PRESCRIBING INFORMATION

Not be sold by retail without the prescription of a "Registered Medical Practitioner only

SORAFENIB TABLETS IP 200 MG
SORAFEKAST™

1. GENERIC NAME:

Sorafenib Tablets I.P. 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 Red USP-NF, Titanium Dioxide IP.

The excipients used are Microcrystalline Cellulose, Croscarmellose Sodium, Hypromellose, Sodium Lauryl Sulphate, Magnesium stearate, Titanium Dioxide, Macrogol/PEG and Ferric Oxide Red".

3. DOSAGE FORM AND STRENGTH:-

Oral (Film-coated tablets) and 200 mg

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indication

- For the treatment of patients with advanced renal cell carcinoma (RCC).
- For hepatocellular Carcinoma (HCC).
- For the treatment of patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC) refractory to radioactive iodine.

4.2 Posology and method of administration

Sorafenib treatment should be supervised by a physician experienced in the use of anticancer therapies.

Posology

The recommended dose of sorafenib in adults is 400 mg (two tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg).

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

Posology adjustments

Management of suspected adverse drug reactions may require temporary interruption or dose reduction of sorafenib therapy.

When dose reduction is necessary during the treatment of hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC), the sorafenib dose should be reduced to two tablets of 200 mg sorafenib once daily.

When dose reduction is necessary during the treatment of differentiated thyroid carcinoma (DTC), the sorafenib dose should be reduced to 600 mg sorafenib daily in divided doses (two tablets of 200 mg and one tablet of 200 mg twelve hours apart).

If additional dose reduction is necessary, sorafenib may be reduced to 400 mg sorafenib daily in divided doses (two tablets of 200 mg twelve hours apart), and if necessary further reduced to one tablet of 200 mg once daily. After improvement of non-haematological adverse reactions, the dose of sorafenib may be increased.

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).

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.

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

- Sorafenib is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of Sorafenib.
- Sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer.

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.

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 in patients with RCC, 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 for patients with 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.

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.

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.

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, 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 DTC study, 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 DTC study, 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.

4.5 Drugs 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 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/m^2) 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/m^2, 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/m^2 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/m^2 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, Metabolism and Elimination), 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.)

Pregnancy

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.

Lactation

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.

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

Sorafenib Tablets may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Sorafenib Tablets.

Males

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

Infertility

Males

Based on findings in animal studies, Sorafenib Tablets may impair fertility in males of reproductive potential.

Pediatric Use

The safety and effectiveness of Sorafenib Tablets 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 Tablets were age 65 years or older and 19% were 75 and older. In total, 32% of RCC patients treated with Sorafenib Tablets 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.

4.7 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 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

System organ class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations	infection	folliculitis			
Blood and lymphatic system disorders	lymphopenia	leucopenia neutropenia anaemia thrombocytopenia			
Immune system disorders			hypersensitivity reactions (including skin reactions and urticaria) anaphylactic reaction	angioedema	
Endocrine disorders		hypothyroidism	hyperthyroidism		
Metabolism and nutrition disorders	anorexia hypophosphataemia	hypocalcaemia hypokalaemia hyponatraemia hypoglycaemia	dehydration		
Psychiatric disorders		depression			
Nervous system disorders		peripheral sensory neuropathy dysgeusia	reversible posterior leukoencephalopathy*		encephalopathy°
Ear and labyrinth disorders		tinnitus			
Cardiac disorders		congestive heart failure* myocardial ischaemia and infarction*		QT prolongation	
Vascular disorders	haemorrhage (inc. gastrointestinal*, respiratory tract* and cerebral haemorrhage*) hypertension	flushing	hypertensive crisis*		
Respiratory, thoracic and mediastinal disorders		rhinorrhoea dysphonia	interstitial lung disease-like events* (pneumonitis, radiation pneumonitis, acute respiratory distress, etc.)		

Gastrointestinal disorders	diarrhoea nausea vomiting constipation	stomatitis (including dry mouth and glossodynia) dyspepsia dysphagia gastro oesophageal reflux disease	pancreatitis gastritis gastrointestinal perforations*		
Hepatobiliary disorders			increase in bilirubin and jaundice, cholecystitis, cholangitis	drug induced hepatitis*	
Skin and subcutaneous tissue disorders	dry skin rash alopecia hand foot skin reaction** erythema pruritus	keratoacanthoma/ squamous cell cancer of the skin dermatitis exfoliative acne skin desquamation hyperkeratosis	eczema erythema multiforme	radiation recall dermatitis Stevens-Johnson syndrome leucocytoclastic vasculitis toxic epidermal necrolysis*	
Musculo-skeletal 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 pain (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 clinical trials congestive heart failure was reported as an adverse event in 1.9% of patients treated with sorafenib . In study for patient with RCCadverse events consistent with congestive heart failure were reported in 1.7% of patients treated with sorafenib and 0.7% receiving placebo. In study for patients with 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 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 RCC study and HCC study, 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 study, 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 study, 1 of 297 sorafenib treated patients in HCC study (CTCAE Grade 2), and 1 of 451 patients (CTCAE Grade 2) in the placebo group in RCC study .
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 study and HCC study , respectively. CTCAE Grade 3 hypophosphataemia (1 – 2 mg/dl) in RCC study occurred in 13 % of sorafenib treated patients and 3 % of patients in the placebo group, in HCC study 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 study , and 1 case in the placebo group in HCC study . 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 study and HCC study, 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 study and HCC study, respectively. The aetiology of hypocalcaemia associated with sorafenib is not known.
In RCC & HCC studies, 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
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 study are shown in table 2.

Table 2: Treatment-emergent laboratory test abnormalities reported in DTC patients

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

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.

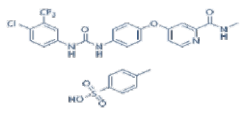
5. PHARMACOLOGICAL PROPERTIES:
5.1 Mechanism of Action:
Sorafenib is a kinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib was shown to inhibit multiple intracellular (c-CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT- 3, RET, RET/PTC, VEGFR-1, VEGFR- 2, VEGFR- 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.

5.2 Pharmacodynamic properties
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.

5.3 Pharmacokinetic properties
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.

6. NONCLINICAL PROPERTIES:
6.1 Animal Toxicology or Pharmacology
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been performed with sorafenib. Sorafenib was clastogenic when tested in an in vitro mammalian cell assay (Chinese hamster ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the in vitro Ames bacterial cell assay or clastogenic in an in vivo mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was positive for mutagenesis in an in vitro bacterial cell assay (Ames test) when tested independently.
No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for sorafenib to impair reproductive function and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration of epididymis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested follicular development. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses ≥ 5 mg/kg (30 mg/m^2). This dose results in an exposure (AUC) that is approximately 0.5 times the AUC in patients at the recommended human dose. Dogs showed tubular degeneration in the testes at 30 mg/kg/day (600 mg/m^2 /day). This dose results in an exposure that is approximately 0.3 times the AUC at the recommended human dose. Oligospermia was observed in dogs at 60 mg/kg/day (1200 mg/m^2 /day) of sorafenib.

7. DESCRIPTION:
Sorafenib, a kinase inhibitor, is the tosylate salt of sorafenib. Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)N2- methylpyridine-2-carboxamide 4-methylbenzenesulfonate and its structural formula is:
Lapatinib ditosylate monohydrate has the following chemical structure:



Chemical formula: $C_{21}H_{16}ClF_3N_4O_3 \times C_7H_8O_3S$
Molecular weight: 637.0 g/mol
ATC code: L01XE05
Pharmacotherapeutic group: Antineoplastic agent, Protein kinase inhibitor.
Sorafenib tosylate is a cream to yellow crystalline powder. Sorafenib tosylate is soluble in dimethylsulphoxide, and insoluble in water.
Sorafenib Tablets are Circular, Red colored film coated tablets, debossed with “BA3” on one side and plain on another side. The excipients used are Microcrystalline Cellulose, Croscarmellose Sodium, Hypromellose, Sodium Lauryl Sulphate, Magnesium stearate, Titanium Dioxide, Macrogol/PEG and Ferric Oxide Red”.

8. PHARMACEUTICAL PARTICULARS
8.1 Incompatibilities
Not Applicable
8.2 Shelf-life
Please see manufacturing date and expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.
8.3 Packaging information
HDPE bottle containing 30 tablets are packed in a mono carton along with pack insert.
8.4 Storage and handing instructions:
Store below 30°C, protected from light.
Keep all medicine out of reach & sight of children.

9. PATIENT COUNSELLING INFORMATION
9.1. What Sorafeb are and what they are used for
Sorafeb is a prescription medicine used to treat:
• a type of liver cancer called hepatocellular carcinoma (HCC) that cannot be removed by surgery
• a type of kidney cancer called renal cell carcinoma (RCC)
• a type of thyroid cancer called differentiated thyroid carcinoma (DTC) that can no longer be treated with radioactive iodine and is progressing
It is not known if Sorafeb is safe and effective in children.

9.2. What you need to know before you use Sorafeb
• have heart problems including a condition called “congenital long QT syndrome”
• have chest pain
• have abnormal magnesium, potassium, or calcium blood levels
• have bleeding problems
• have high blood pressure
• plan to have any surgical procedures or have had recent surgery
• are pregnant or plan to become pregnant. Sorafeb may harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with Sorafeb.
For females who are able to become pregnant:
• Your healthcare should do a pregnancy test before you start treatment with Sorafeb.
• Use effective birth control (contraception) during your treatment with Sorafeb and for 6 months after the last dose of Sorafeb.
For males with female partners who are able to become pregnant:
▪Use effective birth control (contraception) during your treatment with Sorafeb and for 3 months after the last dose of Sorafeb.
▪are breastfeeding or plan to breastfeed. It is not known if Sorafeb passes into your breast milk. Do not breastfeed during treatment with Sorafeb and for 2 weeks after receiving the last dose of Sorafeb.

9.3. How to use Sorafeb
Take Sorafeb exactly as your healthcare provider tells you to take it.
• Take Sorafeb 2 times a day. Your healthcare provider may change your dose, temporarily stop treatment or completely stop treatment with Sorafeb if you have side effects.
• Take Sorafeb without food (at least 1 hour before or 2 hours after a meal).
• If you miss a dose of Sorafeb, skip the missed dose, and take your next dose at your regular time. Do not double your dose of Sorafeb.
• If you take too much Sorafeb call your doctor or go to the nearest hospital emergency room right away.

9.4. Possible side effects
Decreased blood flow to the heart, heart attack and heart failure. Get emergency help right away if you get symptoms such as chest pain, shortness of breath, racing heartbeat, swelling in lower legs, feet and abdomen, feel lightheaded or faint, tiredness, nausea, vomiting, or sweat a lot.
• **increased risk of bleeding. Bleeding is a common side effect of** Sorafeb that can be serious and can lead to death. Tell your healthcare provider right away if you have any signs of bleeding during treatment with Sorafeb:
- vomiting blood or if your vomit looks like coffee-grounds
- pink or brown urine
- red or black (looks like tar) stools
- coughing up blood or blood clots
- heavier than normal menstrual cycle
- unusual vaginal bleeding
- frequent nose bleeds
- bruising

The most common side effects of Sorafeb include:
- diarrhea (frequent or loose bowel movements)
- tiredness
- infection
- hair thinning or patchy hair loss
- rash
- weight loss
- loss of appetite
- nausea
- stomach-area (abdomen) pain
- low blood calcium levels in people with differentiated thyroid cancer.

9.5. How to store Sorafeb
- Store Sorafeb tablets at below 30° C, protected from light.
- Keep Sorafeb and all medicines out of the reach of children

9.6. Contents of the pack and other information
HDPE bottle containing 30 tablets are packed in a mono carton along with pack insert.
HDPE bottle containing 120 tablets are packed in a mono carton along with pack insert.

10. DETAILS OF MANUFACTURER
BDR Pharmaceuticals International Pvt. Ltd.
R. S. No. 578, Near Effluent Channel Road,
Vill. Luna, Tal. Padra,
Dist. Vadodara-391 440. Gujarat.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
G/25/2071 issued on 24.10.2019

12. DATE OF REVISION
November, 2019

References:
1. Prescribing Information for NEXAVAR.

Marketed by :
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Aprazer Healthcare Pvt. Ltd.
B-256, 2nd Floor, Naraina Phase-1, New Delhi-110028, India
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