SONIB 200mg Tablet
(Sorafenib)

سونب ۲۰۰ ملی گرام ٹیبلٹ
(سورافینب)

COMPOSITION

Sonib Tablet 200mg

Each film coated tablet contains:

Sorafenib (as tosylate) 200mg

(BP specifications)

DESCRIPTION

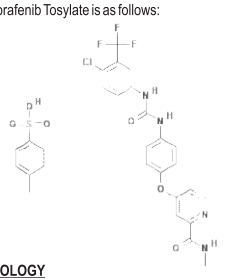
The active component of SONIB is sorafenib. Sorafenib as sorafenib tosylate is an antineoplastic agent and shows its activity by kinase inhibitor. Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl) phenyl] uredo} phenoxy) N2methylpyridine-2-carboxamide 4-methylbenzenesulfonate.It is approved for the treatment of primary kidney cancer (advanced renal cell carcinoma), advanced primary liver cancer (hepatocellular carcinoma), and radioactive iodine resistant advanced thyroid carcinoma.

MOLECULAR & STRUCTURAL FORMULA

Molecular formula of Sorafenib Tosylate is as follows:

$C_{28}H_{24}ClF_3N_4O_5S$

Structural formula of Sorafenib Tosylate is as follows:



CLINICAL PHARMACOLOGY

MODE OF ACTION

Sorafenib is a kinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib was shown to inhibit multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis. Sorafenib inhibited tumor growth and angiogenesis of human carcinoma and renal cell carcinoma, and several other human tumor xenografts in immunocompromised mice.

INDICATIONS

Hepatocellular Carcinoma

SONIB is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC).

Renal Cell Carcinoma

SONIB is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

DOSAGE & ADMINISTRATION

The recommended daily dose of SONIB is 400 mg (2 x 200 mg tablets) taken twice daily without food (at least 1 hour before or 2 hours after a meal). Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Dose Adjustments

- Management of suspected adverse drug reactions may require temporary interruption or dose reduction of sorafenib therapy.
- When dose reduction is necessary during the treatment of hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC), the SONIB dose should be reduced to two tablets of 200 mg sorafenib once daily.
- When dose reduction is necessary during the treatment of differentiated thyroid carcinoma (DTC), the SONIB dose should be reduced to 600 mg sorafenib daily in divide doses (two tablets of 200 mg and one tablet of 200 mg twelve hours apart).
- If additional dose reduction is necessary, SONIB may be reduced to 400 mg sorafenib daily in divided doses (two tablets of 200 mg twelve hours apart), and if necessary further reduced to one tablet of 200 mg once daily. After improvement of non-haematological adverse reactions, the dose of SONIB may be increased.

Pediatric population

The safety and efficacy of SONIB in children and adolescents aged < 18 years have not yet been established. No data are available.

Elderly population

No dose adjustment is required in the elderly (patients above 65 years of age).

Renal impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring dialysis.

Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.

Hepatic impairment

No dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment. No data is available on patients with Child Pugh C (severe) hepatic impairment.

Method of administration

For oral use.

It is recommended that sorafenib should be administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water.

PHARMACOKINETICS

After administration of SONIB tablets, the mean relative bioavailability was 38–49% when compared to an oral solution. The mean elimination half-life of sorafenib was approximately 25 to 48 hours. Multiple doses of SONIB for 7 days resulted in a 2.5- to 7-fold accumulation compared to a single dose. Steady-state plasma sorafenib concentrations were achieved within 7 days, with a peak-to-trough ratio of mean concentrations of less than 2.

Absorption and Distribution

Following oral administration, sorafenib reached peak plasma levels in approximately 3 hours. With a moderate-fat meal (30% fat; 700 calories), bioavailability was similar to that in the fasted state. With a high-fat meal (50% fat; 900 calories), bioavailability was reduced by 29% compared to that in the fasted state. It is recommended that SONIB be administered without food.

Mean Cmax and AUC increased less than proportionally beyond oral doses of 400 mg administered twice daily. In vitro binding of sorafenib to human plasma proteins was 99.5%.

Metabolism and Elimination

Sorafenib undergoes oxidative metabolism by hepatic CYP3A4, as well as glucuronidation by UGT1A9. Inducers of CYP3A4 activity can decrease the systemic exposure of sorafenib. Sorafenib accounted for approximately 70–85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, of which 5 have been detected in plasma. The main circulating metabolite of sorafenib, the pyridine N-oxide that comprises approximately 9–16% of circulating analytes at steady-state, showed in vitro potency similar to that of sorafenib.

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

PRECAUTIONS

Hand foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with sorafenib. Rash and hand foot skin reaction are usually CTC (Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib. Management of dermatological toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib.

Hypertension

An increased incidence of arterial hypertension was observed in sorafenib-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of sorafenib should be considered.

Haemorrhage

An increased risk of bleeding may occur following sorafenib administration. If any bleeding event necessitates medical intervention it is recommended that permanent discontinuation of sorafenib should be considered.

Cardiac ischemia and/or infarction

In a randomized, placebo-controlled, double-blind study the incidence of treatment-emergent cardiac ischemia/infarction events was higher in the sorafenib group (4.9 %) compared with the placebo group (0.4 %). In study 3 the incidence of treatment-emergent cardiac ischemia/infarction events was 2.7 % in sorafenib patients compared with 1.3 % in the placebo group. Patients with unstable coronary artery disease or recent myocardial infarction were excluded from these studies. Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia and/or infarction.

QT interval prolongation

Sorafenib has been shown to prolong the QT/QTcinterval which may lead to an increased risk for ventricular arrhythmias. Use sorafenib with caution in patients who have, or may develop prolongation of QTc, such as patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using sorafenib in these patients, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium, and calcium) should be considered.

Gastrointestinal perforation

Gastrointestinal perforation is an uncommon event and has been reported in less than

1% of patients taking sorafenib. In some cases this was not associated with apparent intra-abdominal tumor. Sorafenib therapy should be discontinued.

Hepatic impairment

No data is available on patients with Child Pugh C (severe) hepatic impairment. Since sorafenib is mainly eliminated via the hepatic route exposure might be increased in patients with severe hepatic impairment.

Warfarin co-administration

Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy. Patients taking concomitant warfarin or Phenprocoumonshould be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes.

Wound healing complications

No formal studies of the effect of sorafenib on wound healing have been conducted. Temporary interruption of sorafenib 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 sorafenib therapy following a major surgical intervention should be based on clinical judgement of adequate wound healing.

Elderly population

Cases of renal failure have been reported. Monitoring of renal function should be considered.

Pregnancy

Pregnancy Category D

Based on its mechanism of action and findings in animals, SONIB may cause fetal harm when administered to a pregnant woman. Sorafenib caused embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. There are no adequate and well-controlled studies in pregnant women using SONIB. Inform patients of childbearing potential that SONIB can cause birth defects or fetal loss. Instruct both men and women of childbearing potential to use effective birth control during treatment with SONIB and for at least 2 weeks after stopping treatment. Counsel female patients to contact their healthcare provider if they become pregnant while taking SONIB.

Lactation

It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because sorafenib could harm infant growth and development, women must not breast-feed during sorafenib treatment.

SIDE EFFECTS

The most important serious adverse reactions were myocardial infarction/ischemia, gastrointestinal perforation, drug induced hepatitis, haemorrhage, and hypertension/hypertensive crisis.

The most common adverse reactions were diarrhea, fatigue, alopecia, infection, hand foot skin reaction (corresponds to palmar plantar erythrodysaesthesia syndrome in MedDRA) and rash.

DRUG INTERACTIONS

Inducers of metabolic enzymes

Administration of rifampicin for 5 days before administration of a single dose of sorafenib resulted in an average 37 % reduction of sorafenib AUC. Other inducers of CYP3A4 activity and/or glucuronidation (e.g. Hypericumperforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations.

CYP3A4 inhibitors

Ketoconazole, a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of sorafenib. These data suggest that clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.

CYP2B6, CYP2C8 and CYP2C9 substrates

Sorafenib inhibited CYP2B6, CYP2C8 and CYP2C9 in vitro with similar potency. However, in clinical pharmacokinetic studies, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, or paclitaxel, a CYP2C8 substrate, did not result in a clinically meaningful inhibition. These data suggest that sorafenib at the recommended dose of 400 mg twice daily may not be an in vivo inhibitor of CYP2B6 or CYP2C8.

Additionally, concomitant treatment with sorafenib and warfarin, a CYP2C9 substrate, did not result in changes in mean PT-INR compared to placebo. Thus, also the risk for a clinically relevant in vivo inhibition of CYP2C9 by sorafenib may be expected to be low. However, patients taking warfarin or Phenprocoumon should have their INR checked regularly.

CYP3A4, CYP2D6 and CYP2C19 substrates

Concomitant administration of sorafenib and midazolam, dextromethorphan or omeprazole, which are substrates for cytochromes CYP3A4, CYP2D6 and CYP2C19 respectively, did not alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. Therefore, clinical pharmacokinetic interactions of sorafenib with substrates of these enzymes are unlikely.

UGT1A1 and UGT1A9 substrates

In vitro, sorafenib inhibited glucuronidation via UGT1A1 and UGT1A9. The clinical relevance of this finding is unknown.

In vitro studies of CYP enzyme induction

CYP1A2 and CYP3A4 activities were not altered after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 and CYP3A4.

P-gp-substrates

In vitro, sorafenib has been shown to inhibit the transport protein p-glycoprotein (P-gp). Increased plasma concentrations of P-gp substrates such as digoxin cannot be excluded with concomitant treatment with sorafenib.

Combination with other anti-neoplastic agents

In clinical studies sorafenib has been administered with a variety of other anti-neoplastic agents at their commonly used dosing regimens including gemcitabine, cisplatin, oxaliplatin, paclitaxel, carboplatin, capecitabine, doxorubicin, irinotecan, docetaxel and cyclophosphamide. Sorafenib had no clinically relevant effect on the pharmacokinetics of gemcitabine, cisplatin, carboplatin, oxaliplatin or cyclophosphamide.

Paclitaxel/carboplatin

Administration of paclitaxel (225 mg/m2) and carboplatin (AUC = 6) with sorafenib (≤ 400 mg twice daily), administered with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration), resulted in no significant effect on the pharmacokinetics of paclitaxel.

Co-administration of paclitaxel (225 mg/m2, once every 3 weeks) and carboplatin (AUC=6) with sorafenib (400 mg twice daily, without a break in sorafenib dosing) resulted in a 47% increase in sorafenib exposure, a 29% increase in paclitaxel exposure and a 50% increase in 6-OH paclitaxel exposure. The pharmacokinetics of carboplatin were unaffected.

These data indicate no need for dose adjustments when paclitaxel and carboplatin are co-administered with sorafenib with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration). The clinical significance of the increases in sorafenib and paclitaxel exposure, upon co-administration of sorafenib without a break in dosing, is unknown.

Capecitabine

Co-administration of capecitabine (750-1050 mg/m2 twice daily, Days 1-14 every 21 days) and sorafenib (200 or 400 mg twice daily, continuous uninterrupted administration) resulted in no significant change in sorafenib exposure, but a 15-50% increase in capecitabine exposure and a 0-52% increase in 5-FU exposure. The clinical significance of these small to modest increases in capecitabine and 5-FU exposure when co-administered with sorafenib is unknown.

Doxorubicin/Irinotecan

Concomitant treatment with sorafenib resulted in a 21 % increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolised by the UGT1A1 pathway, there was a 67 - 120 % increase in the AUC of SN-38 and a 26 - 42 % increase in the AUC of irinotecan. The clinical significance of these findings is unknown.

Docetaxel

Docetaxel (75 or 100 mg/m2 administered once every 21 days) when co-administered with sorafenib (200 mg twice daily or 400 mg twice daily administered on Days 2 through 19 of a 21-day cycle with a 3-day break in dosing around administration of docetaxel) resulted in a 36-80 % increase in docetaxel AUC and a 16-32 % increase in docetaxel Cmax. Caution is recommended when sorafenib is co-administered with docetaxel.

Combination with other agents

Neomycin

Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate gastrointestinal flora, interferes with the enterohepatic recycling of sorafenib (see section 5.2, Metabolism and Elimination), resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average exposure to sorafenib decreased by 54%. Effects of other antibiotics have not been studied, but will likely depend on their ability to interfere with microorganisms with glucuronidase activity.

CONTRAINDICATIONS

- SONIB is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of SONIB.
- SONIB in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer.

STORAGE & INSTRUCTIONS:

Store between 20-25°C. Protect from heat, sunlight & moisture. Keep medicine out of the reach of children.

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

HOW SUPPLIED

Sonib Tablet 200mg

30's, 60's, 120's Tablets.

خوراک وطریقہ استعمال:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

۲۰-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف مستند کینسر ہسپتال یا اونکولوجسٹ کے نسخے پر فروخت کریں۔

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