SORANIB Tablets (Sorafenib tosylate)

Composition

SORANIB 200 mg Tablets
Each film-coated tablet contains:
Sorafenib (as tosylate) ................. 200 mg

Dosage Form

Film-coated tablet for oral use

Pharmacology

Mechanism of action

Sorafenib is a kinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib was shown to inhibit multiple intracellular (c-CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT- 3, RET, RET/PTC, 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 of HCC, RCC, and DTC human tumor xenografts in immunocompromised mice. Reductions in tumor angiogenesis were seen in models of HCC and RCC upon sorafenib treatment, and increases in tumor apoptosis were observed in models of HCC, RCC, and DTC.

Cardiac Electrophysiology

The effect of Sorafenib 400 mg twice daily on the QTc interval was evaluated in a multi-center, open-label, non-randomized trial in 53 patients with advanced cancer. No large changes in the mean QTc intervals (that is, >20 ms) from baseline were detected in the trial. After one 28-day treatment cycle, the largest mean QTc interval change of 8.5 ms (upper bound of two-sided 90% confidence interval, 13.3 ms) was observed at 6 hours post-dose on day 1 of cycle 2.

Pharmacokinetics

Absorption and Distribution

After administration of sorafenib tablets the mean relative bioavailability is 38 - 49 % when compared to an oral solution. The absolute bioavailability is not known. Following oral administration sorafenib reaches peak plasma concentrations in approximately 3 hours. When given with a high-fat meal sorafenib absorption was reduced by 30 % compared to administration in the fasted state.

Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered twice daily. In vitro binding of sorafenib to human plasma proteins is 99.5 %.

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.

The steady-state concentrations of sorafenib administered at 400 mg twice daily were evaluated in DTC, RCC and HCC
patients. The highest mean concentration was observed in DTC patients (approximately twice that observed in patients with RCC and HCC), though variability was high for all tumour types. The reason for the increased concentration in DTC patients is unknown.

**Biotransformation and Elimination**

The elimination half-life of sorafenib is approximately 25 - 48 hours. Sorafenib is metabolised primarily in the liver and undergoes oxidative metabolism, mediated by CYP 3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib conjugates may be cleaved in the gastrointestinal tract by bacterial glucuronidase activity, allowing reabsorption of unconjugated active substance. Co-administration of neomycin has been shown to interfere with this process, decreasing the mean bioavailability of sorafenib by 54%.

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 faeces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in faeces but not in urine, indicating that biliary excretion of unchanged active substance might contribute to the elimination of sorafenib.

**Pharmacokinetics in Special Populations**

Analyses of demographic data suggest that there is no relationship between pharmacokinetics and age (up to 65 years), gender or body weight.

**Paediatric Population**

No studies have been conducted to investigate the pharmacokinetics of sorafenib in paediatric patients.

**Race**

There are no clinically relevant differences in pharmacokinetics between Caucasian and Asian subjects.

**Renal Impairment**

In four Phase I clinical trials, steady state exposure to sorafenib was similar in patients with mild or moderate renal impairment compared to the exposures in patients with normal renal function. In a clinical pharmacology study (single dose of 400 mg sorafenib), no relationship was observed between sorafenib exposure and renal function in subjects with normal renal function, mild, moderate or severe renal impairment. No data is available in patients requiring dialysis.

**Hepatic Impairment**

In hepatocellular carcinoma (HCC) patients with Child-Pugh A or B (mild to moderate) hepatic impairment, exposure values were comparable and within the range observed in patients without hepatic impairment. The pharmacokinetics (PK) of sorafenib in Child-Pugh A and B non-HCC patients were similar to the PK in healthy volunteers. There are no data for patients with Child-Pugh C (severe) hepatic impairment. Sorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population.

**Indications**

- **Hepatocellular Carcinoma (HCC)**

  SORANIB Tablets are indicated for the treatment of patients with HCC.

- **Renal Cell Carcinoma (RCC)**

  SORANIB Tablets are indicated for the treatment of patients with advanced RCC.
Differentiated Thyroid Carcinoma

SORANIB Tablets are indicated for the treatment of patients with locally advanced or metastatic differentiated thyroid carcinoma refractory to radioactive iodine.

Dosage And Administration

Recommended Dose for Hepatocellular Carcinoma, Renal Cell Carcinoma, and Differentiated Thyroid Carcinoma

The recommended daily dose of SORANIB Tablets 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.

Dose Modifications for Suspected Adverse Drug Reactions

Temporary interruption of SORANIB Tablets is recommended in patients undergoing major surgical procedures.

Temporary interruption or permanent discontinuation of SORANIB Tablets may be required for the following:

- Cardiac ischemia or infarction:
- Hemorrhage requiring medical intervention
- Severe or persistent hypertension despite adequate anti-hypertensive therapy
- Gastrointestinal perforation
- QTc prolongation
- Severe drug-induced liver injury

Dose Modifications for Hepatocellular Carcinoma and Renal Cell Carcinoma

When dose reduction is necessary, the SORANIB Tablets dose may be reduced to 400 mg once daily. If additional dose reduction is required, SORANIB Tablets may be reduced to a single 400 mg dose every other day.

Suggested dose modifications for dermatologic toxicities are outlined in Table 1.

Table 1: Suggested dose modifications for dermatologic toxicities in patients with hepatocellular or renal cell carcinoma

<table>
<thead>
<tr>
<th>Dermatologic Toxicity Grade</th>
<th>Occurrence</th>
<th>Suggested Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>Any occurrence</td>
<td>Continue treatment with SORANIB Tablets and consider topical therapy for symptomatic relief</td>
</tr>
<tr>
<td>Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient’s normal activities</td>
<td>1st occurrence</td>
<td>Continue treatment with SORANIB Tablets and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below</td>
</tr>
</tbody>
</table>
No improvement within 7 days or 2nd or 3rd occurrence

Interrupt SORANIB Tablets treatment until toxicity resolves to Grade 0–1
When resuming treatment, decrease SORANIB Tablets dose by one dose level (400 mg daily or 400 mg every other day)

4th occurrence
Discontinue SORANIB Tablets 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 SORANIB Tablets treatment until toxicity resolves to Grade 0–1
When resuming treatment, decrease SORANIB Tablets dose by one dose level (400 mg daily or 400 mg every other day)

3rd occurrence
Discontinue SORANIB Tablets treatment

### Dose modifications for Differentiated Thyroid Carcinoma

#### Table 2: Recommended doses for patients with differentiated thyroid carcinoma requiring dose reduction

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>SORANIB Tablets Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Dose Reduction</td>
<td>600 mg daily dose</td>
</tr>
<tr>
<td></td>
<td>400 mg and 200 mg 12 hours apart (2 tablets and 1 tablet 12 hours apart – either dose can come first)</td>
</tr>
<tr>
<td>Second Dose Reduction</td>
<td>400 mg daily dose</td>
</tr>
<tr>
<td></td>
<td>200 mg twice daily (1 tablet twice daily)</td>
</tr>
<tr>
<td>Third Dose Reduction</td>
<td>200 mg daily dose</td>
</tr>
<tr>
<td></td>
<td>200 mg once daily (1 tablet once daily)</td>
</tr>
</tbody>
</table>

When dose reduction is necessary for dermatologic toxicities, reduce the SORANIB Tablets dose as indicated in Table 3 below.

#### Table 3: Recommended dose modifications for dermatologic toxicities for patients with differentiated thyroid carcinoma

<table>
<thead>
<tr>
<th>Dermatologic Toxicity Grade</th>
<th>Occurrence</th>
<th>SORANIB Tablets Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>Any occurrence</td>
<td>Continue treatment with SORANIB Tablets</td>
</tr>
<tr>
<td>Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient’s normal activities</td>
<td>1st occurrence</td>
<td>Decrease SORANIB Tablets dose to 600 mg daily If no improvement within 7 days, see below</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>No improvement within 7 days at reduced dose or 2nd occurrence</td>
<td>Interrupt SORANIB Tablets until resolved or improved to grade 1 If SORANIB Tablets is resumed, decrease dose (see Table 2)</td>
<td></td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Interrupt SORANIB Tablets until resolved or improved to grade 1 If SORANIB Tablets is resumed, decrease dose (see Table 2)</td>
<td></td>
</tr>
<tr>
<td>4th occurrence</td>
<td>Discontinue SORANIB Tablets permanently</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities of daily living</th>
<th>1st occurrence</th>
<th>Interrupt SORANIB Tablets until resolved or improved to grade 1 If SORANIB Tablets is resumed, decrease dose by one dose level (see Table 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd occurrence</td>
<td>Interrupt SORANIB Tablets until resolved or improved to grade 1 When SORANIB Tablets is resumed, decrease dose by 2 dose levels (see Table 2)</td>
<td></td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Discontinue SORANIB Tablets permanently</td>
<td></td>
</tr>
</tbody>
</table>

Following improvement of Grade 2 or 3 dermatologic toxicity to Grade 0–1 after at least 28 days of treatment on a reduced dose of SORANIB Tablets, the dose of SORANIB Tablets may be increased one dose level from the reduced dose. Approximately 50% of patients requiring a dose reduction for dermatologic toxicity are expected to meet these criteria for resumption of the higher dose and roughly 50% of patients resuming the previous dose are expected to tolerate the higher dose (that is, maintain the higher dose level without recurrent Grade 2 or higher dermatologic toxicity).

**Method of Administration**

For oral use
It is recommended that sorafenib should be administered without food or with a low- or moderate-fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water.

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 sorafenib.

**Paediatric Use**

The safety and efficacy of SORANIB Tablets in children and adolescents aged below 18 years have not yet been established. No data are available.
Geriatric Use

No dose adjustment is required in the elderly (patients above 65 years of age).

Renal Impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring dialysis. Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.

Hepatic Impairment

No dose adjustment is required in patients with Child-Pugh A or B (mild-to-moderate) hepatic impairment. No data is available on patients with Child-Pugh C (severe) hepatic impairment.

Contraindications

SORANIB Tablets are contraindicated in patients with known severe hypersensitivity to SORANIB Tablets or any other component of SORANIB Tablets. SORANIB Tablets in combination with carboplatin and paclitaxel are contraindicated in patients with squamous cell lung cancer.

Warnings And Precautions

Drug Interactions

Inducers of Metabolic Enzymes
Administration of rifampicin for 5 days before administration of a single dose of sorafenib resulted in an average 37% reduction of the sorafenib AUC. Other inducers of CYP3A4 activity and/or glucuronidation (e.g., St. John's wort (Hypericum perforatum), phenytoin, carbamazepine, phenobarbital and dexamethasone) may also increase the metabolism of sorafenib and, thus, decrease sorafenib concentrations.

CYP3A4 Inhibitors
Ketoconazole, a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of sorafenib. These data suggest that clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.

CYP2B6, CYP2C8 and CYP2C9 Substrates
Sorafenib inhibited CYP2B6, CYP2C8 and CYP2C9 in vitro with similar potency. However, in clinical pharmacokinetic studies, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, or paclitaxel, a CYP2C8 substrate, did not result in a clinically meaningful inhibition. These data suggest that sorafenib at the recommended dose of 400 mg twice daily may not be an in vivo inhibitor of CYP2B6 or CYP2C8. Additionally, concomitant treatment with sorafenib and warfarin, a CYP2C9 substrate, did not result in changes in the mean prothrombin time/international normalized ratio (PT-INR), compared to placebo. Thus, also the risk for a clinically relevant in vivo inhibition of CYP2C9 by sorafenib may be expected to be low. However, patients taking warfarin or phenprocoumon should have their INR checked regularly.

CYP3A4, CYP2D6 and CYP2C19 Substrates
Concomitant administration of sorafenib and midazolam, dextromethorphan or omeprazole, which are substrates for cytochromes CYP3A4, CYP2D6 and CYP2C19, respectively, did not alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these CYP450 isoenzymes. Therefore, clinical pharmacokinetic interactions of sorafenib with substrates of these enzymes are unlikely.
**UGT1A1 and UGT1A9 Substrates**

*In vitro*, sorafenib inhibited glucuronidation via UGT1A1 and UGT1A9. The clinical relevance of this finding is unknown.

**In vitro Studies of CYP Enzyme Induction**

CYP1A2 and CYP3A4 activities were not altered after the treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 and CYP3A4.

**P-gp Substrates**

*In vitro*, sorafenib has been shown to inhibit the transport protein, P-gp. Increased plasma concentrations of P-gp substrates such as digoxin cannot be excluded with concomitant treatment with sorafenib.

**Combination with other anti-neoplastic agents**

In clinical studies sorafenib has been administered with a variety of other anti-neoplastic agents at their commonly used dosing regimens including gemcitabine, cisplatin, oxaliplatin, paclitaxel, carboplatin, capecitabine, doxorubicin, irinotecan, docetaxel and cyclophosphamide. Sorafenib had no clinically relevant effect on the pharmacokinetics of gemcitabine, cisplatin, carboplatin, oxaliplatin or cyclophosphamide.

**Paclitaxel/carboplatin**

Administration of paclitaxel (225 mg/m²) and carboplatin (AUC = 6) with sorafenib (≤ 400 mg twice daily), administered with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration), resulted in no significant effect on the pharmacokinetics of paclitaxel.

Co-administration of paclitaxel (225 mg/m², once every 3 weeks) and carboplatin (AUC=6) with sorafenib (400 mg twice daily, without a break in sorafenib dosing) resulted in a 47% increase in sorafenib exposure, a 29% increase in paclitaxel exposure and a 50% increase in 6-OH paclitaxel exposure. The pharmacokinetics of carboplatin were unaffected. These data indicate no need for dose adjustments when paclitaxel and carboplatin are co-administered with sorafenib with a 3-day break in sorafenib dosing (two days prior to and on the day of paclitaxel/carboplatin administration). The clinical significance of the increases in sorafenib and paclitaxel exposure, upon co-administration of sorafenib without a break in dosing, is unknown.

**Capecitabine**

Co-administration of capecitabine (750–1,050 mg/m² twice daily, days 1–14 every 21 days) and sorafenib (200 or 400 mg twice daily, continuous uninterrupted administration) resulted in no significant change in sorafenib exposure, but a 15–50% increase in capecitabine exposure and a 0–52% increase in 5-FU exposure. The clinical significance of these small to modest increases in capecitabine and 5-FU exposure when co-administered with sorafenib is unknown.

**Doxorubicin/Irinotecan**

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.

**Docetaxel**

Docetaxel (75 or 100 mg/m² administered once every 21 days) when co-administered with sorafenib (200 mg twice daily or 400 mg twice daily administered on Days 2 through 19 of a 21-day cycle 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.

**Neomycin**

Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate gastrointestinal flora, interferes with the enterohepatic recycling of sorafenib, resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average exposure to sorafenib decreased by 54%. Effects of other antibiotics have not been studied, but will likely depend on their ability to interfere with microorganisms with glucuronidase activity.
Drugs that Increase Gastric pH

The aqueous solubility of sorafenib is pH dependent, with higher pH resulting in lower solubility. However, omeprazole, a proton pump inhibitor, administered at a dose of 40 mg once daily for 5 days, did not result in a clinically meaningful change in sorafenib single dose exposure. No dose adjustment for Sorafenib is necessary.

Drug-drug interactions

Caution is recommended when administering sorafenib with compounds that are metabolised/eliminated predominantly by the UGT1A1 (e.g. irinotecan) or UGT1A9 pathways.

Caution is recommended when sorafenib 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 sorafenib bioavailability. The risk of reduced plasma concentrations of sorafenib 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 sorafenib 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 sorafenib 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 sorafenib as add-on to platinum-based chemotherapies.

Disease Specific Warnings

Differentiated Thyroid Cancer (DTC)

Before initiating treatment, physicians are recommended to carefully evaluate the prognosis in the individual patient considering maximum lesion size, symptoms related to the disease and progression rate.

Management of suspected adverse drug reactions may require temporary interruption or dose reduction of sorafenib therapy. In study 5, 37% of subjects had dose interruption and 35% had dose reduction already in cycle 1 of sorafenib treatment.

Dose reductions were only partially successful in alleviating adverse reactions. Therefore repeat evaluations of benefit and risk is recommended taking anti-tumour activity and tolerability into account.

Haemorrhage in DTC

Due to the potential risk of bleeding, tracheal, bronchial, and oesophageal infiltration should be treated with localized therapy prior to administering sorafenib in patients with DTC.

Hypocalcaemia in DTC

When using sorafenib in patients with DTC, close monitoring of blood calcium level is recommended. In clinical trials, hypocalcaemia was more frequent and more severe in patients with DTC, especially with a history of hypoparathyroidism, compared to patients with renal cell or hepatocellular carcinoma. Hypocalcaemia grade 3 and 4 occurred in 6.8% and 3.4% of sorafenib-treated patients with DTC. Severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes (see section QT prolongation).

TSH suppression in DTC

In study 5, increases in TSH levels above 0.5mU/L were observed in sorafenib treated patients. When using sorafenib in DTC patients, close monitoring of TSH level is recommended.

Risk of Cardiac Ischaemia and/or Infarction

In the HCC study, the incidence of cardiac ischemia/infarction was 2.7% in Sorafenib-treated patients compared with 1.3% in the placebo-treated group, in RCC Study 1, the incidence of cardiac ischemia/infarction was higher in the
sorafenib-treated group (2.9%) compared with the placebo-treated group (0.4%), and in the DTC study, the incidence of cardiac ischemia/infarction was 1.9% in the sorafenib-treated group compared with 0% in the placebo-treated group. 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 Haemorrhage

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-treated patients and 4% in placebo-treated patients. Bleeding with a fatal outcome from any site was reported in 2.4% of sorafenib-treated patients and 4% in placebo-treated patients. In RCC Study 1, bleeding regardless of causality was reported in 15.3% of patients in the sorafenib-treated group and 8.2% of patients in the placebo-treated group. The incidence of CTCAE Grade 3 and 4 bleeding was 2% and 0%, respectively, in sorafenib-treated patients, and 1.3% and 0.2%, respectively, in placebo-treated patients. There was one fatal hemorrhage in each treatment group in RCC Study 1. In the DTC study, bleeding was reported in 17.4% of sorafenib-treated patients and 9.6% of placebo-treated patients; however, the incidence of CTCAE Grade 3 bleeding was 1% in sorafenib-treated patients and 1.4% in placebo-treated patients. There was no Grade 4 bleeding reported and there was one fatal hemorrhage in a placebo-treated patient. If any bleeding necessitates medical intervention, permanent discontinuation of sorafenib should be considered. Due to the potential risk of bleeding, tracheal, bronchial, and esophageal infiltration should be treated with local therapy prior to administering sorafenib in patients with DTC.

### Risk of Hypertension

Monitor blood pressure weekly during the first 6 weeks of sorafenib. Thereafter, monitor blood pressure and treat hypertension, 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-treated group. In RCC Study 1, hypertension was reported in approximately 16.9% of sorafenib-treated patients and 1.8% of patients in the placebo-treated group. In the DTC study, hypertension was reported in 40.6% of sorafenib-treated patients and 12.4% of placebo-treated patients. 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, consider temporary or permanent discontinuation of sorafenib. Permanent discontinuation due to hypertension occurred in 1 of 297 sorafenib-treated patients in the HCC study, 1 of 451 sorafenib-treated patients in RCC Study 1, and 1 of 207 sorafenib-treated patients in the DTC study.

### 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. 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 4 (1.3%) of 297 sorafenib-treated patients with HCC, 3 (0.7%) of 451 sorafenib-treated patients with RCC, and 11 (5.3%) of 207 sorafenib-treated patients with DTC.

There have been reports of severe dermatologic toxicities, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These cases may be life-threatening. Discontinue sorafenib if SJS or TEN are suspected.

### 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 an apparent intra-abdominal tumor. In the event of a gastrointestinal perforation, sorafenib should be discontinued.

▲ Warfarin

Infrequent bleeding or elevations in the INR have been reported in some patients taking warfarin while on sorafenib. Patients taking concomitant warfarin should be monitored regularly for changes in the PT and INR or for clinical bleeding episodes.

▲ Wound Healing Complications

No formal studies of the effect of sorafenib on wound healing have been conducted. Temporary interruption of sorafenib is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiating of sorafenib following major surgical intervention. Therefore, the decision to resume sorafenib following a major surgical intervention should be based on clinical judgment of adequate wound healing.

▲ Increased Mortality Observed with sorafenib Administered in Combination with Carboplatin/Paclitaxel and Gemcitabine/Cisplatin in Squamous Cell Lung Cancer

In a subset analysis of two randomized controlled trials in chemo-naive patients with Stage IIIIB-IV non-small cell lung cancer, patients with squamous cell carcinoma experienced higher mortality with the addition of sorafenib compared to those treated with carboplatin/paclitaxel alone (HR 1.81, 95% CI 1.19–2.74) and gemcitabine/cisplatin alone (HR 1.22, 95% CI 0.82-1.80). The use of sorafenib in combination with carboplatin/paclitaxel is contraindicated in patients with squamous cell lung cancer. Sorafenib in combination with gemcitabine/cisplatin is not recommended in patients with squamous cell lung cancer. The safety and effectiveness of sorafenib has not been established in patients with non-small cell lung cancer.

▲ Risk of QT Interval Prolongation

Sorafenib can prolong the QT/QTc interval. QT/QTc interval prolongation increases the risk for ventricular arrhythmias. Avoid sorafenib in patients with congenital long QT syndrome. Monitor electrolytes and electrocardiograms in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Correct electrolyte abnormalities (magnesium, potassium, calcium). Interrupt sorafenib if QTc interval is greater than 500 milliseconds or for an increase from baseline of 60 milliseconds or greater.

▲ Drug-Induced Hepatitis

Sorafenib-induced hepatitis is characterized by a hepatocellular pattern of liver damage with significant increases of transaminases which may result in hepatic failure and death. Increases in bilirubin and INR may also occur. The incidence of severe drug-induced liver injury, defined as elevated transaminase levels above 20 times the upper limit of normal or transaminase elevations with significant clinical sequelae (for example, elevated INR, ascites, fatal, or transplantation), was two of 3,357 patients (0.06%) in a global monotherapy database. Monitor liver function tests regularly. In case of significantly increased transaminases without alternative explanation, such as viral hepatitis or progressing underlying malignancy, discontinue sorafenib.

▲ Impairment of Thyroid Stimulating Hormone Suppression in Differentiated Thyroid Carcinoma

Sorafenib impairs exogenous thyroid suppression. In the DTC study, 99% of patients had a baseline thyroid stimulating hormone (TSH) level less than 0.5 mU/L. Elevation of TSH level above 0.5 mU/L was observed in 41% of Sorafenib -treated patients as compared with 16% of placebo-treated patients. For patients with impaired TSH suppression while receiving sorafenib, the median maximal TSH was 1.6 mU/L and 25% had TSH levels greater than 4.4 mU/L.
Monitor TSH levels monthly and adjust thyroxine replacement medication as needed in patients with DTC.

Renal Cell Carcinoma

High-risk patients, according to the MSKCC (Memorial Sloan Kettering Cancer Center) prognostic group, were not included in the Phase III clinical study in RCC; the benefit-risk in these patients has not been evaluated.

Renal Impairment

No correlation between sorafenib exposure and renal function was observed following administration of a single oral dose of sorafenib 400 mg to subjects with normal renal function and subjects with mild (CrCl 50–80 mL/min), moderate (CrCl 30–<50 mL/min) or severe (CrCl <30 mL/min) renal impairment who are not on dialysis. No dose adjustment is necessary for patients with mild, moderate or severe renal impairment who are not on dialysis. The pharmacokinetics of sorafenib has not been studied in patients who are on dialysis.

Hepatic Impairment

In a trial of HCC patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, the systemic exposure (AUC) of sorafenib was within the range observed in patients without hepatic impairment. In another trial in subjects without HCC, the mean AUC was similar for subjects with mild (N=15) and moderate (N=14) hepatic impairment compared to subjects (N=15) with normal hepatic function. No dose adjustment is necessary for patients with mild or moderate hepatic impairment. The pharmacokinetics of sorafenib has not been studied in patients with severe (Child-Pugh C) hepatic impairment. No data is available on patients with Child Pugh C (severe) hepatic impairment. Since sorafenib is mainly eliminated via the hepatic route exposure might be increased in patients with severe hepatic impairment.

Fertility

Results from animal studies further indicate that sorafenib can impair male and female fertility.

Pregnancy

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. There are no adequate and well-controlled studies in pregnant women using sorafenib. Inform patients of childbearing potential that sorafenib can cause birth defects or fetal loss. Instruct both men and women of childbearing potential to use effective birth control during treatment with sorafenib and for at least 2 weeks after stopping treatment. Counsel female patients to contact their healthcare provider if they become pregnant while taking sorafenib.

When administered to rats and rabbits during the period of organogenesis, sorafenib was teratogenic and induced 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 ≥0.2 mg/kg/day (1.2 mg/m²/day) in rats and 0.3 mg/kg/day (3.6 mg/m²/day) in rabbits. These doses result in exposures (AUC) approximately 0.008 times the AUC seen in 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.

Lactation

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.
Following administration of radiolabeled 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.

### Paediatric 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, 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, 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.

### Effects on the Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. There is no evidence that sorafenib affects the ability to drive or to operate machinery.

### Undesirable Effects

The most important serious adverse reactions were myocardial infarction/ischaemia, gastrointestinal perforation, drug induced hepatitis, haemorrhage, and hypertension/hypertensive crisis. The most common adverse reactions were diarrhoea, fatigue, alopecia, infection, hand foot skin reaction (corresponds to palmar plantar erythrodysaesthesia syndrome in MedDRA) and rash. Adverse reactions reported in multiple clinical trials or through post-marketing use are listed below in table 1, by system organ class (in MedDRA) and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1: All adverse reactions reported in patients in multiple clinical trials or through post-marketing use**

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>infection</td>
<td>folliculitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>lymphopenia</td>
<td>leucopenia</td>
<td>neutropenia</td>
<td>anaemia</td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>hypersensitivity reactions (including skin reactions and urticaria) anaphylactic reaction</td>
<td>angioedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>hypothyroidism</td>
<td>hyperthyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>anorexia hypo-phosphataemia hypocalcaemia hypokalaemia hyponatraemia</td>
<td>dehydration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>peripheral sensory neuropathy dysgeusia</td>
<td>reversible posterior leukoencephalo-pathy*</td>
<td>encephalopathy*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>tinnitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>congestive heart failure* myocardial ischaemia and infarction*</td>
<td></td>
<td>QT prolongation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>flushing</td>
<td>hypertensive crisis*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>rhinorrhoea dysphonia</td>
<td>interstitial lung disease-like events* (pneumonitis, radiation pneumonitis, acute respiratory distress, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>diarrhoea nausea vomiting constipation stomatitis (including dry mouth and glossodynia) dyspepsia dysphagia gastro oesophageal reflux disease</td>
<td>pancreatitis gastritis gastrointestinal perforations*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>increase in bilirubin and jaundice, cholecystitis, cholangitis</td>
<td></td>
<td>drug induced hepatitis*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Skin and subcutaneous tissue disorders**
dry skin rash
alopecia
hand foot skin reaction**
erythema
pruritus
keratoacanthoma/
squamous cell cancer of the skin
dermatitis
exfoliative
acute
skin
desquamation
hyperkeratosis
eczema
erythema multiforme
radiation recall
dermatitis
Stevens-Johnson
syndrome
leucocytoclastic
vasculitis
toxic epidermal
necrolysis*

**Musculoskeletal and connective tissue disorders**
arthralgia
myalgia
muscle spasms
rhabdomyolysis

**Renal and urinary disorders**
renal failure
proteinuria
nephrotic
syndrome

**Reproductive system and breast disorders**
erectile dysfunction
gynaecomastia

**General disorders and administration site conditions**
fatigue
including
mouth, abdominal,
bone, tumour pain and headache
fever
asthenia
influenza like illness
mucosal inflammation

**Investigations**
weight decreased
increased amylase
increased lipase
transient increase
in transaminases
transient increase in
blood alkaline
phosphatase
INR abnormal,
prothrombin level abnormal

* The adverse reactions may have a life-threatening or fatal outcome. Such events are either uncommon or less frequent than uncommon.

** Hand foot skin reaction corresponds to palmar plantar erythrodysaesthesia syndrome in MedDRA.

° Cases have been reported in the post marketing setting.

Further information on selected adverse drug reactions

**Congestive Heart Failure**
In company sponsored clinical trials congestive heart failure was reported as an adverse event in 1.9% of patients treated with sorafenib (N= 2276). In study 11213 (RCC) adverse events consistent with congestive heart failure were reported in 1.7% of patients treated with sorafenib and 0.7% receiving placebo. In study 100554 (HCC), 0.99% of those treated with sorafenib and 1.1% receiving placebo were reported with these events.

**Additional Information on Special Populations**
In clinical trials, certain adverse drug reactions such as hand foot skin reaction, diarrhoea, alopecia, weight decrease, hypertension, hypocalcaemia, and keratoacanthoma/squamous cell carcinoma of skin occurred at a substantially higher frequency in patients with differentiated thyroid compared to patients in the renal cell or hepatocellular carcinoma studies.

**Laboratory test abnormalities in HCC (study 3) and RCC (study 1) patients**
Increased lipase and amylase were very commonly reported. CTCAE Grade 3 or 4 lipase elevations occurred in 11 % and
9% of patients in the sorafenib group in study 1 (RCC) and study 3 (HCC), respectively, compared to 7% and 9% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% and 2% of patients in the sorafenib group in study 1 and study 3, respectively, compared to 3% of patients in each placebo group. Clinical pancreatitis was reported in 2 of 451 sorafenib treated patients (CTCAE Grade 4) in study 1, 1 of 297 sorafenib treated patients in study 3 (CTCAE Grade 2), and 1 of 451 patients (CTCAE Grade 2) in the placebo group in study 1.

Hypophosphataemia was a very common laboratory finding, observed in 45% and 35% of sorafenib treated patients compared to 12% and 11% of placebo patients in study 1 and study 3, respectively. CTCAE Grade 3 hypophosphataemia (1 – 2 mg/dl) in study 1 occurred in 13% of sorafenib treated patients and 3% of patients in the placebo group, in study 3 in 11% of sorafenib treated patients and 2% of patients in the placebo group. There were no cases of CTCAE Grade 4 hypophosphataemia (< 1 mg/dl) reported in either sorafenib or placebo patients in study 1, and 1 case in the placebo group in study 3. The aetiology of hypophosphataemia associated with sorafenib is not known.

CTCAE Grade 3 or 4 laboratory abnormalities occurring in ≥ 5% of sorafenib treated patients included lymphopenia and neutropenia.

Hypocalcaemia was reported in 12% and 26.5% of sorafenib treated patients compared to 7.5% and 14.8% of placebo patients in study 1 and study 3, respectively. Most reports of hypocalcaemia were low grade (CTCAE Grade 1 and 2). CTCAE grade 3 hypocalcaemia (6.0 – 7.0 mg/dL) occurred in 1.1% and 1.8% of sorafenib treated patients and 0.2% and 1.1% of patients in the placebo group, and CTCAE grade 4 hypocalcaemia (< 6.0 mg/dL) occurred in 1.1% and 0.4% of sorafenib treated patients and 0.5% and 0% of patients in the placebo group in study 1 and 3, respectively. The aetiology of hypocalcaemia associated with sorafenib is not known.

In studies 1 and 3 decreased potassium was observed in 5.4% and 9.5% of sorafenib-treated patients compared to 0.7% and 5.9% of placebo patients, respectively. Most reports of hypokalaemia were low grade (CTCAE Grade 1). In these studies CTCAE Grade 3 hypokalaemia occurred in 1.1% and 0.4% of sorafenib treated patients and 0.2% and 0.7% of patients in the placebo group. There were no reports of hypokalaemia CTCAE grade 4.

Laboratory test abnormalities in DTC patients (study 5)

Hypocalcaemia was reported in 35.7% of sorafenib treated patients compared to 11.0% of placebo patients. Most reports of hypocalcaemia were low grade. CTCAE grade 3 hypocalcaemia occurred in 6.8% of sorafenib treated patients and 1.9% of patients in the placebo group, and CTCAE grade 4 hypocalcaemia occurred in 3.4% of sorafenib treated patients and 1.0% of patients in the placebo group.

Other clinically relevant laboratory abnormalities observed in the study 5 are shown in table 2.

<table>
<thead>
<tr>
<th>Laboratory parameter, (in % of samples investigated)</th>
<th>Sorafenib N=207</th>
<th>Placebo N=209</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades*</td>
<td>Grade 3*</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>30.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18.4</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>42</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Table 2: Treatment-emergent laboratory test abnormalities reported in DTC patient (study 5) double blind period
### Metabolism and nutrition disorders

<table>
<thead>
<tr>
<th></th>
<th>17.9</th>
<th>1.9</th>
<th>0</th>
<th>2.4</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia**</td>
<td>19.3</td>
<td>12.6</td>
<td>0</td>
<td>2.4</td>
<td>1.4</td>
<td>0</td>
</tr>
</tbody>
</table>

### Hepatobiliary disorders

<table>
<thead>
<tr>
<th></th>
<th>8.7</th>
<th>0</th>
<th>0</th>
<th>4.8</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT increased</td>
<td>58.9</td>
<td>3.4</td>
<td>1.0</td>
<td>24.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>53.6</td>
<td>1.0</td>
<td>1.0</td>
<td>14.8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Investigations

<table>
<thead>
<tr>
<th></th>
<th>12.6</th>
<th>2.4</th>
<th>1.4</th>
<th>6.2</th>
<th>0</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase increased</td>
<td>11.1</td>
<td>2.4</td>
<td>0</td>
<td>2.9</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

* Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

** The aetiology of hypophosphatemia associated with sorafenib is not known.

---

The following additional drug-related adverse reactions and laboratory abnormalities were reported from clinical trials of Sorafenib (very common 10% or greater, common 1 to less than 10%, uncommon 0.1% to less than 1%, rare less than 0.1 %):

**Cardiovascular:** Common: congestive heart failure*, myocardial ischemia and/or infarction Uncommon: hypertensive crisis* Rare: QT prolongation*

**Dermatologic:** Very common: erythema Common: exfoliative dermatitis, acne, flushing, folliculitis, hyperkeratosis Uncommon: eczema, erythema multiforme

**Digestive:** Very common: increased lipase, increased amylase Common: mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia, gastrointestinal reflux Uncommon: pancreatitis, gastritis, gastrointestinal perforations*, cholecystitis, cholangitis

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: infection, hemorrhage (including gastrointestinal* and respiratory tract* and uncommon cases of cerebral hemorrhage*), asthenia, pain (including mouth, bone, and tumor pain), pyrexia, decreased appetite Common: influenza-like illness

**Hematologic:** Very common: leukopenia, lymphopenia Common: anemia, neutropenia, thrombocytopenia Uncommon: INR abnormal

**Hepatobiliary disorders:** Rare: drug-induced hepatitis (including hepatic failure and death)

**Hypersensitivity:** Uncommon: hypersensitivity reactions (including skin reactions and urticaria), anaphylactic reaction

**Metabolic and Nutritional:** Very common: hypophosphatemia Common: transient increases in transaminases, hypocalcemia, hypokalemia, hyponatremia, hypothyroidism Uncommon: dehydration, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hyperthyroidism

**Musculoskeletal:** Very common: arthralgia Common: myalgia, muscle spasms

**Nervous System and Psychiatric:** Common: depression, dysgeusia Uncommon: tinnitus, reversible posterior
leukoencephalopathy*

Renal and Genitourinary: Common: renal failure, proteinuria Rare: nephrotic syndrome
Reproductive: Common: erectile dysfunction Uncommon: gynecomastia
Respiratory: Common: rhinorrhea Uncommon: interstitial lung disease-like events (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis and lung inflammation)

In addition, the following medically significant adverse reactions were uncommon during clinical trials of SORAFENIB: transient ischemic attack, arrhythmia, and thromboembolism. For these adverse reactions, the causal relationship to SORAFENIB has not been established.

*adverse reactions may have a life-threatening or fatal outcome.
†reported in 1.9% of patients treated with Sorafenib (N=2276).

Postmarketing Experience

The following adverse drug reactions have been identified during post-approval use of sorafenib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dermatologic: Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN).

Hypersensitivity: Angio-oedema.

Musculoskeletal: Rhabdomyolysis, osteonecrosis of the jaw

Respiratory: Interstitial lung disease-like events (which may have a life-threatening or fatal outcome)

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

There is no specific treatment for sorafenib overdose. The highest dose of sorafenib studied clinically was 800 mg twice daily. The adverse events observed at this dose were primarily diarrhoea and dermatological events. In the event of a suspected overdose, sorafenib should be withheld and supportive care instituted where necessary.

Storage

Store between 15°C to 30°C

Packaging Information

SORANIB

Container pack of 30 Tablets
Container pack of 120 Tablets

Last Updated: Jun 2017
Last Reviewed: Dec 2017

SORANIB Tablets

Source URL: https://ciplamed.com/content/soranib-tablets