PACKAGE INSERT

(*For the use of a Registered Medical Practitioner or a Hospital or a Laboratory*.)

SORAVAR 200
Sorafenib Film Coated Tablets 200mg

1. NAME OF THE MEDICINAL PRODUCT

SORAVAR 200

Sorafenib Film Coated Tablets 200mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contain
Sorafenib Tosylate Ph. Eur. equivalent to Sorafenib…200 mg

3. PHARMACEUTICAL FORM

12 mm Red, Round, Biconvex, bevel- edged, film coated tablets debossed with "H1" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Indication(s)

SORAVAR is indicated for the treatment of patients with hepatocellular carcinoma.

SORAVAR is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

SORAVAR is indicated for the treatment of patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine.

4.2 Dosage and method of administration

Recommended dose

The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken twice a day, either without food or together with a low fat or moderate fat meal.

Method of administration

For oral use. To be swallowed with a glass of water.

Dosage regimen Duration of treatment

Treatment should be continued until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Dose titration, dose adjustment, special monitoring advice

Dose Reduction for Hepatocellular Carcinoma and advanced Renal Cell Carcinoma.

Management of suspected adverse drug reactions may require temporary interruption and/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 once daily (see section Special warnings and precautions for use).

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

Table 1: Suggested Dose Modifications for Dermatologic Toxicities in Patients with Hepatocellular or Renal Cell Carcinoma

Dermatologic Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with SORAVAR and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Continue treatment with SORAVAR and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt SORAVAR treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease SORAVAR dose by one dose level (400 mg daily or 400 mg every other day)

	4th occurrence	Discontinue SORAVAR treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt SORAVAR treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease SORAVAR dose by one dose level (400 mg daily or 400 mg every other day)
	3rd occurrence	Discontinue SORAVAR treatment

Dose Reduction for Differentiated Thyroid Carcinoma

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

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

If additional dose reduction is necessary, sorafenib may be reduced to one tablet of 200mg twice daily, followed by one tablet of 200mg once daily. After improvement of non-hematological adverse reactions, the dose of sorafenib may be increased.

Table 2: Recommended Dose Modifications for Dermatologic Toxicities for Patients with Differentiated Thyroid Carcinoma:

Dermatologic Toxicity Grade	**Occurrence**	**SORAVAR Dose Modification**
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with SORAVAR
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Decrease SORAVAR dose to 600 mg daily If no improvement within 7 days, see below.
	No improvement within 7 days at reduced dose or 2nd occurrence	Interrupt SORAVAR until resolved or improved to grade 1 If SORAVAR is resumed, decrease dose. (See "Dose Reduction for Differentiated Thyroid Carcinoma").
	3rd occurrence	Interrupt SORAVAR until resolved or improved to grade 1 If SORAVAR is resumed, decrease dose. (See "Dose Reduction for Differentiated Thyroid Carcinoma").
	4th occurrence	Discontinue SORAVAR permanently.
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 SORAVAR until resolved or improved to grade 1 If SORAVAR is resumed, decrease dose by one dose level. (See "Dose Reduction for Differentiated Thyroid Carcinoma").
	2nd occurrence	Interrupt SORAVAR until resolved or improved to grade 1 When SORAVAR is resumed, decrease dose by 2 dose levels. (See "Dose Reduction for Differentiated Thyroid Carcinoma").
	3rd occurrence	Discontinue SORAVAR permanently

Additional information on special populations

Pediatric Patients

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

Geriatric patients

Elderly (above 65 years), Gender and Body Weight

No dose adjustment is required on the basis of patient age (above 65 years), gender, or body weight.

Patients with hepatic impairment

No dose adjustment is required in patients with Child-Pugh A or B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment (see section Pharmacokinetic Properties – Pharmacokinetics in special populations - Hepatic Impairment).

Patients with renal impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment not requiring dialysis. Sorafenib has not been studied in patients undergoing dialysis (see section Pharmacokinetic Properties –Special populations – Renal impairment).

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

4.3 Contraindications

Sorafenib is contraindicated in patients with known severe hypersensitivity to sorafenib or any of the excipients.
Sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer [see Warnings and Precautions]

4.4 Special warnings and precautions for use

Pregnancy

Women should avoid becoming pregnant while on therapy.

Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity).

Sorafenib should not be used during pregnancy. Prescribers may only consider it to be used, if the potential benefits justify the potential risks to the fetus.

Breastfeeding should be discontinued during sorafenib therapy.

(See section Fertility, Pregnancy, and Lactation).

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 (National Cancer Institute Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib.

Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib (see section Undesirable Effects).

Hypertension

An increased incidence of 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 adequate antihypertensive therapy, permanent discontinuation of sorafenib should be considered (see section Undesirable Effects).

Hemorrhage

An increase in the risk of bleeding may occur following sorafenib administration. The incidence of severe bleeding events is uncommon. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of sorafenib should be considered (see section Undesirable Effects). Due to the potential risk of bleeding, tracheal, bronchial, and esophageal infiltration should be treated with localized therapy prior to administering sorafenib in patients with differentiated thyroid carcinoma.

Warfarin

Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy. Patients taking warfarin concomitantly should be monitored regularly for changes in prothrombin time, INR and for clinical bleeding episodes (see section Undesirable Effects).

Increased Mortality Observed with SORAVAR 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 non-small cell lung cancer, patients with squamous cell carcinoma experienced higher mortality with the addition of SORAVAR 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 SORAVAR in combination with carboplatin / paclitaxel is contraindicated in patients with squa mous cell lung cancer. SORAVAR in combination with gemcitabine/cisplatin is not recommended in patients with squamous cell lung cancer. The safety and effectiveness of SORAVAR has not been established in patients with non-small cell lung cancer.

Wound healing complications

No formal studies of the effect of sorafenib on wound healing have been conducted. In patients undergoing major surgical procedures, temporary interruption of sorafenib therapy is recommended for precautionary reasons. 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 judgment of adequate wound healing.

Cardiac Ischemia and/or Infarction

In Study 11213, the incidence of treatment-emergent cardiac ischemia/infarction events was higher in the sorafenib group (4.9%) compared with the placebo group (0.4%). In Study 100554, the incidence of treatment-emergent cardiac ischemia/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 theses studies. Temporary

or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia and/or infarction (see sections Undesirable Effects, Pharmacokinetic Properties-Clinical Efficacy and safety).

QT interval prolongation

SORAVAR has been shown to prolong the QT/QTc interval (see Pharmacological Properties:- Pharmacodynamic properties), 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 hypokalemia, hypocalcemia, or hypomagnesemia. When using SORAVAR 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 tumor. Sorafenib therapy should be discontinued (see section Undesirable Effects).

Tumour lysis syndrome (TLS)

Cases of TLS, some fatal, have been reported in postmarketing surveillance in patients treated with sorafenib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.

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 (see section Pharmacokinetic Properties).

Hypocalcaemia

When using sorafenib in patients with differentiated thyroid carcinoma, close monitoring of blood calcium level is recommended. In clinical trials, hypocalcaemia was more frequent and more severe in patients with differentiated thyroid carcinoma, especially with a history of hypoparathyroidism, compared to patients with renal cell or hepatocellular carcinoma. (see section Undesirable effects)

TSH Suppression in Differentiated Thyroid Carcinoma (DTC)

In the DTC clinical trials, increases in TSH levels above 0.5mU/L were observed in sorafenib treated patients. When using sorafenib in differentiated thyroid carcinoma patients, close monitoring of TSH level is recommended.

Drug-Drug Interactions

UGT1A pathway

Caution is recommended when administering sorafenib together with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan) (see section Interactions with other medicinal products and other forms of interaction).

Docetaxel

Concomitant use of docetaxel (75 or 100 mg/m^2) with sorafenib (200 or 400 mg twice daily), administered with a 3-day break in dosing around administration of docetaxel, resulted in a 36-80% increase in docetaxel AUC. Caution is recommended when sorafenib is co- administered with docetaxel (see section Interactions with other medicinal products and other forms of interactions).

Neomycin

Co-administration of neomycin may cause a decrease in sorafenib bioavailability (see Interaction with other medicinal products and other forms of interaction).

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 Inducers

Continuous concomitant administration of sorafenib and rifampicin resulted in an average 37% reduction of sorafenib AUC. Other inducers of CYP3A4 activity (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. Therefore, clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.

CYP2C9 substrates

The possible effect of sorafenib on warfarin, a CYP2C9 substrate, was assessed in sorafenib- treated patients compared to placebo treated patients. The concomitant treatment with sorafenib and warfarin did not result in changes in mean PT-INR compared to placebo. However, patients taking warfarin should have their INR checked regularly (see section Special warnings and precautions for use).

CYP isoform-selective substrates

Concomitant administration of midazolam, dextromethorphan, and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6, and CYP2C19, respectively, following 4 weeks of sorafenib administration did not alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. In a separate clinical study, concomitant administration of sorafenib with paclitaxel resulted in an increase, instead of a decrease, in the exposure of 6-OH paclitaxel, the active metabolite of paclitaxel that is formed by CYP2C8. These data suggest that sorafenib may not be an *in vivo* inhibitor of CYP2C8. In another clinical study, concomitant administration of sorafenib with cyclophosphamide resulted in a small decrease in cyclophosphamide exposure, but no decrease in the systemic exposure of 4-OH cyclophosphamide, the active metabolite of cyclophosphamide that is formed primarily by CYP2B6. These data suggest that sorafenib may not be an *in vivo* inhibitor of CYP2B6.

Combination with other anti-neoplastic agents

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

Based on cumulative data from clinical studies, a favorable benefit/risk profile of the use of sorafenib in combination with systemically administered anti-neoplastic agents has not been established.

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 around administration of paclitaxel/carboplatin, 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. The clinical significance of the increases in sorafenib and paclitaxel exposure, upon co-administration of sorafenib without a break in dosing, is unknown.

Sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer (see Contraindications)

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 metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown (see section Special warnings and precautions for use).

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 Day 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 (see section Special warnings and precautions for use).

Combination with antibiotics Neomycin

Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate GI flora, interferes with the enterohepatic recycling of sorafenib (see Pharmacokinetic properties- Metabolism and Elimination), resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average bioavailability of sorafenib decreased by 54%. The clinical significance of these findings is unknown. Effects of other antibiotics have not been studied, but will likely depend on their ability to decrease glucuronidase activity.

4.6 Fertility, pregnancy and lactation

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.

4.7 Effects on ability to drive or use machines

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

4.8 Undesirable effects

The most important serious adverse reactions were myocardial infarction/ischaemia, gastrointestinal perforation, drug induced, hepatits, 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), rash.

Adverse reactions reported in multiple clinical trials or through postmarketing use are listed below in Table 1 and Table 2, by system organ class (in MedDRA) and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the data available).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse reactions reported in at least 5% of patients in any treatment group – Study 11213 in renal cell carcinoma (see study 11213).

	Sorafenib N=451			Placebo N=451		
	all grades	**grade 3**	**grade 4**	**all grades**	**grade 3**	**grade 4**
Metabolism and Nutrition Disorders						
anorexia	9%	<1%	0%	5%	<1%	0%
Nervous System Disorders						
headache	6%	0%	0%	3%	0%	0%
Vascular Disorders						
hypertension	12%	2%	<1%	1%	<1%	0%
flushing	6%	0%	0%	2%	0%	0%
Gastrointestinal Disorders						
diarrhoea	38%	2%	0%	9%	<1%	0%
nausea	16%	<1%	0%	12%	<1%	0%
vomiting	10%	<1%	0%	6%	<1%	0%
constipation	6%	0%	0%	3%	0%	0%
Skin and Subcutaneous Tissue Disorders						
rash	28%	<1%	0%	9%	<1%	0%
alopecia	25%	<1%	0%	3%	0%	0%
Hand-foot skin reaction**	19%	4%	0%	3%	0%	0%
pruritus	17%	<1%	0%	4%	0%	0%
erythema	15%	0%	0%	4%	0%	0%
dry skin	11%	0%	0%	2%	0%	0%
skin exfoliation	7%	<1%	0%	2%	0%	0%
Musculoskeletal, Connective Tissue and Bone Disorders						
arthralgia	6%	<1%	0%	3%	0%	0%
pain in extremity	6%	<1%	0%	3%	0%	0%
General Disorders and Administrative Site conditions						
fatigue	15%	2%	0%	12%	<1%	0%
asthenia	9%	<1%	0%	4%	<1%	0%

Table 4: Adverse reactions reported in at least 5% of patients in any treatment group – Study 100554 in hepatocellular carcinoma (see study

100554).

	Sorafenib N=297			Placebo N=302		
	all grades	**grade 3**	**grade 4**	**all grades**	**grade 3**	**grade 4**
Metabolism and Nutrition Disorders						
anorexia	11%	<1%	0%	3%	<1%	0%

Gastrointestinal Disorders

	Sorafenib N= 297			Placebo N= 302		
	all grades	**grade 3**	**grade 4**	**all grades**	**grade 3**	**grade 4**
diarrhoea	39 %	8 %	0 %	11 %	2 %	0 %
nausea	11 %	<1 %	0 %	8 %	1 %	0 %
abdominal pain	7 %	2 %	0 %	3 %	<1 %	0 %
vomiting	5 %	1 %	0 %	3 %	<1 %	0 %
Skin and Subcutaneous Tissue Disorders						
Hand-foot skin reaction**	18 %	7 %	0 %	2 %	0 %	0 %
alopecia	14 %	0 %	0 %	2 %	0 %	0 %
rash	11 %	<1 %	0 %	8 %	0 %	0 %
pruritus	8 %	0 %	0 %	7 %	<1 %	0 %
dry skin	8 %	0 %	0 %	4 %	0 %	0 %
General Disorders and Administration Site conditions						
fatigue	17 %	2 %	<1 %	13 %	3 %	<1 %
asthenia	6 %	1 %	<1 %	2 %	<1 %	0 %
Investigations						
weight decreased	9 %	2 %	0 %	<1 %	0 %	0 %
Respiratory, thoracic and mediastinal disorders						
hoarseness	5 %	0 %	0 %	<1 %	0 %	0 %

Adverse reactions that occurred either during clinical studies or have been identified through postmarketing use are listed below in Table 3, by system organ class (in MedDRA) and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), not known (cannot be estimated from the data available).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5: All Adverse Drug Reactions reported in patients in multiple clinical trials or through post-marketing use

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1000**	**Not Known**

Infections and Infestations	infection	folliculitis			
Blood and Lymphatic System Disorders	lymphopenia	leucopenia neutropenia anaemia thrombocytopenia			
Immune system Disorders			anaphylactic reaction hypersensitivity reactions (including skin reactions and urticaria)		angioedema
Endocrine Disorders		hypothyroidism	hyperthyroidism		
Metabolism and Nutrition Disorders	anorexia hypophosphatae mia	hypocalcaemia hypokalemia hyponatraemia	dehydration		
Psychiatric Disorders		depression			
Nervous System Disorders		peripheral sensory neuropathy dysgeusia	reversible posterior leukoencephalo- pathy*		
Ear and Labyrinth Disorders		tinnitus			
Cardiac Disorders		congestive heart failure* myocardial ischemia and/or infarction*		QT prolongation	
Vascular Disorders	hemorrhage (inc. gastrointestinal* & respiratory tract* and cerebral hemorrhage*) hypertension	flushing	hypertensive crisis*		
Respiratory, Thoracic and Mediastinal Disorders		rhinorrhoea dysphonia	interstitial lung disease-like events*		
Gastrointestinal Disorders	diarrhoea nausea vomiting constipation	stomatitis (including dry mouth and glossodynia) dyspepsia dysphagia	pancreatitis gastritis gastrointestinal perforations*		
Hepato-biliary Disorders			increase in bilirubin and jaundice, cholecystitis, cholangitis	drug induced hepatitis*	
Skin and Subcutaneous Tissue Disorders	dry skin rash alopecia hand - foot skin reaction ** pruritus erythema	keratoacanthoma/s quamous cell cancer of skin dermatitis exfoliative acne skin desquamation hyperkeratosis	eczema erythema multiforme		radiation recall dermatitis Stevens-Johnson syndrome leukocytoclastic vasculitis toxic epidermal necrolysis*
Musculoskeletal, Connective Tissue and Bone Disorders	arthralgia	myalgia muscle spasms			rhabdomyolysis
Renal and Genitourinary 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 in increase in blood alkaline phosphatase INR abnormal prothrombin level abnormal		

* these adverse reactions may have a life-threatening or fatal outcome. Such events are either uncommon or less frequent than uncommon
** palmar-plantar erythrodysaethesia syndrome in MedDRA

Additional information on special populations

Two randomized placebo-controlled trials comparing safety and efficacy of sorafenib in combination with doublet platinum-based chemotherapies (carboplatin/paclitaxel and separately gemcitabine/cisplatin) versus the respective doublet platinum-based chemotherapies alone as first-line treatment for patients with advanced Non-Small Cell Lung Carcinoma (NSCLC) did not meet their primary endpoint of improved overall survival. Safety events were generally consistent with those previously reported. However, in both trials, higher mortality was observed in the subset of patients with squamous cell carcinoma of the lung treated with sorafenib and doublet platinum-based chemotherapies versus those treated with doublet platinum-based chemotherapies alone (paclitaxel/carboplatin: HR 1.81, 95% CI 1.19-2.74 gemcitabine/cisplatin: HR 1.22, 95% CI 0.82 – 1.80). No definitive cause was identified for the findings.

Other special populations

Laboratory test abnormalities in RCC patients (study 11213)

Elevated lipase and amylase levels were very commonly reported. In Study 11213, CTCAE grade 3 or 4 lipase elevations occurred in 12% of patients in the sorafenib group compared to 7% of patients in the placebo group. CTCAE grade 3 or 4 amylase elevations were reported in 1% of patients in the sorafenib group compared to 3% of patients in the placebo group. Clinical pancreatitis was reported in 2 of 451 sorafenib treated patients (CTCAE grade 4) and 1 of 451 patients (CTCAE grade 2) in the placebo group in Study 1.

Laboratory test abnormalities in HCC patients (study 100554)

Elevated lipase was observed in 40% of patients treated with SORAVAR compared to 37% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 9% of patients in each group. Elevated amylase was observed in 34% of patients treated with SORAVAR compared to 29% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 2% of patients in each group. Many of the lipase and amylase elevations were transient, and in the majority of cases SORAVAR treatment was not interrupted. Clinical pancreatitis was reported in 1 of 297 SORAVAR-treated patients (CTCAE Grade 2).

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 reactions observed at this dose were primarily diarrhea and dermatologic events.

In the event of suspected overdose, sorafenib should be withheld and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Protein kinase inhibitor

QT interval prolongation

In a clinical pharmacology study, QT/QTc measurements were recorded in 31 patients at baseline (pre-treatment) and post-treatment. After one 28-day treatment cycle, at the time of maximum concentration of sorafenib, QTcB was prolonged by 4 ±19 msec and QTcF by 9 ±18 msec, as compared to placebo treatment at baseline. No subject showed a QTcB or QTcF >500 msec during the post-treatment ECG monitoring. (see Special warnings and precautions for use)

5.2 Pharmacokinetic properties

Absorption and Distribution

After administration of sorafenib film coated tablets, the mean relative bioavailability is 38-49% when compared to an oral solution. Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal, bioavailability is similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability is reduced by 29% compared to administration in the fasted state.

In vitro binding of sorafenib to human plasma proteins is 99.5%.

Metabolism /Biotransformation

Sorafenib is metabolized primarily in the liver undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib conjugates may be cleaved in the GI tract by bacterial glucuronidase activity, allowing reabsorption of unconjugated drug. Co-administration of neomycin interferes with this process, decreasing the mean bioavailability of sorafenib by 54%.

Elimination/Excretion

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

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

Linearity/Non-linearity

Mean Cmax and AUC increase less than proportionally beyond doses of 400 mg administered orally twice daily.

Steady-state Pharmacokinetics

Multiple dosing of sorafenib for 7 days results 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 pharmacokinetics of sorafenib administered at 400 mg bid were evaluated in thyroid carcinoma, RCC and HCC patients. The highest mean exposure was observed in thyroid carcinoma patients, though variability in exposure was high for all tumor types. The clinical relevance of the increased AUC in thyroid carcinoma patients is unknown.

Additional information on special populations

Studies on enzyme inhibition

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4. Concomitant clinical administration of midazolam, dextromethorphan, and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6, and CYP2C19, respectively, following 4 weeks of sorafenib administration did not alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes.

In vitro data show that sorafenib inhibits glucuronidation by the UGT1A1 (Ki =1 μM) and UGT1A9 (Ki=2 μM) pathways. Concomitant clinical administration of sorafenib with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, resulted in a 67-120% increase in the AUC of SN-38. Systemic exposure to substrates of UGT1A1 and UGT1A9 may be increased when co-administered with sorafenib.

Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with Ki values of 6 and 1–2 μM, respectively. Concomitant clinical administration of sorafenib with paclitaxel resulted in an increase, instead of a decrease, in the exposure of 6-OH paclitaxel, the active metabolite of paclitaxel that is formed by CYP2C8. These data suggest that sorafenib may not be an *in vivo* inhibitor of CYP2C8. Concomitant administration of sorafenib with cyclophosphamide resulted in a small decrease in cyclophosphamide exposure, but no decrease in the systemic exposure of 4-OH cyclophosphamide, the active metabolite of cyclophosphamide that is formed primarily by CYP2B6. These data suggest that sorafenib may not be an *in vivo* inhibitor of CYP2B6.

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9 with a Ki value of 7–8 μM. The possible effect of sorafenib on a CYP2C9 substrate was assessed in patients receiving sorafenib or placebo in combination with warfarin. The mean changes from baseline in PT-INR were not higher in sorafenib patients compared to placebo patients, suggesting that sorafenib may not be an *in vivo* inhibitor of CYP2C9.

Effect of CYP3A4 inhibitors

Ketoconazole (400 mg), 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. Therefore, clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.

Effect of CYP inducers

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. Continuous concomitant clinical administration of sorafenib and rifampicin resulted in an average 37% reduction of sorafenib AUC. Other inducers of CYP3A4 activity (e.g. Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase the metabolism of sorafenib and thus decrease sorafenib concentrations.

Combination with other anti-neoplastic agents

In clinical studies, sorafenib has been administered together with a variety of other anti- neoplastic agents at their commonly used dosing regimens, including gemcitabine, cisplatin, oxaliplatin, paclitaxel, carboplatin, capecitabine, doxorubicin, docetaxel, irinotecan, 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 around administration of paclitaxel/carboplatin, 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. 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 upon co-administered with sorafenib is unknown.

Doxorubicin/Irinotecan

Concomitant treatment with sorafenib resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown (see section Special warnings and precautions for use)

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 Day 2 through 19 of a 21-day cycle), with a 3-day break in dosing, around administration of docetaxel, resulted in a 36-80% increase in docetaxel AUC and a 16-32% increase in docetaxel Cmax. Caution is recommended when sorafenib is co-administered with docetaxel. (see section Special warnings and precautions for use).

Combination with antibiotics Neomycin

Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate GI flora, interferes with the enterohepatic recycling of sorafenib (see above), resulting in decreased sorafenib exposure. In healthy volunteers treated with a 5-day regimen of neomycin the average bioavailability of sorafenib decreased by 54%. The clinical significance of these findings for is unknown. Effects of other antibiotics have not been studied, but will likely depend on their ability to decrease glucuronidase activity.

Pediatric patients

There are no pharmacokinetic data in pediatric patients.

Geriatric patients

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

Patients with hepatic impairment

Sorafenib is cleared primarily by the liver.

In HCC patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, exposure values were within the range observed in patients without hepatic impairment. The pharmacokinetics (PK) of sorafenib in Child-Pugh A and Child-Pugh B non-HCC patients were similar to the PK in healthy volunteers. The pharmacokinetics of sorafenib has not been studied in patients with severe (Child-Pugh C) hepatic impairment (see sections Special Warnings and Precautions for use and Dosage and Method of Administration).

Patients with renal impairment

In a clinical pharmacology study, the pharmacokinetics of sorafenib were evaluated following administration of a single 400 mg dose to subjects with normal renal function, and in subjects with mild (CrCl 50-80 mL/min), moderate (CrCl 30 to < 50 mL/min), or severe (CrCl< 30mL/min) renal impairment, not requiring dialysis. There was no relationship observed between sorafenib exposure and renal function. No dosage adjustment is necessary based on mild, moderate or severe renal impairment not requiring dialysis (see section Dosage and Method of Administration).

Gender

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

6. PHARMACEUTICAL PARTICULARS

Active Ingredients

Sorafenib Tosylate

Inactive Ingredients

Microcrystalline cellulose,
Croscarmellose sodium,
Hypromellose E5,
Sodium lauryl sulphate,
Magnesium stearate

Film coating (Opadry 03F540266 Pink):

Hypromellose,
Titanium dioxide,
Macrogol/PEG,
Iron oxide red.

'This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free''.

Special precautions for storage and use

Do not store above 30 °C.

Keep out of the sight and reach of children.

Nature and contents of container

Sorafenib Film Coated Tablets 200mg are packed in Alu-Alu blister pack of 10 tablets. 6 such blisters are packed in one printed carton (6 × 10 Tablets).

Name and address of manufacturer
Intas Pharmaceuticals Ltd.
Plot No 5-14, Pharmez, Near Village Matoda
Sarkhej-Bavla National Highway
No. 8-A, Sanand Taluka, Ahmedabad
Gujarat, IN 382213, India

Product Registration Holder
Accord Healthcare Sdn Bhd (1035160 D)
Suite 12A-15, Level 12A, Wisma Zelan
No 1 Jalan Tasik Permaisuri 2 Bandar Tun Razak,
56000 Kuala Lumpur, Malaysia

Shelf life
24 months

Date of revision of PI
Nov 2024

(Suggested font size: 7, as measure in Times New Roman)