SOFENIB®

Sorafenib 200 mg

COMPOSITION

SOFENIB® Tablet: Each film coated tablet contains Sofenib Tosylate INN equivalent to Sofenib 200 mg.

CLINICAL PHARMACOLOGY

SOFENIB® is a multikinase inhibitor that targets various receptor tyrosine kinases and RAF kinases (serine/threonine kinases) associated with tumour growth. SOFENIB® inhibits the activity of targets present in tumour cells and in the tumour vasculature. SOFENIB® decreases tumor cell proliferation in vitro. Inhibition of tumour growth was accompanied by a reduction in tumour angiogenesis.

Pharmacodynamics/Kinetics:

Absorption

Following oral administration, SOFENIB® reaches peak plasma levels in approximately 3 hours. Bioavailability is 38% to 49%. Steady state plasma SOFENIB® concentrations are achieved within 7 days. Administration with high-fat meals reduced SOFENIB® bioavailability 29%.

Distribution

In vitro protein binding is 99.5%.

Metabolism

SOFENIB® is metabolised primarily in the liver undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9.

Elimination

The elimination half-life of SOFENIB® is approximately 25-48 hours. Following oral administration of a 100 mg dose of a solution formulation of SOFENIB®, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in faeces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged SOFENIB®, accounting for 51% of the dose, was found in faeces but not in urine.

INDICATIONS

Hepatocellular Carcinoma

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

Renal Cell Carcinoma

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

Differentiated Thyroid carcinoma

SOFENIB® is indicated for the treatment of patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine.

DOSAGE AND ADMINISTRATION

Recommended dose

The recommended daily dose of SOFENIB® is 400 mg (2 x 200 mg tablets) taken twice a day, either without food or together with a moderate fat meal.

Duration of treatment

Treatment should be continued until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Dose titration, dose adjustment, special monitoring advice

Management of suspected adverse medicine reactions may require temporary interruption and/or dose reduction of SOFENIB® therapy.

When dose reduction is necessary during the treatment of hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC), the SOFENIB® dose should be reduced to two tablets of 200 mg once daily.

When dose reduction is necessary during the treatment of differentiated thyroid carcinoma, the SOFENIB® dose should be reduced to 600 mg daily in divided doses (two tablets of 200 mg and one tablet of 200 mg twelve hours apart).

If additional dose reduction is necessary, SOFENIB® may be reduced to one tablet of 200 mg twice daily, followed by one tablet of 200 mg once daily.

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.

Pregnancy and Lactation

SOFENIB® should not be used during pregnancy. Breastfeeding should be discontinued during SOFENIB® therapy.

Use in Children

The safety and effectiveness of SOFENIB® in paediatric patients has not been established.

ADVERSE EFFECTS

The most common adverse reactions were diarrhoea, fatigue, alopecia, infection, rash, and hand-foot skin reaction.

CONTRAINDICATIONS

SOFENIB® is contraindicated in patients with known severe hypersensitivity to SOFENIB® or any other component of Sofenib. SOFENIB® in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer.

PRECAUTIONS

- Cardiac ischemia and/or infarction may occur. Consider temporary or permanent discontinuation of SOFENIB®.
- Bleeding may occur. If bleeding necessitates medical intervention, consider discontinuation of SOFENIB®.
- 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, SOFENIB® should be discontinued.
- Temporary interruption of SOFENIB® is recommended in patients undergoing major surgical procedures.
- 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.

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 SOFENIB® 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 SOFENIB® 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 SOFENIB® treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease SOFENIB® dose by one dose level (400 mg daily or 400 mg every other day)
	4th occurrence	Discontinue SOFENIB® 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	3rd occurrence	Discontinue SOFENIB® 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 Sofenib.

OVERDOSE

There is no specific treatment for SOFENIB® overdose. The highest dose of SOFENIB® 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, SOFENIB® should be withheld and supportive care instituted.

DRUG INTERACTIONS

CYP3A4 inducers: Can increase the metabolism of SOFENIB® and decrease the AUC of SOFENIB®.

Caution is recommended when administering SOFENIB® with compounds that are metabolised/eliminated predominantly by the UGT1A1 (e.g. irinotecan) or UGT1A9 pathways. Caution is recommended when SOFENIB® 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 SOFENIB® bioavailability .The risk of reduced plasma concentrations of SOFENIB® 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 SOFENIB® 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 SOFENIB® 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 SOFENIB® as add-on to platinum- based chemotherapies.

PHARMACEUTICAL INFORMATION

Storage condition: Store in cool and dry (below 30°C.) place, away from light. Keep out of the reach of children.

Presentation & Packaging

SOFENIB® Tablet: Each commercial box contains 3×4 tablets in Alu-Alu blister pack.

Marketed by
Renata Limited
Mirpur, Dhaka, Bangladesh.

Manufactured by
Renata Oncology
Rajendrapur, Gazipur, Bangladesh.

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