210mm

140mm

Capsule

SUNETIC

(S u n i t i n i b)

سونیٹک کیپسول

(سونیٹینب)

COMPOSITION:

Sunetic Capsule 12.5mg

Each capsule contains:

Sunitinib (as malate).....12.5mg

(Innovator's Specifications)

Sunetic Capsule 25mg

Each capsule contains:

Sunitinib (as malate).....25mg

(Innovator's Specifications)

Sunetic Capsule 50mg

Each capsule contains:

Sunitinib (as malate).....50mg

(Innovator's Specifications)

DESCRIPTION:

Sunitinib is an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor that was approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). Sunitinib was the first cancer drug simultaneously approved for two different indications.

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. 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 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.

INDICATIONS:

Gastrointestinal Stromal Tumor (GIST)

SUNETIC is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

Advanced Renal Cell Carcinoma (RCC)

SUNETIC is indicated for the treatment of advanced renal cell carcinoma.

Adjuvant Treatment of Renal Cell Carcinoma (RCC)

SUNETIC is indicated for the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy.

Advanced Pancreatic Neuroendocrine Tumors (pNET)

SUNETIC 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 SUNETIC 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). SUNETIC may be taken with or without food.

Recommended Dose for Adjuvant Treatment of RCC

The recommended dose of SUNETIC 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. SUNETIC may be taken with or without food.

Recommended Dose for pNET

The recommended dose of SUNETIC for pancreatic neuroendocrine tumors (pNET) is 37.5 mg taken orally once daily continuously without a scheduled off-treatment period. SUNETIC may be taken with or without food.

PHARMACOKINETICS:

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and in 266 patients with solid tumors. Maximum plasma concentrations (C_{max}) of sunitinib are generally observed between 6 and 12 hours (time to maximum plasma concentration [T_{max}]) following oral administration. Food has no effect on the bioavailability of sunitinib. SUNETIC 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 C_{max} increase proportionately with dose. 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 is primarily via feces. In a human mass balance study of [^{14}C] sunitinib, 61% of the dose was eliminated in feces, with renal elimination 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 not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/h with an interpatient variability of 40%. 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. The pharmacokinetics were similar

in healthy volunteers and in the solid tumor patient populations tested, including patients with GIST and RCC.

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 SUNETIC or the primary active metabolite.

Pediatric Use: The pharmacokinetics of SUNETIC have not been evaluated in pediatric patients.

Renal Insufficiency: Sunitinib systemic exposure after a single dose of SUNETIC was similar in patients with severe renal impairment (CL_{cr} 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 SUNETIC 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.

WARNINGS AND PRECAUTIONS:

Hepatotoxicity

WARNING: HEPATOTOXICITY

Hepatotoxicity has been observed in clinical trials and post marketing experience. Hepatotoxicity may be severe, and in some cases, fatal. Monitor hepatic funtion and interrupt, reduce, or discontinue dosing as recommended.

SUNETIC has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, and bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUNETIC should be interrupted for Grade 3 or 4 drug related hepatic adverse events and discontinued if there is no resolution. Do not restart SUNETIC 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 ULN or, if due to liver metastases, >5.0 x ULN has not been established.

Cardiovascular Events

Discontinue SUNETIC in the presence of clinical manifestations of congestive heart failure (CHF). Interrupt SUNETIC and/or reduce 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. Carefully monitor patients for clinical signs and symptoms of CHF while receiving SUNETIC. Baseline and periodic evaluations of left ventricular ejection fraction (LVEF) should also be considered while these patients are receiving SUNETIC.

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported.

In patients treated with SUNETIC (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 SUNETIC 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 SUNETIC were diagnosed with CHF.

Patients who presented with cardiac events within 12 months prior to SUNETIC 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 SUNETIC clinical studies. Patients with prior anthracyclines use or cardiac radiation were also excluded from some 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

SUNETIC 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 SUNETIC-exposed patients.

Monitor patients with a history of QT interval prolongation, patients who are taking anti arrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUNETIC, 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 SUNETIC should be considered.

Hypertension

Monitor patients for hypertension and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUNETIC is recommended until hypertension is controlled. In patients treated with SUNETIC (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 post marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract, and brain hemorrhages. In patients treated with SUNETIC (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 SUNETIC. 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

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trials and have been reported in post marketing experience in patients treated with SUNETIC for metastatic RCC, GIST, and metastatic lung cancer. SUNETIC 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 SUNETIC.

Tumor Lysis Syndrome (TLS)

Cases of TLS, some fatal, occurred in clinical trials and have been with high tumor burden prior to treatment. Monitor these patients closely and treat 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 post marketing experience of SUNETIC as monotherapy and administered in combination with bevacizumab. Discontinue SUNETIC 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. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalyses during treatment, with follow up measurement of 24-hour urine protein as clinically indicated. Interrupt SUNETIC and dose reduce for 24-hour urine protein ≥3 grams. Discontinue SUNETIC for patients with nephrotic syndrome or repeat episodes of urine protein ≥3 grams despite dose reductions. The safety of continued SUNETIC 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, discontinue SUNETIC treatment. If a diagnosis of SJS or TEN is suspected, SUNETIC treatment must not be re-started. Necrotizing fasciitis, including fatal cases, has been reported in patients treated with SUNETIC, including of the perineum and secondary to fistula formation. Discontinue SUNETIC 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 SUNETIC treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, while on SUNETIC 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 post marketing experience

Hypoglycemia

SUNETIC 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 SUNETIC for advanced RCC and GIST and in approximately 10% of the patients treated with SUNETIC for pNET. In the adjuvant treatment of RCC study, no patients on SUNETIC experienced hypoglycemia. For patients being treated with SUNETIC 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 SUNETIC. 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 post

Osteonecrosis of the Jaw (ONJ)

ONJ has been observed in clinical trials and has been reported in post marketing experience in patients treated with SUNETIC. Concomitant exposure to other risk factors, such as bisphosphonates or dental disease, may increase the risk of osteonecrosis of the jaw. Consider preventive dentistry prior to treatment with SUNETIC. If possible, avoid invasive dental procedures while on SUNETIC treatment, particularly in patients receiving intravenous bisphosphonate therapy.

Wound Healing

Cases of impaired wound healing have been reported during SUNETIC therapy. Temporary interruption of SUNETIC 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 SUNETIC therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, SUNETIC can cause fetal harm when administered to pregnant woman. Administration of sunitinib to pregnant rats and rabbits during the period of organogenesis resulted in teratogenicity at approximately 5.5 and 0.3 times the clinical systemic exposure (AUC) at the recommended daily doses (RDD) of 50 mg/day, respectively. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with SUNETIC and for 4 weeks following the final dose.

Pregnancy

Pregnancy Category D

SUNETIC can cause fetal harm when administered to a pregnant woman. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUNETIC should be expected to result in adverse effects on pregnancy. In animal reproductive studies in rats and rabbits, sunitinib was teratogenic, embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of SUNETIC in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUNETIC.

Nursing Mothers

Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether this drug or its primary active metabolite are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SUNETIC, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

SIDE EFFECTS:

Blood and lymphatic system disorders:

Hemorrhage associated with thrombocytopenia. Suspension of SUNETIC is recommended; following resolution, treatment may be resumed at the discretion of the treating healthcare provider.

Gastrointestinal disorders:

Esophagitis.

Hepatobiliary disorders:

Cholecystitis, particularly acalculous cholecystitis.

Immune system disorders:

Hypersensitivity reactions, including angioedema.

Infections and infestations:

Serious infection (with or without neutropenia). The infections most commonly observed with SUNETIC treatment include respiratory, urinary tract, skin infections, and sepsis/septic shock.

Musculoskeletal and connective tissue disorders:

Fistula formation, sometimes associated with tumor necrosis and/or regression; myopathy and/or rhabdomyolysis with or without acute renal failure. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Renal and urinary disorders:

Renal impairment and/or failure.

Respiratory disorders:

Pulmonary embolism.

Skin and subcutaneous tissue disorders:

Pyoderma gangrenosum, including positive dechallenges.

Vascular disorders:

Arterial thromboembolic events. The most frequent events included cerebrovascular accident, transient ischemic attack, and cerebral infarction.

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 SUNETIC with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUNETIC in healthy volunteers. Co administration of SUNETIC 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 concentrations of sunitinib. A dose reduction for SUNETIC should be considered when it must be co administered 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 SUNETIC with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUNETIC in healthy volunteers. Co administration of SUNETIC 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 SUNETIC should not take St. John's Wort concomitantly. A dose increase for SUNETIC should be considered when it must be co administered with CYP3A4 inducers.

CONTRAINDICATIONS:

None.

OVERDOSAGE:

Treatment of overdose with SUNETIC should consist of general supportive measures. There is no specific antidote for over dosage with SUNETIC. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. 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 & INSTRUCTIONS:

Store between 15-30°C. Protect from heat, sunlight and moisture. Keep away from the reach of the children.

To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.

HOW SUPPLIED:

Sunetic Capsule 12.5mg
30 capsules
Sunetic Capsule 25mg
30 capsules
Sunetic Capsule 50mg
30 capsules

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۳۰ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔ دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔ صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخے پر فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.

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