NOBOKIN

Sorafenib Tosylate INN 200 mg

"Please carefully read the full leaflet"

NAME OF THE MEDICINAL PRODUCT
NOBOKIN 200 mg tablet for orally use.

DESCRIPTION
Sorafenib, is a kinase inhibitor, is the tosylate salt of Sorafenib. Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(-trifluoromethyl)phenyl]ureido}phenoxy)N2-methylpyridine-2-carboxamide4-methylbenzenesulfonate.

COMPOSITION
Nobokin Tablet: Each film coated tablet contains Sorafenib Tosylate INN equivalent to Sorafenib 200 mg.

CLINICAL PHARMACOLOGY

Mechanism 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 hepatocellular carcinoma and renal cell carcinoma, and several other human tumor xenografts in immunocompromised mice.

Pharmacokinetics

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 Cmax and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily. In vitro binding of Sorafenib to human plasma proteins is 99.5%.

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.

Special Populations

Age
Analyses of demographic data suggest that no dose adjustments are necessary for age.

Gender
Analyses of demographic data suggest that no dose adjustments are necessary for gender.

Race
A study of the pharmacokinetics of Sorafenib indicated that the mean AUC of Sorafenib in Asians (N=78) was 30% lower than in Caucasians (N=40).

Pediatric
There are no pharmacokinetic data in pediatric patients.

THERAPEUTIC INDICATIONS

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

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

Differentiated thyroid carcinoma (DTC)
Sorafenib is indicated for the treatment of patient with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment.

DOSAGE AND ADMINISTRATION
The recommended daily dose of Sorafenib for Hepatocellular carcinoma, Renal cell carcinoma, and Differentiated thyroid carcinoma is 400 mg (2X200 mg tablets) taken twice daily without food (at least 1 hour before meal or 2 hour after meal). Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Dose Modifications
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.
Suggested dose modifications for skin toxicity are outlined in Table 1.

Table 1: Suggested Dose Modifications for Skin Toxicity

DOSE MODIFICATION GUIDELINES

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 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

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.

WARNING AND PRECAUTIONS

Risk of Cardiac Ischemia and/or Infarction
In the HCC study, the incidence of cardiac ischemia/infarction was 2.7% in Sorafenib patients compared with 1.3% in the placebo group and in RCC Study 1, the incidence of cardiac ischemia/infarction was higher in the Sorafenib group (2.9%) compared with the placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. 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. In the HCC study, an excess of bleeding regardless of causality was not apparent and the rate of bleeding from esophageal varices was 2.4% in Sorafenib patients and 4% in placebo patients. Bleeding with a fatal outcome from any site was reported in 2.4% of Sorafenib patients and 4% in placebo patients. In RCC Study 1, bleeding regardless of causality was reported in 15.3% of patients in the Sorafenib group and 8.2% of patients in the placebo group. The incidence of CTCAE Grade 3 and 4 bleeding was 2% and 0%, respectively, in Sorafenib patients, and 1.3% and 0.2%, respectively, in placebo patients. There was one fatal hemorrhage in each treatment group in RCC Study 1. If any bleeding necessitates medical intervention, permanent discontinuation of Sorafenib should be considered.

Risk of Hypertension
Blood pressure should be monitored weekly during the first 6 weeks of Sorafenib therapy and thereafter monitored and treated, if required, in accordance with standard medical practice. In the HCC study, hypertension was reported in approximately 9.4% of Sorafenib-treated patients and 4.3% of patients in the placebo group. In RCC Study 1, hypertension was reported in approximately 16.9% of Sorafenib-treated patients and 1.8% of patients in the placebo group. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of Sorafenib should be considered. Permanent discontinuation due to hypertension occurred in 1 of 297 Sorafenib patients in the HCC study and 1 of 451 Sorafenib patients in RCC Study 1.

Risk of Dermatologic Toxicities
Hand-foot skin reaction and rash represent the most common adverse reactions attributed to Sorafenib. Rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with Sorafenib. Manage-

ment of dermatologic 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. Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 4 of 297 Sorafenib HCC patients and 3 of 451 Sorafenib RCC patients.

Risk of Gastrointestinal Perforation
Gastrointestinal perforation is an uncommon adverse reaction and has been reported in less than 1% of patients taking Sorafenib. In some cases this was not associated with apparent intra-abdominal tumor. In the event of a gastrointestinal perforation, Sorafenib therapy should be discontinued.

Warfarin Co-Administration
Infrequent bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking Warfarin while on Sorafenib therapy. Patients taking concomitant Warfarin should 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 in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of Sorafenib therapy following major surgical intervention. Therefore, the decision to resume Sorafenib therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Hepatic Impairment
Hepatic impairment may reduce plasma concentrations of Sorafenib. Comparison of data across studies suggests that Sorafenib levels are lower in HCC patients than in non-HCC patients (without hepatic impairment). The AUC of Sorafenib is similar between HCC patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. The optimal dose in non-HCC patients with hepatic impairment is not established.

Use in Pregnancy
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. 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. Women of childbearing potential should be advised to avoid becoming pregnant while on Sorafenib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

Dermatological	: Hand-Foot skin reaction, Alopecia Constitutional Symptoms: Fatigue, Weight loss
Gastrointestinal	: Diarrhea, Anorexia, Nausea
Hepatobiliary	: Liver dysfunction

DRUG INTERACTIONS

Carboplatin and Paclitaxel
Concomitant use of Carboplatin (AUC=6 mg/ml•min) and Paclitaxel (225 mg/m2) once every three weeks with Sorafenib (400 mg twice daily) resulted in a 30% increase in Paclitaxel AUC, a 50% increase in Sorafenib AUC, and no change in Carboplatin AUC. 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
Caution is recommended when administering Sorafenib with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (for example, Irinotecan). Sorafenib inhibits glucuronidation by the UGT1A1 (Ki value: 1 micromolar) and UGT1A9 pathways (Ki value: 2 micromolar). Systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with Sorafenib.
In clinical studies, when Sorafenib was administered with Irinotecan, whose active metabolite SN-38 is further metabolized 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
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 Cmax. 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
Sorafenib inhibits CYP2B6 and CYP2C8 in vitro with Ki values of 6 and 1–2 micromolar, respectively. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with Sorafenib. Caution is recommended when administering substrates of CYP2B6 and CYP2C8 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 may also increase metabolism of Sorafenib and thus decrease Sorafenib concentrations.

CYP3A4 Inhibitors and CYP Isoform Substrates
In vitro data indicate that Sorafenib is metabolized by CYP3A4 and UGT1A9 pathways. Ketoconazole (400 mg), a potent inhibitor of CYP3A4, administered once daily for 7 days did not alter the mean AUC of a single oral 50 mg dose of Sorafenib in healthy volunteers. Therefore, Sorafenib metabolism is unlikely to be altered by CYP3A4 inhibitors.
Studies with human liver microsomes demonstrated that Sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4 as indicated by Ki values of 17 micromolar, 22 micromolar, and 29 micromolar, respectively. Administration of Sorafenib 400 mg twice daily for 28 days did not alter the exposure of concomitantly administered Midazolam (CYP3A4 substrate), Dextromethorphan (CYP2D6 substrate), and Omeprazole (CYP2C19 substrate). This indicates that Sorafenib is unlikely to alter the metabolism of substrates of these enzymes in vivo.
Studies with human liver microsomes demonstrated that Sorafenib is a competitive inhibitor of CYP2C9 with a Ki value of 7–8 micromolar. The possible effect of Sorafenib on the metabolism of the CYP2C9 substrate Warfarin was assessed indirectly by measuring PT-INR. The mean changes from baseline in PT-INR were not higher in Sorafenib patients compared to placebo patients, suggesting that Sorafenib did not inhibit Warfarin metabolism in vivo.

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.

Combination with Other Antineoplastic Agents
In clinical studies, Sorafenib has been administered with a variety of other antineoplastic agents at their commonly used dosing regimens, including Gemcitabine, Oxaliplatin, Doxorubicin, Docetaxel, and Irinotecan. Sorafenib had no effect on the pharmacokinetics of Gemcitabine or Oxaliplatin.

Neomycin
The average plasma exposure (AUC) of Sorafenib was decreased by 54% in healthy volunteers who first received Neomycin 1 g three times daily for 5 days orally. Therefore, the co-administration of Sorafenib with oral Neomycin should be carefully considered. Effects of other antibiotics on Sorafenib pharmacokinetics have not been studied.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category D

Nursing Mothers
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.

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

Geriatric Use
In total, 59% of HCC patients treated with Sorafenib were age 65 years or older, and 19% were 75 and older. In total, 32% of RCC patients treated with Sorafenib were age 65 years or older, and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients.

Patients with Hepatic Impairment
In vitro and in vivo data indicate that Sorafenib is primarily metabolized by the liver. Comparison of data across studies suggests that patients with 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.

Patients with Renal Impairment
Sorafenib has not been studied in patients undergoing dialysis. No dosage adjustment is necessary when administering Sorafenib to patients with mild, moderate or severe renal impairment not undergoing dialysis.

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

OVERDOSAGE
There is no specific treatment for Sorafenib overdose.

PHAMARCEUTICAL INFORMATION

Storage Condition
NOBOKIN (Sorafenib) should keep in a dry place and should store at 25^0 C; excursions permitted to 15^0 - 30^0 C.
Keep out of the reach of children.

PRESENTATION AND PACKAGING

Nobokin tablet: Each commercial box contains 8 (1X8's), 16 (2X8's), 24 (3X8's), 32 (4X8's), 40 (5X8's) tablets in Alu-Alu blister pack.

Manufactured by

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