Fenitab®

Sorafenib Tosylate INN Film Coated Tablet

DESCRIPTION

Fenitab® is a preparation of Sorafenib Tosylate. 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 hepatocellular carcinoma and renal cell carcinoma, and several other human tumor xenografts in immunocompromised mice.

PHARMACOKINETICS

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

Absorption and Distribution: Following oral administration, Sorafenib reaches peak plasma levels in approximately 3 hours. When given 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), Sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. It is recommended that Sorafenib be administered without food. Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily.

Metabolism and Elimination: Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib accounts for approximately 70–85% of the circulating analytes in plasma at steady-state. Eight metabolites of Sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of Sorafenib in plasma, the pyridine N-oxide, shows in vitro potency similar to that of Sorafenib. This metabolite comprises approximately 9–16% of circulating analytes at steady-state. 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.

INDICATIONS

- Unresectable hepatocellular carcinoma
- Advanced renal cell carcinoma

DOSAGE AND ADMINISTRATION

- 2 tablets (400 mg) orally twice daily without food.
- Treatment interruption and/or dose reduction may be needed to manage suspected adverse drug reactions. Dose may be reduced to 400 mg once daily or to 400 mg every other day.

CONTRAINDICATIONS

- Hypersensitivity of Sorafenib.
- In combination with Carboplatin and Paclitaxel is contraindicated in patients with squamous cell lung cancer.

SIDE EFFECTS

- Fatigue, weight loss
- Rash/desquamation
- Hand-foot skin reaction, alopecia
- Diarrhea, anorexia, nausea and abdominal pain

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.

WARNINGS AND 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 therapy should be discontinued.
- Temporary interruption of Sorafenib therapy is recommended in patients undergoing major surgical procedures
- Caution is recommended when co-administering substances metabolized/eliminated predominantly by the UGT1A1 pathway (for example, irinotecan).
- Caution is recommended when co-administering docetaxel.
- Caution is recommended when co-administering doxorubicin.
- 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 .

DRUG INTERACTIONS

- **Carboplatin and Paclitaxel:** Caution, Sorafenib and paclitaxel AUC increases when co-administered.
- **UGT1A1 (for example, irinotecan) and UGT1A9 substrates:** Caution, drug AUC increases when co-administered with Sorafenib.
- **Docetaxel:** Caution, docetaxel AUC increases when co-administered with Sorafenib.
- **Doxorubicin:** Caution, doxorubicin AUC increases when co-administered with Sorafenib.
- **Fluorouracil:** Caution, fluorouracil AUC changes when co-administered with Sorafenib.
- **CYP2B6 and CYP2C8 substrates:** Caution, systemic exposure is expected to increase when co-administered with Sorafenib.
- **CYP3A4 inducers:** Expected to increase metabolism of Sorafenib and decrease Sorafenib concentrations.
- **Neomycin:** Caution, Sorafenib AUC decreases when co-administered with oral neomycin.

USE IN PREGNANCY AND LACTATION

Pregnancy category D. There are no adequate and well-controlled studies in pregnant women using Sorafenib. However, based on its mechanism of action and findings in animals, Sorafenib may cause fetal harm when administered to a pregnant woman.

It is not known whether Sorafenib is 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 Sorafenib, 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.

PHARMACEUTICAL PRECAUTION

Store below 30 °C temperature. Keep away from light & wet place. Keep out of reach of children.

PACKAGING

Fenitab® Tablet: Box containing 7 strips of 4 tablets each. Each film coated tablet contains Sorafenib Tosylate INN equivalent to Sorafenib 200 mg.

SK+F ONCOLOGY

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