For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

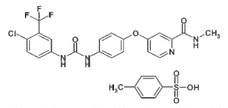
℞

Sorafenib Tablets IP 200 mg

SORAFEKAST™

Composition :
Each film coated tablet contains :
Sorafenib Tosylate IP
eq. to Sorafenib 200 mg
Excipients qs.
Colour: Yellow Oxide of Iron

Sorafenib, a multikinase inhibitor targeting several serine/threonine and receptor tyrosine kinases, 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-carboxamide 4-methylbenzenesulfonate and its structural formula is:



Sorafenib tosylate is a white to yellowish or brownish solid with a molecular formula of $C^{21}H^{16}ClF^3N^4O^3$ x $C^7H^8O^3S$ and a molecular weight of 637.0 g/mole. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

CLINICAL PHARMACOLOGY
Mechanism of Action
Sorafenib is a multikinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib inhibited tumor growth of the murine renal cell carcinoma, RENCA, and several other human tumor xenografts in athymic mice. A reduction in tumor angiogenesis was seen in some tumor xenograft models. Sorafenib was shown to interact with multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT- 3, VEGFR- 2, VEGFR- 3, and PDGFR- ß). Several of these kinases are thought to be involved in angiogenesis.

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, bioavailability was similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. It is recommended that Sorafenib be administered without food (at least 1 hour before or 2 hours after eating)

DOSAGE AND ADMINISTRATION
Mean C_{max} 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 steadystate. 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
Analyses of demographic data suggest that no dose adjustments are necessary for age or gender.

Race
Limited pharmacokinetic data on sorafenib 400 mg twice daily in a study in Japanese patients (n=6) showed a 45% lower systemic exposure (mean steady-state AUC) as compared to pooled Phase 1 pharmacokinetic data in Caucasian patients (n=25). The clinical significance of this finding is not known (see **PRECAUTIONS** – General - Race).

Pediatric
There are no pharmacokinetic data in pediatric patients.
Hepatic Impairment
Sorafenib is cleared primarily by the liver. In patients with mild (Child-Pugh A, n=14) or moderate (Child-Pugh B, n=8) hepatic impairment, exposure values were within the range observed in patients without hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment (See **PRECAUTIONS** – **Patients with Hepatic Impairment section).**

Renal Impairment
In a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy subjects, 19% of the administered dose of sorafenib was excreted in urine. In four Phase 1 clinical trials, sorafenib was evaluated in patients with normal renal function (n=71) and in patients with mild renal impairment (CrCl >50–80 mL/min, n=24) or moderate renal impairment (CrCl 30–50 mL/min, n=4). No relationship was observed between renal function and steady-state sorafenib AUC at doses of 400 mg twice daily. The pharmacokinetics of sorafenib have not been studied in patients with severe renal impairment (CrCl <30 ml/min) or in patients undergoing dialysis (see **PRECAUTIONS – Patients with Renal Impairment section**).

Drug-Drug Interactions
CYP3A4 inhibitors: 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.

CYP isoform-selective substrates: Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4 as indicated by Ki values of 17 µM, 22 µM, and 29 µM, 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*.

CYP2C9 substrates: Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9 with a Ki value of 7-8 µM. 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* (see **PRECAUTIONS –** *Warfarin Co-administration* section).

CYP3A4 inducers: There is no clinical information on the effect of CYP3A4 inducers on the pharmacokinetics of sorafenib. Substances that are inducers of CYP3A4 activity (e.g. rifampin, St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations.

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, and irinotecan. Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. Concomitant treatment with Sorafenib resulted in a 21% increase in the AUC of doxorubicin. When 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 (see **PRECAUTIONS – Drug Interactions** sections).

***In vitro* studies**
In vitro studies of enzyme inhibition: Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with Ki values of 6 and 1-2 µM, respectively. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with Sorafenib. Sorafenib inhibits glucuronidation by the UGT1A1 (Ki value: 1 µM) and UGT1A9 pathways (Ki value: 2 µM). Systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with Sorafenib.

***In vitro studies of 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.

CLINICAL STUDIES
The safety and efficacy of Sorafenib in the treatment of advanced renal cell carcinoma (RCC) were studied in the following 2 randomized controlled clinical trials. **Study 1** was a Phase 3, international, multicenter, randomized, double blind, placebo controlled trial in patients with advanced renal cell carcinoma who had received one prior systemic therapy. Primary study endpoints included overall survival and progression-free survival (PFS). Tumor response rate was a secondary endpoint. The PFS analysis included 769 patients stratified by MSKCC (Memorial Sloan Kettering Cancer Center) prognostic risk category1 (low or intermediate) and country and randomized to Sorafenib 400 mg twice daily (N=384) or to placebo (N=385). Table 1 summarizes the demographic and disease characteristics of the study population analyzed. Baseline demographics and disease characteristics were well balanced for both treatment groups. The median time from initial diagnosis of RCC to randomization was 1.6 and 1.9 years for the Sorafenib and placebo groups, respectively.

Table 1: Demographic and Disease Characteristics - Study 1

Characteristics	Sorafenib N	N=384 (%)	Placebo n	N=385 (%)
Gender				
Male	267	(70)	287	(75)
Female	116	(30)	98	(25)
Race				
White	276	(72)	278	(73)
Black/Asian/ Hispanic/Other	11	(3)	10	(2)
Not reported [a]	97	(25)	97	(25)
Age group				
< 65 years	255	(67)	280	(73)
≥ 65 years	127	(33)	103	(27)
ECOG performance status at baseline				
0	184	(48)	180	(47)
1	191	(50)	201	(52)
2	6	(2)	1	(<1)
Not reported	3	(<1)	3	(<1)
MSKCC prognostic risk category[1]				
Low	200	(52)	194	(50)
Intermediate	184	(48)	191	(50)
Prior IL-2 and/or interferon				
Yes	319	(83)	313	(81)
No	65	(17)	72	(19)

a. Race was not collected from the 186 patients enrolled in France due to local regulations. In 8 other patients, race was not available at the time of analysis.

Progression-free survival, defined as the time from randomization to progression or death from any cause, whichever occurred earlier, was evaluated by blinded independent radiological review using RECIST criteria. Figure 1 depicts Kaplan-Meier curves for PFS. The PFS analysis was based on a two-sided Log-Rank test stratified by MSKCC prognostic risk category[1]and country. The median PFS for patients randomized to Sorafenib was 167 days compared to 84 days for patients randomized to placebo. The estimated hazard ratio (risk of progression with Sorafenib compared to placebo) was 0.44 (95% CI: 0.35, 0.55). A series of patient subsets were examined in exploratory univariate analyses of PFS. The subsets included age above or below 65 years, ECOG PS 0 or 1, MSKCC prognostic risk category1, whether the prior therapy was for progressive metastatic disease or for an earlier disease setting, and time from diagnosis of less than or greater than 1.5 years. The effect of Sorafenib on PFS was consistent across these subsets, including patients with no prior IL-2 or interferon therapy (n=137; 65 patients receiving Sorafenib and 72 placebo), for whom the median PFS was 172 days on Sorafenib compared to 85 days on placebo. Tumor response was determined by independent radiological review according to RECIST criteria. Overall, of 672 patients who were evaluable for response, 7 (2%) Sorafenib patients and 0 (0%) placebo patients had a confirmed partial response. Thus the gain in PFS in Sorafenib-treated patients primarily reflects the stable disease population. At the time of a planned interim survival analysis, based on 220 deaths, overall survival was longer for Sorafenib than placebo with a hazard ratio (Sorafenib over placebo) of 0.72. This analysis did not meet the prespecified criteria for statistical significance. Additional analyses are planned as the survival data mature. Study 2 was a Phase 2 randomized discontinuation trial in patients with metastatic malignancies, including RCC. The primary endpoint was the percentage of randomized patients remaining progression-free at 24 weeks. All patients received Sorafenib for the first 12 weeks. Radiologic assessment was repeated at week 12. Patients with <25% change in bi-dimensional tumor measurements from baseline were randomized to Sorafenib or placebo for a further 12 weeks. Patients who were randomized to placebo were permitted to cross over to open-label Sorafenib upon progression. Patients with tumor shrinkage ≥25% continued Sorafenib, whereas patients with tumor growth ≥25% discontinued treatment. Two hundred and two patients with advanced RCC were enrolled into Study 2, including patients who had received no prior therapy and patients with tumor histology other than clear cell carcinoma. After the initial 12 weeks of Sorafenib therapy, 79 RCC patients continued on open-label Sorafenib, and 65 patients were randomized to Sorafenib or placebo. After an additional 12 weeks, at week 24, for the 65 randomized patients, the progression-free rate was significantly higher in patients randomized to Sorafenib (16/32, 50%) than in patients randomized to placebo (6/33, 18%) (p=0.0077). Progression-free survival was significantly longer in the Sorafenib group (163 days) than in the placebo group (41 days) (p=0.0001, HR=0.29).

INDICATIONS AND USAGE
Sorafenib is indicated for the treatment of patients with advanced renal cell carcinoma.

CONTRAINDICATIONS
Sorafenib is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of Sorafenib.

WARNINGS
Pregnancy Category D
In rats and rabbits, sorafenib has been shown to be teratogenic and to induce embryo-fetal toxicity (including increased post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight). The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (approximately 500 mg/m2/day on a body surface area basis). Adverse intrauterine development effects were seen at doses ≥ 1.2 mg/m2/day in rats and 3.6 mg/m2/day in rabbits (approximately 0.008 times the AUC seen in cancer patients at the recommended human dose). A NOAEL (no observed adverse effect level) was not defined for either species, since lower doses were not tested. Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, sorafenib should be assumed to cause fetal harm when administered to a pregnant woman. 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 (see **PRECAUTIONS – Information for Patients**)
There are no adequate and well-controlled studies in pregnant women using Sorafenib. Women of childbearing potential should be advised to avoid becoming pregnant while on Sorafenib. Sorafenib should be used during pregnancy only if the potential benefits justify the potential risks to the fetus (see **PRECAUTIONS – Information for Patients** section).
PRECAUTIONS
General
Dermatologic Toxicities: Hand-foot skin reaction and rash represent the most common adverse events attributed to Sorafenib. Analysis of cumulative event rates from Study 1 suggest that 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. Management 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 3 of 451 Sorafenib patients.
Hypertension: In Study 1, treatment-emergent 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. 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 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 451 Sorafenib patients.
Hemorrhage: An increased risk of bleeding may occur following Sorafenib administration. In 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 events 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 Study 1. If any bleeding event necessitates medical intervention, permanent discontinuation of Sorafenib should be considered. *Cardiac Ischemia and/or Infarction:* In Study 1, the incidence of treatment-emergent cardiac ischemia/infarction events 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.
Race: Limited pharmacokinetic data on sorafenib 400 mg twice daily in a study in Japanese patients (n=6) showed a 45% lower systemic exposure (mean steady-state AUC) as compared to pooled Phase 1 pharmacokinetic data in Caucasian patients (n=25). The clinical significance of this finding is not known.
Warfarin Co-administration: Infrequent bleeding events 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.

Drug Interactions
Caution is recommended when administering Sorafenib with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan) (see

CLINICAL PHARMACOLOGY – Drug-Drug Interactions section).
Concomitant treatment with Sorafenib resulted in a 21% increase in the AUC of doxorubicin. Caution is recommended when administering doxorubicin with Sorafenib. Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with Ki values of 6 and 1-2 µM, 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.

Patients with Hepatic Impairment
In vitro and *in vivo* data indicate that sorafenib is primarily metabolized by the liver. Systemic exposure and safety data were comparable in patients with Child-Pugh A and B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment. No dose adjustment is necessary when administering Sorafenib to patients
with Child-Pugh A and B hepatic impairment (see **CLINICAL PHARMACOLOGY – Hepatic Impairment** section).

Patients with Renal Impairment
Sorafenib has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or in patients undergoing dialysis.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been performed with sorafenib. Sorafenib was clastogenic when tested in an *in vitro* mammalian cell assay (Chinese Hamster Ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the *in vitro* Ames bacterial cell assay or clastogenic in an *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test) when tested independently. No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for sorafenib to impair reproductive performance and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration of epididymis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested follicular development. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses ≥30 mg/m2 (approximately 0.5 times the AUC in cancer patients at the recommended human dose). Dogs showed tubular degeneration in the testes at 600 mg/m2/day (approximately 0.3 times the AUC at the recommended human dose) and oligospermia at 1200 mg/m2/day of sorafenib. Adequate contraception should be used during therapy and for at least 2 weeks after completing therapy.

Pregnancy Category D (see WARNINGS)
Nursing Mothers
It is not known whether sorafenib is excreted in human milk. Following administration of 14C-sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was secreted into the milk. The milk to plasma AUC ratio was approximately 5:1. Because many drugs are excreted in human milk and because the effects of sorafenib on infants have not been studied, women should be advised against breast-feeding while receiving Sorafenib.

Pediatric Use
The safety and effectiveness of Sorafenib in pediatric patients have not been studied. Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses ≥600 mg/m2 (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m2/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m2/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

Geriatric Use
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, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Information for Patients (see Patient Information About: Sorafenib)
Physicians should inform female patients that Sorafenib may cause birth defects or fetal loss and that they should not become pregnant during treatment with Sorafenib and for at least 2 weeks after stopping treatment. Both male and female patients should be counseled to use effective birth control during treatment with Sorafenib and for at least 2 weeks after stopping treatment. Female patients should also be advised against breast-feeding while receiving Sorafenib. Patients should be advised of the possible occurrence of hand-foot skin reaction and rash during Sorafenib treatment and appropriate countermeasures. Patients should be informed that hypertension may develop during Sorafenib treatment, especially during the first six weeks of therapy, and that blood pressure should be monitored regularly during treatment. Physicians should inform patients that Sorafenib may increase the risk of bleeding and that they should promptly report any episodes of bleeding. Physicians should also discuss with patients that cardiac ischemia and/or infarction has been reported during Sorafenib treatment, and that they should immediately report any episodes of chest pain or other symptoms of cardiac ischemia and/or infarction.

ADVERSE REACTIONS
Safety evaluation of Sorafenib is based on 1286 cancer patients who received Sorafenib as monotherapy and 165 patients who received Sorafenib concurrently with chemotherapy. A total of 346 patients were exposed to Sorafenib monotherapy for greater than 6 months. A total of 664 RCC patients received Sorafenib monotherapy, of whom 215 were treated for at least 6 months. Table 2 shows the percent of patients experiencing treatment-emergent adverse events that were reported in at least 10% of patients who received Sorafenib in Study 1. CTCAE Grade 3 treatment-emergent adverse events were reported in 31% of patients receiving Sorafenib compared to 22% of patients receiving placebo. CTCAE Grade 4 treatmentemergent adverse events were reported in 7% of patients receiving Sorafenib compared to 6% of patients receiving placebo.The rate of adverse events (including events associated with progressive disease) resulting in permanent discontinuation was similar in both the Sorafenib and placebo groups (10% of Sorafenib patients and 8% of placebo patients). Safety was also assessed in a Phase 2 study pool comprised of 638 Sorafenib-treated patients, including 202 patients with RCC, 137 patients with hepatocellular carcinoma, and 299 patients with other cancers. The most common drug-related adverse events reported in Sorafenib-treated patients in this pool were rash (38%), diarrhea (37%), hand-foot skin reaction (35%), and fatigue (33%). The respective rates of CTC (v 2.0) Grade 3 and 4 drugrelated adverse events in Sorafenib-treated patients were 37% and 3%, respectively.

Additional Data from Multiple Clinical Trials
The following additional drug-related adverse events and laboratory abnormalities were reported from clinical trials of Sorafenib in 1286 cancer patients who received Sorafenib as monotherapy (*very common* 10% or greater, *common* 1 to less than 10%, *uncommon* 0.1% to less than 1%):

Cardiovascular: *Uncommon:* hypertensive crisis, myocardial ischemia and/or infarction
Dermatologic: *Very common:* erythema *Common:* exfoliative dermatitis, acne, flushing *Uncommon:* folliculitis, eczema, erythema multiforme
Digestive: *Very common:* increased lipase, increased amylase *Common:* mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia *Uncommon:* pancreatitis, gastrointestinal reflux, gastritis Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values

General Disorders: *Very common:* asthenia, pain (including mouth pain, bone pain, and muscle pain) *Common:* decreased appetite, influenza-like illness, pyrexia *Uncommon:* infection
Hematologic: *Very common:* leukopenia, lymphopenia *Common:* anemia, neutropenia, thrombocytopenia *Uncommon:* INR abnormal
Hypersensitivity: *Uncommon:* hypersensitivity reactions (including skin reactions and urticaria)
Metabolic and Nutritional: *Very common:* hypophosphatemia *Common:* transient increases in transaminases *Uncommon:* dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism
Musculoskeletal: *Common:* arthralgia, myalgia
Nervous System and Psychiatric: *Common:* depression *Uncommon:* tinnitus
Reproductive: *Common:* erectile dysfunction *Uncommon:* gynecomastia
Respiratory: *Common:* hoarseness *Uncommon:* rhinorrhea

Nervous System and Psychiatric: *Common:* depression *Uncommon:* tinnitus
Reproductive: *Common:* erectile dysfunction *Uncommon:* gynecomastia
Respiratory: *Common:* hoarseness *Uncommon:* rhinorrhea In addition, the following medically significant adverse events were reported infrequently during clinical trials of Sorafenib: cerebral hemorrhage, transient ischemic attack, cardiac failure, arrhythmia, thromboembolism, acute renal failure. For these events, the causal relationship to Sorafenib has not been established.

LABORATORY ABNORMALITIES
The following laboratory abnormalities were observed in Study 1: Hypophosphatemia was a common laboratory finding, observed in 45% of Sorafenibtreated patients compared to 11% of placebo patients. CTCAE Grade 3 hypophosphatemia (1-2 mg/dL) occurred in 13% of Sorafenib-treated patients and 3% of patients in the placebo group. There were no cases of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in either Sorafenib or placebo patients. The etiology of hypophosphatemia associated with Sorafenib is not known. Elevated lipase was observed in 41% of patients treated with Sorafenib compared to 30% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 12% of patients in the Sorafenib group compared to 7% of patients in the placebo group. Elevated amylase was observed in 30% of patients treated with Sorafenib compared to 23% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% of patients in the Sorafenib group compared to 3% of patients in the placebo group. Many of the lipase and amylase elevations were transient, and in the majority of cases Sorafenib treatment was not interrupted. Clinical pancreatitis was reported in 3 of 451 Sorafenibtreated patients (one CTCAE Grade 2 and two Grade 4) and 1 of 451 patients (CTCAE Grade 2) in the placebo group. Lymphopenia was observed in 23% of Sorafenib-treated patients and 13% of placebo patients. CTCAE Grade 3 or 4 lymphopenia was reported in 13% of Sorafenib-treated patients and 7% of placebo patients. Neutropenia was observed in 18% of Sorafenibtreated patients and 10% of placebo patients. CTCAE Grade 3 or 4 neutropenia was reported in 5% of Sorafenib-treated patients and 2% of placebo patients. Anemia was observed in 44% of Sorafenib-treated patients and 49% of placebo patients. CTCAE Grade 3 or 4 anemia was reported in 2% of Sorafenib-treated patients and 4% of placebo patients. Thrombocytopenia was observed in 12% of Sorafenib-treated patients and 5% of placebo patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of Sorafenib-treated patients and 0% of placebo patients.

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 events. 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.

DOSAGE AND 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 eating). 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 (see **PRECAUTIONS**).
No dose adjustment is required on the basis of patient age, gender, body weight, or in patients with Child-Pugh A or B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment or severe renal impairment including dialysis patients
(see **CLINICAL PHARMACOLOGY – Special Populations - Hepatic Impairment**, **Renal Impairment, and PRECAUTIONS** sections).

Presentation : A Bottle of 30 / 60 / 120 Tablets

Storage : **Store below 30ºC, Protected from light**

Made in India by:
APRAZER
Aprazer Healthcare Pvt. Ltd.
Kharuni-Lodhimajra Road
Vil. Nandpur, Baddi, Distt-Solan,
Himachal Pradesh-173205
www.aprazerhealthcare.com

PMA0003458-00