Sunitix

Sunitinib

COMPOSITION

Sunitix Capsule: Each capsule contains Sunitinib Malate INN equivalent to Sunitinib 50 mg.

CLINICAL PHARMACOLOGY

Sunitinib malate 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.

Pharmacodynamics/Kinetics:

Maximum plasma concentrations (C_{max}) of Sunitinib are generally observed between 6 and 12 hours (T_{max}) following oral administration. Food has no effect on the bioavailability of Sunitinib. Sunitinib 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 area under the plasma concentration-time curve (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/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 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 ECOG score on the pharmacokinetics of Sunitinib or the primary active metabolite.

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

Renal Insufficiency: Sunitinib systemic exposure after a single dose of Sunitinib was similar in subjects with severe renal impairment (CLcr<30 mL/min) compared to subjects with normal renal function (CLcr>80 mL/min). Although Sunitinib was not eliminated through hemodialysis, the Sunitinib systemic exposure was 47% lower in subjects with ESRD on hemodialysis compared to subjects with normal renal function.

Hepatic Insufficiency: Systemic exposures after a single dose of Sunitinib were similar in subjects with mild exocrine (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment compared to subjects with normal hepatic function.

MECHANISM OF ACTION

Sunitinib works by blocking multiple molecular targets implicated in the growth, proliferation and spread of cancer. Two important sunitinib targets, vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) are expressed by many types of solid tumors and are thought to play a crucial role in angiogenesis, the process by which tumors acquire blood vessels, oxygen and nutrients needed for growth. Sunitinib also inhibits other targets important to tumor growth including KIT, FLT3 and RET.

INDICATIONS

Sunitix is a kinase inhibitor indicated for the treatment of:

- Gastrointestinal stromal tumor (GIST) after disease progression on orintolerance to imatinib mesylate.
- Advanced renal cell carcinoma (RCC).
- Progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.

DOSAGE AND ADMINISTRATION

GIST and RCC: 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off.

pNET: 37.5 mg orally once daily, with or without food, continuously without a scheduled off-treatment period.

Dose Modification: Dose interruptions and/or dose adjustments of 12.5 mg recommended based on individual safety and tolerability.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

Sunitinib 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 Sunitinib 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 Sunitinib 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 sunitinib. Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of Sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at $\geq$1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD). Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postnatal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at doses $\geq$1 mg/kg/day but no maternal reproductive toxicity was observed at doses up to $\geq$3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD). At the high dose of 3 mg/kg/day, reduced body weights were observed at birth and persisted for offspring of both sexes during the pre-weaning period and in males during post-weaning period. No other developmental toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

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 Sunitinib, 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.

Pediatric Use

The safety and efficacy of Sunitinib in pediatric patients have not been established. Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for $\geq$ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with Sunitinib at doses that were > 0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses $\geq$ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was $\leq$ 2 mg/kg/day.

Geriatric Use

Of 825 GIST and RCC patients who received Sunitinib on clinical studies, 277 (34%) were 65 and over. In the Phase 3 pNET study, 22 (27%) patients who received Sunitinib 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 Sunitinib 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 Sunitinib were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. Sunitinib was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

Renal Impairment

No adjustment to the starting dose is required when administering Sunitinib to patients with mild, moderate, and severe renal impairment. Subsequent dose modifications should be based on safety and tolerability. In patients with end-stage renal disease (ESRD) on hemodialysis, no adjustment to the starting dose is required. However, compared to subjects with normal renal function, the Sunitinib exposure is 47% lower in subjects with ESRD on hemodialysis.

OVERDOSAGE

Treatment of overdose with Sunitinib should consist of general supportive measures. There is no specific antidote for overdosage with Sunitinib. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. A few cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of Sunitinib or without adverse reactions. A case of intentional overdose involving the ingestion of 1,500 mg of Sunitinib in an attempted suicide was reported without adverse reaction. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) 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.

CONTRAINDICATIONS

None

PRECAUTIONS

Hepatotoxicity, including liver failure has been observed. Monitor liver function tests before initiation of treatment during each cycle of treatment, and as clinically indicated. Sunitinib should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart Sunitinib if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

Cardiac toxicity including left ventricular ejection fraction declines to below the lower limit of normal and cardiac failure including death have occurred. Monitor patients for signs and symptoms of congestive heart failure.

Prolonged QT intervals and Torsade de Pointes have been observed.

Use with caution in patients at higher risk for developing QT interval prolongation. When using Sunitinib, monitoring with on-treatment electrocardiograms and electrolytes should be considered.

Hypertension may occur. Monitor blood pressure and treat as needed.

Hemorrhagic events including tumor-related hemorrhage have occurred.

Perform serial complete blood counts and physical examinations.

Osteonecrosis of the jaw has been reported. Consider preventive dentistry prior to treatment with Sunitinib. If possible, avoid invasive dental procedures, particularly in patients receiving intravenous bisphosphonate therapy.

Cases of Tumor Lysis Syndrome (TLS) have been reported primarily in patients with RCC and GIST with high tumor burden. Monitor these patients closely and treat as clinically indicated.

Thyroid dysfunction may occur. Patients with signs and/or symptoms suggestive of hypothyroidism or hyperthyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Temporary interruption of therapy with Sunitinib is recommended in patients undergoing major surgical procedures.

Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma or severe infection.

ADVERSE EFFECTS

The most common adverse reactions ($\geq$20%) are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia and bleeding.

DRUG INTERACTIONS

CYP3A4 Inhibitors: Consider dose reduction of Sunitinib when administered with strong CYP3A4 inhibitors.

CYP3A4 Inducers: Consider dose increase of Sunitinib when administered with CYP3A4 inducers.

PHARMACEUTICAL INFORMATION

Storage condition

Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packing

Sunitix Capsule: Each commercial box contains 6 Capsules in Alu-Alu blister pack.

Manufactured By
BEACON
Pharmaceuticals Limited
Mymensingh, Bangladesh

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