **Hemorrhagic Events and Viscus Perforation:** Hemorrhagic events reported through postmarketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract, and brain hemorrhages. In patients treated with Sutinib (N=7527) for GIST, advanced RCC, adjuvant treatment of RCC and pNET, 30% of patients experienced hemorrhagic events, and 4.2% of patients experienced a Grade 3 or 4 event. Epistaxis was the most common hemorrhagic adverse reaction and gastrointestinal hemorrhage was the most common Grade ≥3 event. Tumor-related hemorrhage has been observed in patients treated with Sutinib. 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 postmarketing experience in patients treated with Sutinib for metastatic RCC, GIST, and metastatic lung cancer. Sutinib is not approved for use in patients with lung cancer. Clinical assessment of hemorrhagic events should include serial complete blood counts (CBCs) and physical examinations. Serious, sometimes fatal, gastrointestinal complications including gastrointestinal perforation, have been reported in patients with intra-abdominal malignancies treated with Sutinib. **Tumor Lysis Syndrome (TLS):** Cases of TLS, some fatal, occurred in clinical trials and have been reported in postmarketing experience, primarily in patients with RCC or GIST treated with Sutinib. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These patients should be closely monitored and treated as clinically indicated. Thrombotic Microangiopathy: Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, occurred in clinical trials and in postmarketing experience of Sutinib as monotherapy and administered in combination with Bevacizumab. Sutinib should be discontinued in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued. **Proteinuria:** Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Patients should be monitored for the development or worsening of proteinuria. Baseline and periodic urinalyses should be performed during treatment, with follow up measurement of 24-hour urine protein as clinically indicated. Sutinib should be interrpted and dose reduce for 24-hour urine protein ≥3 grams. Sutinib should be discontinued for patients with nephrotic syndrome or repeat episodes of urine protein ≥3 grams despite dose reductions. The safety of continued Sutinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated. **Dermatologic Toxicities:** Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN (e.g., progressive skin rash often with blisters or mucosal lesions) are present, Sutinib treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, Sutinib treatment must not be re-started. Necrotizing fasciitis, including fatal cases, has been reported in patients treated with Sutinib, including of the perineum and secondary to fistula formation. Sutinib should be discontinued in patients who develop necrotizing fasciitis. **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 Sutinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, while on Sutinib 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. Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through postmarketing experience. **Hypoglycemia:** Sutinib can result in symptomatic hypoglycemia, which may lead to loss of consciousness, or require hospitalization. Hypoglycemia has occurred in clinical trials in 2% of the patients treated with Sutinib for advanced RCC and GIST and in approximately 10% of the patients treated with Sutinib for pNET. In the adjuvant treatment of RCC study, no patients on Sutinib experienced hypoglycemia. For patients being treated with Sutinib for pNET, pre-existing abnormalities in glucose homeostasis were not present in all patients who experienced hypoglycemia. Reductions in blood glucose levels may be worse in diabetic patients. Check blood glucose levels regularly during and after discontinuation of treatment with Sutinib. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia. **Osteonecrosis of the Jaw (ONJ):** ONJ has been observed in clinical trials and has been reported in postmarketing experience in patients treated with Sutinib. Concomitant exposure to other risk factors, such as bisphosphonates or dental disease, may increase the risk of osteonecrosis of the jaw. Preventive dentistry should be considered prior to treatment with Sutinib. If possible, invasive dental procedures should be avoided while on Sutinib treatment, particularly in patients receiving intravenous bisphosphonate therapy. **Wound Healing:** Cases of impaired wound healing have been reported during Sutinib therapy. Temporary interruption of Sutinib 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 Sutinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery. **Embryo-Fetal Toxicity:** Sutinib can cause fetal harm when administered to pregnant woman. Pregnant women should be advised of the potential risk to a fetus. Females should be advised of reproductive potential to use effective contraception during treatment with Sutinib and for 4 weeks following the final dose.

Overdose: Treatment of overdose with Sutinib should be consisted of general supportive measures. There is no specific antidote for overdosage with Sutinib. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of Sutinib, or without adverse reactions. A case of intentional overdose involving the ingestion of 1500 mg of Sutinib in an attempted suicide was reported without adverse reaction. In nonclinical studies, mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection, and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

Storage: Store at 25° C in a cool and dry place, away from light. Keep out of the reach of children.

Packaing: Each box contains 1x7's capsules in blister pack.