# SORANIB Tablets (Sorafenib tosylate)

To be sold by retail on prescription of Oncologist.

## 1.Generic Name

Sorafenib Tablets IP 200 mg

## 2.Qualitative and Quantitative Composition

**Each film coated tablet contains:**

Sorafenib Tosylate IP equivalent to Sorafenib  200 mg

Excipients q.s.

Colours: Ferric oxide USP-NF Red & Titanium dioxide IP

## 3.Dosage Form & Strength

Sorafenib Tablets 200 mg for oral use

## 4.Clinical Particulars

### 4.1 Therapeutic Indications

Sorafenib is indicated for the treatment of:

- Patients with advanced renal cell carcinoma
- Hepatocellular carcinoma
- Patients with locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine

### 4.2 Posology and Method of administration

The recommended dose of sorafenib in adults is 400 mg sorafenib (two tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg) without food (at least 1 hour before or 2 hours after a meal).

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

***Dosage Modifications for Adverse Reactions**:*

The recommended dosage modifications for adverse reactions are provided in the below tables:

**Recommended Dose Reductions for Adverse Reaction**

| Dose Reduction | Hepatocellular Carcinoma and Renal Cell Carcinoma | Differentiated Thyroid Carcinoma |
|---|---|---|
| First Dose Reduction | 400 mg orally once daily | 400 mg orally in the morning and 200 mg orally in the evening about 12 hours apart OR 200 mg orally in the morning and 400 mg orally in the evening about 12 hours apart |
| Second Dose Reduction | 200 mg orally once daily OR 400 every other day | 200 mg orally twice daily |
| Third Dose Reduction | None | 200 mg orally once daily |

**Recommended Dosage Modifications of Sorafenib for Adverse Reactions**

| Adverse Reaction | Severity[1] | Sorafenib Dosage Modification |
|---|---|---|
| Cardiovascular Events | | |
| Cardiac Ischemia and/or Infarction | Grade 2 and above | Permanently discontinue. |
| Congestive Heart Failure | Grade 3 | Interrupt[2] until Grade 1 or less, resume at reduced dose by 1 dose level. [3] |
| | Grade 4 | Permanently discontinue. |
| Hemorrhage | Grade 2 and above requiring medical intervention | Permanently discontinue. |
| Hypertension | Grade 2 (symptomatic/persistent) OR Grade 2 symptomatic increase by greater than 20 mm Hg (diastolic) or greater than 140/90 mm Hg if previously within normal limits OR Grade 3 | Interrupt until symptoms resolve and diastolic blood pressure less than 90 mm Hg, then resume at reduced dose by 1 dose level. [3] If needed, reduce another dose level.[3] |
| | Grade 4 | Permanently discontinue |
| Gastrointestinal Perforation | Any grade | Permanently discontinue. |
| QT Interval Prolongation | Greater than 500 milliseconds OR Increase from baseline of 60 milliseconds or greater | Interrupt and correct electrolyte abnormalities (magnesium, potassium, calcium). Use medical judgement before restarting. |

| | | |
|---|---|---|
| Drug-Induced Liver Injury | Grade 3 ALT or higher in the absence of another cause[4] OR AST/ALT greater than 3 × upper limit normal (ULN) with bilirubin greater than 2 × ULN in the absence of another cause[4] | Permanently discontinue. |
| Non-hematological toxicities | Grade 2 | Continue treatment at reduced dose by 1 dose level |
| | Grade 3 | |
| | 1st occurrence | Interrupt until Grade 2 or less, then resume at reduced dose by 1 dose level. |
| | No improvement within 7 days OR 2nd or 3rd occurrence | Interrupt until Grade 2 or less, then resume at reduced dose by 2 dose levels. |
| | 4th occurrence | Interrupt until Grade 2 or less, then resume at reduced dose by 2 dose levels for HCC and RCC or 3 dose levels for DTC |
| | Grade 4 | Permanently discontinue. |

[1] Adverse reactions graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v3.0).
[2] If no recovery after 30 day interruption, discontinue treatment unless the patient is deriving clinical benefit.
[3] If more than 2 dose reductions are required, permanently discontinue treatment.
[4] In addition, any grade increased alkaline phosphatase in the absence of known bone pathology and Grade 2 or worse increased bilirubin; any 1 of the following: INR of 1.5 or greater, ascites and/or encephalopathy in the absence of underlying cirrhosis or other organ failure considered to be due to drug-induced liver injury.

**Recommended Dosage Modifications for Dermatologic Toxicities**

| **Dermatologic Toxicity Grade** | **Occurrence** | **Sorafenib Dose Modification** | |
|---|---|---|---|
| | | **Hepatocellular and Renal Cell Carcinoma** | **Differentiated Thyroid Carcinoma** |

| | | | |
|---|---|---|---|
| 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 | Decrease sorafenib dose to 600 mg daily If no improvement within 7 days, see below |
| | No improvement within 7 days at reduced dose or 2nd and 3rd occurrence | Interrupt sorafenib treatment until toxicity resolves to Grade 0–1 | Interrupt sorafenib until resolved or improved to Grade 1 |
| | | When resuming treatment, decrease sorafenib dose by 1 dose level (400 mg daily or 400 mg every other day) | When resuming treatment, decrease dose by 1 dose level for 2nd occurrence and 2 doses levels for 3rd occurrence |
| | 4th occurrence | Discontinue Sorafenib treatment | |
| 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 | 1st occurrence | Interrupt sorafenib treatment until toxicity resolves to Grade 0–1 | Interrupt sorafenib until resolved or improved to Grade 1 |
| | | When resuming treatment, decrease sorafenib dose by 1dose level (400 mg daily or 400 mg every other day) | When resuming treatment, decrease dose by 1 dose level. |
| | 2nd occurrence | Interrupt sorafenib treatment until toxicity resolves to Grade 0–1 | Interrupt sorafenib until resolved or improved to Grade 1 |
| | | When resuming treatment, decrease sorafenib dose by 1 dose level (400 mg daily or 400 mg every other day) | When resuming treatment, decrease dose by 2 dose levels |
| | 3rd occurrence | Discontinue sorafenib treatment | |

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 sorafenib, the dose of sorafenib 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).

***Paediatric population***

The safety and efficacy of sorafenib in children and adolescents aged <18 years have not yet been established. No data are available.

***Elderly population***

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

***Patients with 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.

***Patients with 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.

***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.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer

## 4.4 Special warnings and precautions for use

***Dermatological toxicities***

Hand foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with sorafenib. Rash and hand foot skin reaction are usually CTC (Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib. Management of dermatological 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.

***Hypertension***

An increased incidence of arterial hypertension was observed in sorafenib-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of sorafenib should be considered.

***Aneurysms and artery dissections***

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating sorafenib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

***Hypoglycaemia***

Decreases in blood glucose, in some cases clinically symptomatic and requiring hospitalization due to loss of consciousness, have been reported during sorafenib treatment. In case of symptomatic hypoglycaemia, sorafenib should be temporarily interrupted. Blood glucose levels in diabetic patients should be checked regularly in order to assess if anti-diabetic medicinal product's dosage needs to be adjusted.

***Haemorrhage***

An increased risk of bleeding may occur following sorafenib administration. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of sorafenib should be considered.

***Cardiac ischaemia and/or infarction***

In a randomised, placebo-controlled, double-blind study, the incidence of treatment-emergent cardiac ischaemia/infarction events was higher in the sorafenib group (4.9 %) compared with the placebo group (0.4 %). In study 100554 (HCC), the incidence of treatment-emergent cardiac ischaemia/infarction events was 2.7 % in sorafenib patients compared with 1.3 % in the placebo group. Patients with unstable coronary artery disease or recent myocardial infarction were excluded from these studies. Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischaemia and/or infarction.

***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 IIIB-IV nonsmall 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

***QT interval prolongation***

Sorafenib has been shown to prolong the QT/QTc interval, which may lead to an increased risk for ventricular arrhythmias. Use sorafenib with caution in patients who have, or may develop prolongation of QTc, such as patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using sorafenib in these patients, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium, calcium) should be considered.

***Drug-Induced Liver Injury***

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

***Gastrointestinal perforation***

Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking sorafenib. In some cases, this was not associated with apparent intra-abdominal tumour. Sorafenib therapy should be discontinued.

***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.

***Warfarin co-administration***

Infrequent bleeding events or elevations in the International Normalised Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy. Patients taking concomitant warfarin or phenprocoumon 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 for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sorafenib therapy following a major surgical intervention should be based on clinical judgement of adequate wound healing.

***Embryo-Fetal Toxicity***

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. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Sorafenib. Advise male patients with female partners of reproductive potential and pregnant partners to use effective contraception during treatment and for 3 months following the last dose of Sorafenib.

***Elderly population***

Cases of renal failure have been reported. Monitoring of renal function should be considered.

***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, haemorrhages 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 DTC clinical trial, 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.

***TSH suppression in DTC***

In clinical trial 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.

***Renal cell carcinoma***

High Risk Patients, according to MSKCC (Memorial Sloan Kettering Cancer Center) prognostic group, were not included in the phase III clinical study in renal cell carcinoma, and benefit-risk in these patients has not been evaluated.

***Information about excipients***

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free".

## 4.5 Interaction with other medicinal products and other forms of interaction

***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 sorafenib AUC. Other inducers of CYP3A4 activity and/or glucuronidation (e.g. Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations.

***CYP3A4 inhibitors***

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 mean 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 cytochrome P450 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 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-glycoprotein (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 (750-1050 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 metabolised 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 $C_{max}$. Caution is recommended when sorafenib is co-administered with docetaxel.

***Combination with other agents***

***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.

## 4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

***Pregnant women***

There are no data on the use of sorafenib in pregnant women. Studies in animals have shown reproductive toxicity including malformations. In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to cause harmful effects on the foetus. Sorafenib should not be used during pregnancy unless clearly necessary, after careful consideration of the needs of the mother and the risk to the foetus.

Women of childbearing potential must use effective contraception during treatment.

***Lactating women***

It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because sorafenib could harm infant growth and development, women must not breast-feed during sorafenib treatment.

***Fertility***

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

***Pregnancy Testing***

Verify the pregnancy status of females of reproductive potential prior to the initiation of Sorafenib.

*Contraception*

***Females***

Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Sorafenib.

***Males***

Based on genotoxicity and findings in animal reproduction studies, advise males with female partners of reproductive potential and pregnant partners to use effective contraception during treatment with Sorafenib and for 3 months following the last dose of Sorafenib.

***Pediatric Patients***

The safety and effectiveness of sorafenib have not been established in pediatric patients.

***Geriatric Patients***

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.

***Patients with Renal Impairment***

No dose adjustment is necessary for patients with mild, moderate or severe renal impairment who are not on dialysis. The pharmacokinetics of sorafenib have not been studied in patients who are on dialysis.

1. **Effects on 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.

## 4.8 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, 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.

**All adverse reactions reported in patients in multiple clinical trials**

| System organ class | Very common | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|---|
| Infections and infestations | infection | folliculitis | | | |
| Blood and lymphatic system disorders | lymphopenia | leucopenia<br>neutropenia<br>anaemia<br>thrombocytopenia | | | |

| | | | | | |
|---|---|---|---|---|---|
| Immune system disorders | | | hypersensitivity reactions (including skin reactions and urticaria)<br>anaphylactic reaction | angioedema | |
| Endocrine disorders | | hypothyroidism | hyperthyroidism | | |
| Metabolism and nutrition disorders | anorexia<br>hypo-phosphataemia | hypocalcaemia<br>hypokalaemia<br>hyponatraemia<br>hypoglycaemia | dehydration | | |
| Psychiatric disorders | | depression | | | |
| Nervous system disorders | | peripheral sensory neuropathy<br>dysgeusia | reversible posterior leukoencephalopathy* | | encephalopathy° |
| Ear and labyrinth disorders | | tinnitus | | | |
| Cardiac disorders | | congestive heart failure*<br>myocardial ischaemia and infarction* | | QT prolongation | |
| Vascular disorders | haemorrhage (inc. gastrointestinal*, respiratory tract* and cerebral haemorrhage*)<br>hypertension | flushing | hypertensive crisis* | | aneurysms and artery dissections |
| Respiratory, thoracic and mediastinal disorders | | rhinorrhoea<br>dysphonia | Interstitial lung disease-like events* (pneumonitis, radiation pneumonitis, acute respiratory distress, etc.) | | |
| Gastrointestinal disorders | diarrhoea<br>nausea<br>vomiting<br>constipation | stomatitis (including dry mouth and glossodynia)<br>dyspepsia<br>dysphagia<br>gastro oesophageal reflux disease | pancreatitis<br>gastritis<br>gastrointestinal perforations* | | |
| Hepatobiliary disorders | | | increase in bilirubin and jaundice, cholecystitis, cholangitis | drug induced hepatitis* | |
| Skin and subcutaneous tissue disorders | dry skin<br>rash<br>alopecia<br>hand foot skin reaction**<br>erythema<br>pruritus | keratoacanthoma/ squamous cell cancer of the skin<br>dermatitis exfoliative<br>acne<br>skin desquamation<br>hyperkeratosis | eczema<br>erythema multiforme | radiation recall dermatitis<br>Stevens-Johnson syndrome<br>leucocytoclastic vasculitis<br>toxic epidermal necrolysis* | |

| | | | | | |
|---|---|---|---|---|---|
| Musculo-skeletal and connective tissue disorders | arthralgia | myalgia<br>muscle spasms | | rhabdomyolysis | |
| Renal and urinary disorders | | renal failure<br>proteinuria | | nephrotic syndrome | |
| Reproductive system and breast disorders | | erectile dysfunction | gynaecomastia | | |
| General disorders and administration site conditions | fatigue<br>pain (including mouth, abdominal, bone, tumour pain and headache),<br>fever | asthenia<br>influenza like illness<br>mucosal inflammation | | | |
| Investigations | weight decreased<br>increased amylase<br>increased lipase | transient increase in transaminases | transient increase in blood alkaline phosphatase<br>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 and RCC patients from Clinical Trials***

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 RCC and 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 RCC and HCC, 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 RCC, 1 of 297 sorafenib treated patients in HCC (CTCAE Grade 2), and 1 of 451 patients (CTCAE Grade 2) in the placebo group in RCC.

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 RCC and HCC, respectively. CTCAE Grade 3 hypophosphataemia (1 – 2 mg/dl) in RCC occurred in 13 % of sorafenib treated patients and 3 % of patients in the placebo group, in HCC 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 RCC, and 1 case in the placebo group in HCC. 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 RCC and HCC, 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 RCC and HCC, 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 in Clinical Trials***

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 DTC patients are shown in table below:

**Treatment-emergent laboratory test abnormalities reported in DTC patient double blind period**

| Laboratory parameter, (in % of samples investigated) | Sorafenib N=207 | | | Placebo N=209 | | |
|---|---|---|---|---|---|---|
| | All Grades* | Grade 3* | Grade 4* | All Grades* | Grade 3* | Grade 4* |
| Blood and lymphatic system disorders | | | | | | |
| Anemia | 30.9 | 0.5 | 0 | 23.4 | 0.5 | 0 |
| Thrombocytopenia | 18.4 | 0 | 0 | 9.6 | 0 | 0 |
| Neutropenia | 19.8 | 0.5 | 0.5 | 12 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Lymphopenia | 42 | 9.7 | 0.5 | 25.8 | 5.3 | 0 |
| Metabolism and nutrition disorders | | | | | | |
| Hypokalemia | 17.9 | 1.9 | 0 | 2.4 | 0 | 0 |
| Hypophosphatemia** | 19.3 | 12.6 | 0 | 2.4 | 1.4 | 0 |
| Hepatobiliary disorders | | | | | | |
| Bilirubin increased | 8.7 | 0 | 0 | 4.8 | 0 | 0 |
| ALT increased | 58.9 | 3.4 | 1.0 | 24.4 | 0 | 0 |
| AST increased | 53.6 | 1.0 | 1.0 | 14.8 | 0 | 0 |
| Investigations | | | | | | |
| Amylase increased | 12.6 | 2.4 | 1.4 | 6.2 | 0 | 1.0 |
| Lipase increased | 11.1 | 2.4 | 0 | 2.9 | 0.5 | 0 |
| * Common Terminology Criteria for Adverse Events (CTCAE), version 3.0<br>** The aetiology of hypophosphatemia associated with sorafenib is not known. | | | | | | |

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report any side effects, 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 or you can report to Cipla Ltd on 18002677779. By reporting side-effects, you can help provide more information on the safety of this product.

### 4.9 Overdose

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

## 5.Pharmacological Properties

### 5.1 Mechanism of Action

Sorafenib is a multikinase inhibitor that decreases tumour cell proliferation in vitro. Sorafenib inhibits tumour growth of a broad spectrum of human tumour xenografts in athymic mice accompanied by a reduction of tumour angiogenesis. Sorafenib inhibits the activity of targets present in the tumour cell (CRAF, BRAF, V600E BRAF, c-KIT, and FLT-3) and in the tumour vasculature (CRAF, VEGFR-2, VEGFR-3, and PDGFR-ß). RAF kinases are serine/threonine kinases, whereas c-KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-ß are receptor tyrosine kinases.

### 5.2 Pharmacodynamic properties

Cardiac Electrophysiology

The effect of Sorafenib 400 mg twice daily on the QTc interval was evaluated in a multi-center, openlabel, 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.

## 5.3 Pharmacokinetic properties

Multiple doses of sorafenib for 7 days resulted in a 2.5- to 7-fold accumulation compared to a single dose. Steady-state plasma sorafenib concentrations were achieved within 7 days, with a peak-t--trough ratio of mean concentrations of less than 2.

The steady-state concentrations of sorafenib following administration of sorafenib 400 mg twice daily were evaluated in DTC, RCC and HCC patients. Patients with DTC have mean steady-state concentrations that are 1.8-fold higher than patients with HCC and 2.3-fold higher than those with RCC. The reason for increased sorafenib concentrations in DTC patients is unknown.

Mean $C_{max}$ and AUC increased less than proportionally beyond oral doses of 400 mg administered twice daily.

***Absorption***

After administration of Sorafenib tablets, the mean relative bioavailability was 38–49% when compared to an oral solution. Following oral administration, sorafenib reached peak plasma levels in approximately 3 hours.

***Effects of Food***

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), bioavailability was reduced by 29% compared to that in the fasted state.

***Distribution***

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.

***Metabolism***

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.

***Excretion***

The elimination half-life of sorafenib is approximately 25 - 48 hours.

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.

***Patients with 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.

***Patients with 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.

# 6.Nonclinical Properties

## 6.1Animal Toxicology or Pharmacology

The preclinical safety profile of sorafenib was assessed in mice, rats, dogs and rabbits.

Repeat-dose toxicity studies revealed changes (degenerations and regenerations) in various organs at exposures below the anticipated clinical exposure (based on AUC comparisons).

After repeated dosing to young and growing dog's effects on bone and teeth were observed at exposures below the clinical exposure. Changes consisted in irregular thickening of the femoral growth plate, hypocellularity of the bone marrow next to the altered growth plate and alterations of the dentin composition. Similar effects were not induced in adult dogs.

The standard program of genotoxicity studies was conducted and positive results were obtained as an increase in structural chromosomal aberrations in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity in the presence of metabolic activation was seen. Sorafenib was not genotoxic in the Ames test or in the in vivo mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final active substance (< 0.15 %), was positive for mutagenesis in an in vitro bacterial cell assay (Ames test). Furthermore, the sorafenib batch tested in the standard genotoxicity battery included 0.34 % PAPE.

Carcinogenicity studies have not been conducted with sorafenib.

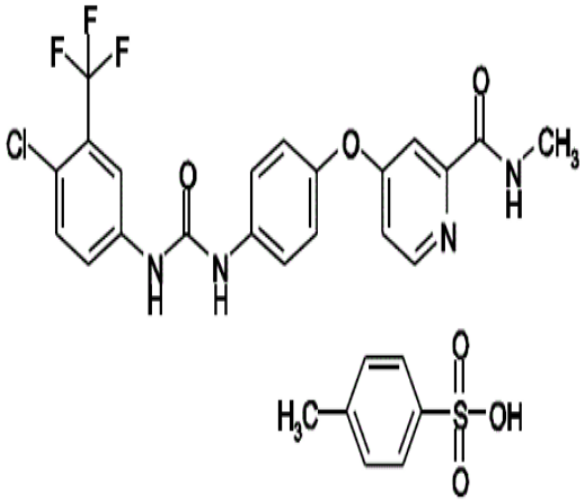
No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. An adverse effect on male and female fertility can however be expected because repeat-dose studies in animals have shown changes in male and female reproductive organs at exposures below the anticipated clinical exposure (based on AUC). Typical changes consisted of signs of degeneration and retardation in testes, epididymides, prostate, and seminal vesicles of rats. Female rats showed central necrosis of the corpora lutea and arrested follicular development in the ovaries. Dogs showed tubular degeneration in the testes and oligospermia.

Sorafenib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below the clinical exposure. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased number of external and visceral malformations.

Environmental Risk assessment studies have shown that sorafenib tosylate has the potential to be persistent, bioaccumulative and toxic to the environment. Environmental Risk Assessment information is available in the EPAR of this medicine.

# 7.Description

Sorafenib a kinase inhibitor, is the tosylate salt of sorafenib. Sorafenib tosylate has the chemical name 4-(4{3[4Chloro3(trifluoromethyl)phenyl]ureido}phenoxy)N2methylpyridine-2-carboxamide 4-methylbenzenesulfonate. The molecular formula of sorafenib tosylate is $C_{21}H_{16}ClF_3N_4O_3$ x $C_7H_8O_3S$ and the molecular weight of sorafenib tosylate is 637.0 g/mole and its structural formula is:



# 8.Pharmaceutical Particulars

## 8.1 Incompatibilities

Not applicable

## 8.2 Shelf-life

24 months

## 8.3 Packing Information

120 CC HDPE Container pack: Contains 120 Tablets &

60 CC HDPE Container pack: Contains 30 Tablets

## 8.4 Storage and handling instructions

Store at a temperature not exceeding 30°C. Protect from light.

Keep out of reach of children.

Keep container tightly closed.

Dispensed in original container.

Do not use if seal over bottle opening is broken or missing.

# 9.Patient Counselling Information

1. **What SORANIB is and what it is used for**

Sorafenib is used to treat liver cancer (hepatocellular carcinoma).

It is also used to treat kidney cancer (advanced renal cell carcinoma) at an advanced stage when standard therapy has not helped to stop your disease or is considered unsuitable.

Sorafenib is used to treat thyroid cancer (differentiated thyroid carcinoma).

It is multikinase inhibitor. It works by slowing down the rate of growth of cancer cells and cutting off the blood supply that keeps cancer cells growing.

1. **What you need to know before you take SORANIB**

*Do not take Sorafenib*

- If you are allergic to sorafenib or any of the other ingredients of this medicine

*Warnings and precautions*

Talk to your doctor before taking Sorafenib.

Take special care with Sorafenib

- If you experience skin problems. Sorafenib can cause rashes and skin reactions, especially on the hands and feet. These can usually be treated by your doctor. If not, your doctor may interrupt treatment or stop it altogether.
- If you have high blood pressure. Sorafenib can raise blood pressure, and your doctor will usually monitor your blood pressure and may give you a medicine to treat your high blood pressure.
- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- If you have diabetes. Blood sugar levels in diabetic patients should be checked regularly in order to assess if anti-diabetic medicine’s dosage needs to be adjusted to minimize the risk of low blood sugar.
- If you get any bleeding problems, or are taking warfarin or phenprocoumon. Treatment with Sorafenib may lead to a higher risk of bleeding. If you are taking warfarin or phenprocoumon, medicines which thin the blood to prevent blood clots, there may be a greater risk of bleeding.
- If you get chest pain or heart problems. Your doctor may decide to interrupt treatment or stop it altogether.
- If you have a heart disorder, such as an abnormal electrical signal called "prolongation of the QT interval".
- If you are going to have surgery, or if you had an operation recently. Sorafenib might affect the way your wounds heal. You will usually be taken off Sorafenib if you are having an operation.

Your doctor will decide when to start with Sorafenib again.

- If you are taking irinotecan or are given docetaxel, which are also medicines for cancer. Sorafenib may increase the effects and, in particular, the side effects of these medicines.
- If you are taking Neomycin or other antibiotics. The effect of Sorafenib may be decreased.
- If you have severe liver impairment. You may experience more severe side effects when taking this medicine.
- If you have poor kidney function. Your doctor will monitor your fluid and electrolyte balance.
- Fertility. Sorafenib may reduce fertility in both men and women. If you are concerned, talk to a doctor.
- Holes in the gut wall (gastrointestinal perforation) may occur during treatment In this case your doctor will interrupt the treatment.
- If you have thyroid cancer. Your doctor will monitor blood calcium and thyroid hormone levels.

Tell your doctor if any of these affect you. You may need treatment for them, or your doctor may decide to change your dose of Sorafenib, or stop treatment altogether

*Children and adolescents*

Children and adolescents have not yet been tested with Sorafenib.

*Other medicines and Sorafenib*

Some medicines may affect Sorafenib or be affected by it. Tell your doctor if you are taking, have recently taken or might take anything in this list or any other medicines, including medicines obtained without a prescription:

- Rifampicin, Neomycin or other medicines used to treat infections (antibiotics)
- St John's wort, a herbal treatment for depression
- Phenytoin, carbamazepine or phenobarbital, treatments for epilepsy and other conditions
- Dexamethasone, a corticosteroid used for various conditions
- Warfarin or phenprocoumon, anticoagulants used to prevent blood clots
- Doxorubicin, capecitabine, docetaxel, paclitaxel and irinotecan, which are cancer treatments
- Digoxin, a treatment for mild to moderate heart failure

*Pregnancy and breast-feeding*

Avoid becoming pregnant while being treated with Sorafenib. If you could become pregnant use adequate contraception during treatment. If you become pregnant while being treated with Sorafenib, immediately tell your doctor who will decide if the treatment should be continued.

You must not breast-feed your baby during Sorafenib treatment, as this medicine may interfere with the growth and development of your baby.

*Driving and using machines*

There is no evidence that Sorafenib will affect the ability to drive or to operate machines.

1. **How to take SORANIB**

The recommended dose of **SORANIB** in adults is 2 x 200 mg tablets, twice daily.

This is equivalent to a daily dose of 800 mg or four tablets a day.

Swallow **SORANIB** tablets with a glass of water, either without food or with a low-fat or moderate fat meal. Do not take this medicine with high fat meals, as this may make Sorafenib less effective. If you intend to have a high fat meal, take the tablets at least 1 hour before or 2 hours after the meal.

Always take this medicine exactly as your doctor has told you to. Check with your doctor if you are not sure.

It is important to take this medicine at about the same times each day, so that there is a steady amount in the bloodstream.

You will usually carry on taking this medicine as long as you are getting clinical benefits, and not suffering unacceptable side effects.

If you take more Sorafenib than you should

Tell your doctor straight away if you (or anyone else) have taken more than your prescribed dose.

Taking too much Sorafenib makes side effects more likely or more severe, especially diarrhoea and skin reactions. Your doctor may tell you to stop taking this medicine.

If you forget to take **SORANIB**

If you have missed a dose, take it as soon as you remember. If it is nearly time for the next dose, forget about the missed one and carry on as normal. Do not take a double dose to make up for forgotten individual doses.

1. **Possible side-effects**

Like all medicines, this medicine can cause side effects although not everybody gets them. This

medicine may also affect the results of some blood tests.

Very common:

may affect more than 1 in 10 people

- diarrhoea
- feeling sick (nausea)
- feeling weak or tired (fatigue)
- pain (including mouth pain, abdominal pain, headache, bone pain, tumour pain)
- hair loss (alopecia)
- flushed or painful palms or soles (hand foot skin reaction)
- itching or rash
- throwing up (vomiting)
- bleeding (including bleeding in the brain, gut wall and respiratory tract; haemorrhage)
- high blood pressure, or increases in blood pressure (hypertension)
- infections
- loss of appetite (anorexia)
- constipation
- joint pain (arthralgia)
- fever
- weight loss
- dry skin

Common:

may affect up to 1 in 10 people

- flu-like illness
- indigestion (dyspepsia)
- difficulty swallowing (dysphagia)
- inflamed or dry mouth, tongue pain (stomatitis and mucosal inflammation)
- low calcium levels in the blood (hypocalcaemia)
- low potassium levels in the blood (hypokalaemia)
- low blood sugar level (hypoglycaemia)
- muscle pain (myalgia)
- disturbed sensations in fingers and toes, including tingling or numbness (peripheral sensory neuropathy)
- depression
- erection problems (impotence)
- altered voice (dysphonia)
- acne

- inflamed, dry or scaly skin that sheds (dermatitis, skin desquamation)
- heart failure
- heart attack (myocardial infarction) or chest pain
- tinnitus (ringing sound in the ear)
- kidney failure
- abnormally high levels of protein in the urine (proteinuria)
- general weakness or loss of strength (asthenia)
- decrease in the number of white blood cells (leucopenia and neutropenia)
- decrease in the number of red blood cells (anaemia)
- low number of platelets in the blood (thrombocytopenia)
- inflammation of hair follicles (folliculitis)
- underactive thyroid gland (hypothyroidism)
- low sodium levels in the blood (hyponatraemia)
- distortion of the sense of taste (dysgeusia)
- red in the face and often other areas of the skin (flushing)
- runny nose (rhinorrhoea)
- heartburn (gastro oesophageal reflux disease)
- skin cancer (keratoacanthomas/squamous cell cancer of the skin)
- a thickening of the outer layer of the skin (hyperkeratosis)
- a sudden, involuntary contraction of a muscle (muscle spasms)

Uncommon:

may affect up to 1 in 100 people

- inflamed stomach lining (gastritis)
- pain in the tummy (abdomen) caused by pancreatitis, inflammation of the gall bladder and/or bile ducts
- yellow skin or eyes (jaundice) caused by high levels of bile pigments (hyperbilirubinaemia)
- allergic like reactions (including skin reactions and hives)
- dehydration
- enlarged breasts (gynaecomastia)
- breathing difficulty (lung disease)
- eczema
- overactive thyroid gland (hyperthyroidism)
- multiple skin eruptions (erythema multiforme)
- abnormally high blood pressure
- holes in the gut wall (gastrointestinal perforation)
- reversible swelling in the rear part of the brain that can be associated with headache, altered consciousness, fits and visual symptoms including visual loss (reversible posterior leukoencephalopathy)
- a sudden, severe allergic reaction (anaphylactic reaction)

Rare: may affect up to 1 in 1,000 people

- allergic reaction with swelling of the skin (e. g. face, tongue) that may cause difficulty in breathing or swallowing (angioedema)
- abnormal heart rhythm (QT prolongation)
- inflammation of the liver, which may lead to nausea, vomiting, abdominal pain, and jaundice (drug induced hepatitis)
- a sunburn-like rash that may occur on skin that has previously been exposed to radiotherapy and can be severe (radiation recall dermatitis)

- serious reactions of the skin and/or mucous membranes which may include painful blisters and fever, including extensive detachment of the skin (Stevens-Johnson syndrome and toxic epidermal necrolysis)
- abnormal muscle breakdown which can lead to kidney problems (rhabdomyolysis)
- damage of the kidney causing them to leak large amounts of protein (nephrotic syndrome)
- inflammation of the vessels in the skin which may result in rash (leucocytoclastic vasculitis)

Not known: frequency cannot be estimated from the available data

- impaired brain function that can be associated with e.g. drowsiness, behavioural changes, or
- confusion (encephalopathy)
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report any side effects, 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 or you can report to Cipla Ltd on 18002677779. By reporting side-effects, you can help provide more information on the safety of this product.

1. **How to store SORANIB**

Store protected from light.

Keep out of reach of children.

Keep container tightly closed.

Dispensed in original container.

Do not use if seal over bottle opening is broken or missing.

1. **Contents of the pack and other information**

120 CC HDPE Container pack: Contains 120 Tablets &

60 CC HDPE Container pack: Contains 30 Tablets

# 10. Details of Manufacturer

Hetero Labs Limited (Unit -I),

Village: Kalyanpur, Chakkan Road, Tehsil: Baddi,

Distt.: Solan, Himachal Pradesh-173 205.

# 11. Marketed By

Cipla House,

Peninsula Business Park,

Ganpatrao Kadam Marg,

Lower Parel, Mumbai - 400 013 INDIA

## 12. Details of Permission or Licence Number with Date

MNB/06/328, Dated: 21 Jan 2021

## 13. Date of Revision

22 July 2021