**Composition :**
**Sonib :** Each film coated tablet contains Sorafenib 200mg as Sorafenib Tosylate INN.
**Clinical Pharmacology :** 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-β). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis. Sorafenib inhibited tumor growth and angiogenesis of human hepatocellular carcinoma and renal cell carcinoma and several other human tumor xenografts in immunocompromised mice.
**Pharmacodynamics/Kinetics:**
**Absorption:** Bioavailability is 38% to 49%. Tmax is 3 h. Steady state plasma levels occur within 7 days. Administration with high-fat meals reduced Sorafenib bioavailability 29%.
**Distribution:** In vitro protein binding is 99.5%.
**Metabolism:** Metabolism occurs primarily in the liver by CYP3A4 and UGT1 A9-mediated glucuronidation. Eight metabolites have been identified, of which pyridine N-oxide has shown in vitro potency similar to the parent drug.
**Elimination:** Mean elimination $t^1/_2$, is about 25 to 48 h. After oral administration of a Sorafenib 100 mg oral solution, 96% was recovered within 14 days (77% in the feces and 19% in the urine).
**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).
**Use in Special Population : Renal Function Impairment:** No dose adjustments are necessary for mild, moderate or severe renal function impairment in patients not undergoing dialysis.
**Hepatic Function Impairment :** Mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic function impairment decreased AUC by 23% and 65% respectively. Not studied in severe (Child-Pugh class C) hepatic function impairment.
**Dosage and 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. 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. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of Sonib. When dose reduction is necessary, the Sonib dose may be reduced to 400 mg once daily. If additional dose reduction is required, Sonib may be reduced to a single 400 mg dose every other day. Or, as directed by the registered physicians.
**Side effects :** The most common side effects of this tablet are- Cardiac ischemia, Infarction, Hemorrhage, Hypertension, Hand-foot skin reaction, rash, Stevens-Johnson syndrome, Gastrointestinal perforation and Drug-Induced Hepatitis.
**Contraindications :** Sorafenib is contraindicated in patients with known severe hypersensitivity to Sorafenib or any other component of Sorafenib. Sorafenib in combination with Carboplatin and Paclitaxel is contraindicated in patients with squamous cell lung cancer.
**Use in pregnancy and lactation :** Pregnancy Category D. Sorafenib should not be used during pregnancy. It is not known whether Sorafenib is excreted in human milk.
**Drug interactions :** CYP3A4 inducers: Can increase the metabolism of Sorafenib and decrease the AUC of Sorafenib. Caution is recommended when administering Sorafenib with compounds that are metabolised/eliminated predominantly by the UGT1A1 (e.g. Irinotecan) or UGT1A9 pathways. Caution is recommended when Sorafenib is co-administered with Docetaxel. Co-administration of Neomycin or other antibiotics that cause major ecological disturbances of the gastrointestinal microflora may lead to a decrease in Sorafenib bioavailability. The risk of reduced plasma concentrations of Sorafenib should be considered before starting a treatment course with antibiotics. Higher mortality has been reported in patients with squamous cell carcinoma of the lung treated with Sorafenib in combination with platinum-based chemotherapies. In two randomised trials investigating patients with Non-Small Cell Lung Cancer in the subgroup of patients with squamous cell carcinoma treated with Sorafenib as add-on to Paclitaxel/Carboplatin, the HR for overall survival was found to be 1.81 (95% CI 1.19; 2.74) and as add-on to Gemcitabine/Cisplatin 1.22 (95% CI 0.82; 1.80). No single cause of death dominated, but higher incidence of respiratory failure, hemorrhages and infectious adverse events were observed in patients treated with Sorafenib as add-on to platinum-based chemotherapies.
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# Sonib

**Sorafenib INN**

DRUG INTERNATIONAL LTD.

**Precautions :**
- Cardiac ischemia and/or infarction may occur. Consider temporary or permanent discontinuation of Sorafenib.
- Bleeding may occur. If bleeding necessitates medical intervention, consider discontinuation of Sorafenib.
- Hypertension usually occurred early in the course of treatment and was managed with antihypertensive therapy. Monitor blood pressure weekly during the first 6 weeks and periodically thereafter and treat as required.
- Hand-foot skin reaction and rash are common. Management may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification or in severe or persistent cases, permanent discontinuation.
- Gastrointestinal perforation is an uncommon adverse reaction. In the event of a gastrointestinal perforation, Sorafenib should be discontinued.
- Temporary interruption of Sorafenib is recommended in patients undergoing major surgical procedures.
- QT Prolongation: Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid in patients with congenital long QT syndrome.
- Sorafenib may cause fetal harm when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while on Sorafenib.

**Table 1: Suggested Dose Modifications for Skin Toxicity**

| Skin Toxicity Grade | Occurrence | Suggested Dose Modification |
|---|---|---|
| Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities | Any occurrence | Continue treatment with Sorafenib and consider topical therapy for symptomatic relief |
| Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities | 1st occurrence | Continue treatment with Sorafenib and consider topical therapy for symptomatic relief if no improvement within 7 days, see below |
| | No improvement within 7 days or 2nd or 3rd occurrence | Interrupt Sorafenib treatment until toxicity resolves to Grade 0-1<br>When resuming treatment, decrease Sorafenib dose by one dose level (400 mg daily or 400 mg every other day) |
| | 4th occurrence | Discontinue Sorafenib treatment |
| Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet or severe discomfort that causes the patient to be unable to work or perform activities of daily living | 1st or 2nd occurrence | Interrupt Sorafenib treatment until toxicity resolves to Grade 0-1<br>When resuming treatment, decrease Sorafenib dose by one dose level (400 mg daily or 400 mg every other day) |
| | 3rd Occurrence | Discontinue Sorafenib treatment |

No dose adjustment is required on the basis of patient age, gender, or body weight.
Concomitant strong CYP3A4 inducers: Avoid concomitant use of strong CYP3A4 inducers (such as, Carbamazepine, Dexamethasone, Phenobarbital, Phenytoin, Rifampin, Rifabutin, St.John's wort), when possible, because inducers can decrease the systemic exposure to Sorafenib.
**Overdose :** There is no specific treatment for Sorafenib overdose.
The highest dose of Sorafenib studied clinically is 800 mg twice daily. The adverse reactions observed at this dose were primarily diarrhea and dermatologic. No information is available on symptoms of acute overdose in animals because of the saturation of absorption in oral acute toxicity studies conducted in animals. In cases of suspected overdose, Sorafenib should be withheld and supportive care instituted.
**Storage :** Store at 25° C in cool and dry place, away from light. Keep out of the reach of children.
**Packaging : Sonib Tablet:** Each box contains 4x7's tablets in Alu-Alu blister pack.