Hepanib

Sorafenib 200 mg

Everest

COMPOSITION

HEPANIB tablet: Each film coated tablet contains Sorafenib Tosylate INN equivalent to Sorafenib 200 mg.

PHARMACOLOGY

Sorafenib is a kinase inhibitor that decreases tumor cell proliferation. 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 hepatocellular carcinoma and renal cell carcinoma, and several other human tumor xenografts in immunocompromised mice.

INDICATIONS AND USAGE

Hepatocellular Carcinoma

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

Renal Cell Carcinoma

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

DOSAGE & ADMINISTRATION

The recommended daily dose of Sorafenib 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.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of Sorafenib therapy. When dose reduction is necessary, the Sorafenib dose may be reduced to 400 mg once daily. If additional dose reduction is required, Sorafenib may be reduced to a single 400 mg dose every other day.

Table: Recommended regimens and treatment duration for Sorafenib therapy.

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	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 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 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.

Missed doses:

If a dose of Sorafenib is missed, skip the missed dose, and take next dose at regular time. Do not double your dose of Sorafenib.

Special populations

Pediatric Use:

The safety and effectiveness of Sorafenib in pediatric patients have not been studied.

Geriatric Use:

No differences in safety or efficacy were observed between older and younger patients

Renal impairment:

No dose adjustment of Sorafenib is required for patients with any degree of renal impairment.

Hepatic impairment:

Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment have Sorafenib AUCs that may be 23 – 65% lower than subjects with normal hepatic function. Systemic exposure and safety data were comparable in HCC patients with Child-Pugh A and B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment.

CONTRAINDICATION

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

WARNINGS AND PRECAUTIONS

Cardiac ischemia, infarction

Temporary or permanent discontinuation of Sorafenib should be considered in patients who develop cardiac ischemia and/or infarction.

Risk of Hemorrhage

An increased risk of bleeding may occur following Sorafenib administration.

There was one fatal hemorrhage in each treatment group in RCC Study. If any bleeding necessitates medical intervention, permanent discontinuation of Sorafenib should be considered.

Risk of Hypertension

In the HCC study, hypertension was reported in approximately 9.4% and In RCC Study, hypertension was reported in approximately 16.9% of Sorafenib -treated patients. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of Sorafenib should be considered.

Risk of Dermatologic Toxicities

Hand-foot skin reaction and rash represent the most common adverse reactions attributed to Sorafenib.

Risk of Gastrointestinal Perforation

In the event of a gastrointestinal perforation, Sorafenib therapy should be discontinued.

Warfarin Co-Administration

Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes.

Wound Healing Complications

Resume Sorafenib therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Use of Sorafenib in combination with Carboplatin and Paclitaxel in Non-small Cell Lung Cancer

Patients with squamous cell carcinoma (prospectively stratified), higher mortality was observed with the addition of Sorafenib compared to those treated with carboplatin and paclitaxel alone.

Interactions with UGT1A1 Substrates

Sorafenib can cause increases in plasma concentrations of drugs that are substrates of UGT1A1.

Interaction with Docetaxel & Doxorubicin

Sorafenib can cause increases in plasma concentrations of Docetaxel and Doxorubicin.

Hepatic Impairment

Hepatic impairment may reduce plasma concentrations of Sorafenib.

Neomycin

Co-administration of oral Neomycin causes a decrease in Sorafenib exposure.

SIDE EFFECTS

Serious adverse reactions are cardiac ischemia, infarction, hemorrhage, hypertension, hand-foot skin reaction and rash, gastrointestinal perforation, wound healing complications.

PREGNANCY & LACTATION

Pregnancy:

Based on its mechanism of action and findings in animals, Sorafenib may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while on Sorafenib.

Lactation:

It is not known whether Sorafenib is excreted in human milk.

DRUG INTERACTIONS

Carboplatin and Paclitaxel

Sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer, due to increased mortality observed with the addition of Sorafenib compared to those treated with carboplatin and paclitaxel alone. No definitive cause was identified for this finding.

UGT1A1 and UGT1A9 Substrates

Systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with Sorafenib

Docetaxel

Concomitant use of Docetaxel (75 or 100 mg/m2 administered every 21 days) with Sorafenib (200 or 400 mg twice daily), administered 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 C_{max}. Caution is recommended when Sorafenib is co-administered with Docetaxel

Doxorubicin

Concomitant treatment with Sorafenib resulted in a 21% increase in the AUC of Doxorubicin. Caution is recommended when administering Doxorubicin with Sorafenib.

Fluorouracil

Both increases (21%–47%) and decreases (10%) in the AUC of Fluorouracil were observed with concomitant treatment with Sorafenib. Caution is recommended when Sorafenib is co-administered with Fluorouracil/Leucovorin.

CYP2B6 and CYP2C8 Substrates

Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with Sorafenib.

CYP3A4 Inducers

Continuous concomitant administration of Sorafenib and Rifampicin resulted in an average 37% reduction of Sorafenib AUC. Other inducers of CYP3A4 activity (for example, Hypericum perforatum 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 and CYP Isoform Substrates

Sorafenib metabolism is unlikely to be altered by CYP3A4 inhibitors and is unlikely to alter the metabolism of substrates of these enzymes.

P-glycoprotein Substrates

Sorafenib is an inhibitor of P-glycoprotein in vitro, therefore may increase the concentrations of concomitant drugs that are P-glycoprotein substrates.

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 or CYP3A4.

Combination with other Antineoplastic Agents

Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin.

Neomycin

Coadministration of Sorafenib with oral Neomycin should be carefully considered because average plasma exposure (AUC) of Sorafenib was decreased by 54%.

OVERDOSAGE

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.

PHARMACEUTICAL INFORMATION

Storage

Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

How Supplied

HEPANIB tablet: Each HDPE bottle of HEPANIB contains 28 film-coated tablets (each tablet contains Sorafenib Tosylate INN equivalent to Sorafenib 200 mg), a silica gel desiccant and polyester coil with a child-resistant closure.

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