1. NAME OF THE MEDICINAL PRODUCT

NEXAVAR® 200 mg film-coated tablets.

2. QUANTITATIVE AND QUALITATIVE COMPOSITION

Sorafenib tosylate. Each tablet contains 200 mg of sorafenib (274 mg sorafenib tosylate).

3. PHARMACEUTICAL FORM

Red round, biconvex film coated tablet for oral use with a diameter of 10 mm and a weight of 350 mg.

3.1 Debossing

One side: Bayer cross. Other side: "200"

3.2 Description

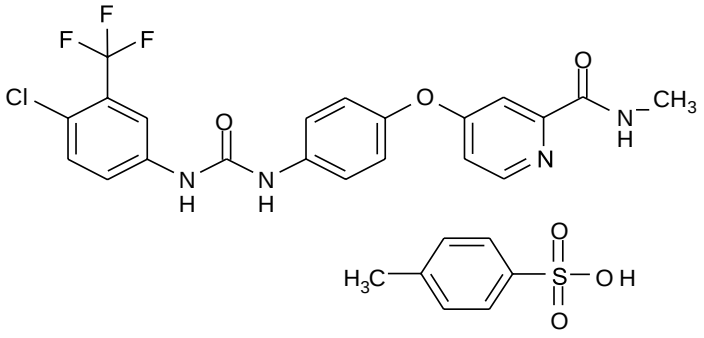
NEXAVAR is a multikinase inhibitor targeting several serine/threonine and receptor tyrosine kinases**.**

Sorafenib tosylate is a white to yellowish or brownish solid with a molecular weight of 637 g/mole.
Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

Chemical name: 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]-ureido}phenoxy)-N2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate.

Empirical formula is $C_{21}H_{16}ClF_3N_4O_3$ x $C_7H_8O_3S$
CAS number is 28844-1-73-01 (sorafenib) and 475207-59-1 (sorafenib tosylate).

3.3 Chemical structure



4. CLINICAL PARTICULARS

4.1 Indication(s)

NEXAVAR is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC).

NEXAVAR is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior systemic therapy or are considered unsuitable for such therapy.

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

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 moderate fat meal.

Method of administration

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

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 "Special Warnings and Precautions for Use").

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 1: Suggested Dose Reduction Levels for Patients with Differentiated Thyroid Carcinoma

Dose Level	Sorafenib Dose	
0	800mg daily dose	400mg twice daily (2 tablets twice daily)
-1	600mg daily dose	400mg and 200mg 12 hours apart (2 tablets and 1 tablet 12 hours apart – either dose can come first)
-2	400mg daily dose	200mg twice daily (1 tablet twice daily)
-3	200mg daily dose	200mg once daily (1 tablet once daily)

Table 2: Suggested Dose Modifications for Skin Toxicity in Patients with Differentiated Thyroid Carcinoma

Grade	Occurrence	Sorafenib dose modification*
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless	Any	Institute supportive measures immediately and continue sorafenib treatment

swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities		
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	First	Institute supportive measures immediately and consider a decrease sorafenib dose to 600mg daily (400mg and 200mg 12 hours apart) If no improvement within 7 days, see below
	No improvement within 7 days or second occurrence	Interrupt sorafenib until resolved to grade 0-1. When sorafenib is resumed, decrease dose by one dose level
	Third	Interrupt sorafenib until resolved to grade 0-1. When sorafenib is resumed, decrease dose by two dose levels
	Fourth	Discontinue sorafenib 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	First	Interrupt sorafenib until resolved to grade 0-1. When sorafenib is resumed, decrease dose by one dose level
	Second	Interrupt sorafenib until resolved to grade 0-1. When sorafenib is resumed, decrease dose by two dose levels
	Third	Discontinue sorafenib permanently

*For patients who require a dose reduction for Grade 2 or 3 skin toxicity, the dose of sorafenib may be increased one dose level from the reduced dose if skin toxicity improved to Grade 0-1 after at least 28 days treatment on the reduced dose of sorafenib.

Special Populations

Pediatric Patients

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

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.

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 "Pharmacokinetics Properties").

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 "Pharmacokinetics Properties").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 in the tablet.

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 "Pregnancy and Lactation" and "Preclinical Safety Data").

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 "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 anti-hypertensive 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 "Undesirable Effects").

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.

Haemorrhage

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 "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 "Undesirable Effects").

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 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 (see "Undesirable Effects", "Pharmacokinetics Properties").

QT interval prolongation

Nexavar has been shown to prolong the QT/QTc interval (see "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 Nexavar 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 (see "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 "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). Severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes (see section QT interval prolongation).

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.

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

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 "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 "Interactions with Other Medicinal Products and Other Forms of Interaction").

Neomycin

Co-administration of neomycin may cause a decrease in sorafenib bioavailability (see "Interactions 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 "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 pharmacokinetic study, concomitant administration of sorafenib 400 mg twice daily with cyclophosphamide, a CYP2B6 substrate, did not result in a clinically meaningful inhibition.

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 ($\leq$ 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 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 "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 "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 "Pharmacokinetics Properties"), 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.

Combination with proton pump inhibitors

Omeprazole:

Co-administered of omeprazole has no impact on the pharmacokinetics of sorafenib. No dose adjustment for sorafenib is necessary.

4.6 Pregnancy And Lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women using sorafenib. Studies in animals have shown reproductive toxicity including malformations (see "Special Warnings and Precautions for Use"). In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to inhibit angiogenesis in the foetus.

Women should avoid becoming pregnant while on therapy. Women of childbearing potential must be apprised of the potential hazard to the foetus, 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 foetus (see "Special Warnings and Precautions for Use"**,** "Preclinical Safety Data").

Women of childbearing-potential

In animals, sorafenib has been shown to be teratogenic and embryotoxic. Adequate contraception should be used during therapy and for at least 2 weeks after completion of therapy. (see "Special Warnings and Precautions for Use", "Preclinical Safety Data").

Lactation
It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because many drugs are excreted in human milk and because the effects of sorafenib on infants have not been studied, women should discontinue breastfeeding during sorafenib treatment.

Fertility

Results from animal studies indicate that sorafenib can impair male and female fertility (see "Preclinical Safety Data").

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 common adverse reactions were diarrhoea, fatigue, alopecia, infection, hand-foot skin reaction (corresponds to palmar-plantar erythrodysaesthesia syndrome in MedDRA), rash.

Renal Cell Carcinoma

Table 3. Adverse Reactions reported in at Least 5% of Patients in Any Treatment Group –Study 11213 in renal cell carcinoma (see study 11213).

	Nexavar 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 Administration Site Conditions						
Fatigue	15	2	0	12	<1	0
Asthenia	9	<1	0	4	<1	0

Hepatocellular carcinoma

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

		Nexavar N= 297			Placebo N= 302		
System organ class	**Preferred term**	**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	**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 %

Differentiated Thyroid Carcinoma

Table 5: Adverse drug reactions (>10%) reported in patients treated with Nexavar and more commonly than in patients receiving placebo. (differentiated thyroid carcinoma study, double blind period, safety analysis set, CTCAE version 3.0)

Adverse Event Category/term	**Nexavar (n=207)**			**Placebo (n=209)**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Cardiac general						
Hypertension	41	10	0	12	2	0
Constitutional symptoms						
Fatigue	50	5	<1	25	1	0
Weight Loss	47	6	0	14	1	0
Fever	11	1	<1	5	0	0
Dermatology/skin						
HFSR	76	20	0	10	0	0

Adverse Event Category/term	Nexavar (n=207)			Placebo (n=209)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Alopecia	67	0	0	8	0	0
Rash/Desquamation	50	5	0	11	0	0
Pruritus	21	1	0	11	0	0
Dry skin	14	<1	0	6	0	0
Gastrointestinal						
Diarrhea	69	5	<1	15	1	0
Anorexia	32	2	0	5	0	0
Mucositis, oral cavity	23	<1	<1	3	0	0
Nausea	21	0	0	11	0	0
Constipation	15	0	0	8	<1	0
Vomiting	11	<1	0	6	0	0
Infection						
Infection (all)	32	4	0	19	2	0
Pain						
Pain, head/headache	18	0	0	7	0	0
Pain, extremity-limb	14	<1	0	9	<1	0
Pain, abdomen	14	1	0	4	<1	0
Pain, other	11	<1	0	8	<1	0
Pain, throat/pharynx/larynx	10	0	0	4	0	0
Metabolic/Laboratory						
Hypocalcemia	19	6	3	5	<1	1
ALT increased	13	2	<1	4	0	0
AST increased	11	1	0	2	0	0
Neuropathy						
Sensory neuropathy	14	1	0	6	0	0
Pulmonary/upper respiratory						
Voice changes	12	<1	0	3	0	0

Adverse reactions that occurred either during clinical studies or have been identified through post-marketing use are listed below in Table 6, 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 6: 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 ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Not Known

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 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			thrombotic microangiopathy
Immune system Disorders			Anaphylactic reaction hypersensitivity reactions (including skin reactions and urticaria)		angioedema
Endocrine Disorders		hypothyroidism	hyperthyroidism		
Metabolism and Nutrition Disorders	anorexia hypophosphataemia	hypocalcaemia hypokalemia hyponatraemia	dehydration		tumour lysis syndrome
Psychiatric Disorders		depression			
Nervous System Disorders		peripheral sensory neuropathy dysgeusia	reversible posterior leukoencephalopathy*		
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*		dyspnea
Gastrointestinal Disorders	diarrhoea nausea vomiting constipation	stomatitis (including dry mouth and glossodynia) dyspepsia	pancreatitis gastritis gastrointestinal perforations*		

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Not Known
		dysphagia gastrooesophageal reflux disease			
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	keratoacanthomas/ squamous cell cancer of the 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		

* the 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

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 1.7% of those treated with sorafenib and 0.7% receiving placebo. In study 100554 (HCC), 0.99% of those treated with sorafenib and in 1.1 % receiving placebo were reported with these events.

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.

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

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.

Hypophosphataemia was a common laboratory finding, observed in 45% of sorafenib treated patients compared to 11% of placebo patients. CTCAE grade 3 hypophosphataemia (1–2 mg/dL) occurred in 13% on sorafenib treated patients and 3% 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. The etiology of hypophosphataemia associated with sorafenib is not known.

Hypocalcaemia was reported in 12% of sorafenib treated patients compared to 7.5% of placebo patients. 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% of sorafenib treated patients and 0.2% of patients in the placebo group, and CTCAE grade 4 Hypocalcaemia (< 6.0 mg/dL) occurred in 1.1% of sorafenib treated patients and 0.5% of patients in the placebo group. The etiology of hypocalcaemia associated with sorafenib is not known.

Hypokalemia was reported in 5.4% of sorafenib treated patients compared to 0.7% of placebo patients. Most reports of hypokalemia were low grade (CTCAE Grade 1). CTCAE grade 3 Hypokalemia occurred in 1.3% of sorafenib treated patients and 0.2% of patients in the placebo group. There were no reports of grade 4 Hypokalemia.

Laboratory abnormalities in HCC patients (study 100554):
Elevated lipase was observed in 40% of patients treated with NEXAVAR 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 NEXAVAR 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, NEXAVAR treatment was not interrupted. Clinical pancreatitis was reported in 1 of 297 NEXAVAR-treated patients (CTCAE Grade 2).

Hypophosphatemia was a common laboratory finding, observed in 35% of NEXAVAR-treated patients compared to 11% of placebo patients; CTCAE Grade 3 hypophosphatemia (1–2 mg/dL) occurred in 11% of NEXAVAR-treated patients and 2% of patients in the placebo group; there was 1 case of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in the placebo group. The etiology of hypophosphatemia associated with NEXAVAR is not known.

Elevations in liver function tests were comparable between the 2 arms of the study. Elevated AST was observed in 94% of NEXAVAR-treated patients and 91% of placebo patients; CTCAE Grade 3 or 4 AST elevations were reported in 16% of NEXAVAR-treated patients and 17% of patients in the placebo group. ALT elevations were observed in 69% of NEXAVAR-treated patients and 68% of placebo patients; CTCAE Grade 3 or 4 ALT elevations were reported in 3% of NEXAVAR-treated patients and 8% of placebo treated patients. Elevated bilirubin was observed in 47% of NEXAVAR-treated patients and 45% of placebo patients; CTCAE Grade 3 or 4 bilirubin elevations were reported in 10% of NEXAVAR-treated patients and 11% of placebo treated patients. Hypoalbuminemia was observed in 59% of NEXAVAR-treated patients and 47% of placebo patients; no CTCAE Grade 3 or 4 hypoalbuminemia was observed in either group.

Alkaline Phosphatase elevations were observed in 82.2% of NEXAVAR-treated patients and 82.5% of placebo patients; CTCAE Grade 3 Alkaline Phosphatase elevations were reported in 6.2% of NEXAVAR-treated patients and 8.2% of placebo treated patients; no CTCAE Grade 4 Alkaline Phosphatase elevation was observed in either group.

Thrombocytopenia was observed in 46% of NEXAVAR-treated patients and 41% of placebo patients; CTCAE Grade 3 or 4 thrombocytopenia was reported in 4% of NEXAVAR-treated patients and less than 1% of placebo patients.

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

Hypokalemia was reported in 9.4% of sorafenib treated patients compared to 5.9% of placebo patients. Most reports of hypokalemia were low grade (CTCAE Grade 1). CTCAE grade 3 Hypokalemia occurred in 0.3% of sorafenib treated patients and 0.7% of patients in the placebo group. There were no reports of grade 4 Hypokalemia.

Laboratory test abnormalities in thyroid carcinoma patients

Hypocalcaemia was reported in 35.7% of Nexavar treated patients compared to 11.0% of the patients in the placebo group. Most reports of hypocalcaemia were low grade. CTCAE grade 3 hypocalcaemia occurred in 6.8% of Nexavar treated patients and 1.9% of patients in the placebo group, and CTCAE grade 4 hypocalcaemia occurred in 3.4% of Nexavar treated patients and 1.0% of patients in the placebo group. Other clinically relevant laboratory abnormalities observed in the study are shown in Table 7.

Table 7: Treatment-emergent laboratory test abnormalities reported_ in Differentiated Thyroid Carcinoma patient _double blind period

Laboratory parameter, (in % of	**Nexavar N=207**			**Placebo N=209**		
	All	**Grade**	**Grade**	**All**	**Grade**	**Grade**

samples investigated)	Grades*	3*	4*	Grades*	3*	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 etiology of hypophosphatemia associated with NEXAVAR 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 reactions observed at this dose were primarily diarrhoea 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
ATC code: L01XE05

Mechanism of Action

Sorafenib is a multikinase inhibitor that decreases tumour 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, VEGFR-1, VEGFR- 2, VEGFR- 3, and PDGFR-ß). Several of these kinases are thought to be involved in tumour cell signaling, angiogenesis and apoptosis. Sorafenib inhibited tumour growth of the human hepatocellular carcinoma, renal cell carcinoma, differentiated thyroid carcinoma and several other human tumour xenografts in immunocompromised mice. A reduction in tumour angiogenesis were seen in models of human hepatocellular carcinoma and renal cell carcinoma and increases in tumour apoptosis wereseen in models of human hepatocellular, renal cell carcinoma and differentiated thyroid carcinoma. Additionally, a reduction in tumour cell signaling was seen in a model of human hepatocellular carcinoma and differentiated thyroid carcinoma.

Clinical Efficacy

The clinical safety and efficacy of NEXAVAR have been studied in patients with

hepatocellular carcinoma (HCC), in patients with advanced renal cell carcinoma (RCC) and in patients with Differentiated Thyroid Carcinoma (DTC).

Hepatocellular carcinoma

Study 3 (study 100554) was a Phase III, international, multi-centre, randomised, double blind, placebo-controlled trial in 602 patients with hepatocellular carcinoma. Overall survival (OS) was a primary endpoint of this study, time to progression (TTP) a secondary endpoint.

Demographics and baseline disease characteristics were comparable between the Nexavar and placebo groups with regard to age, gender, race, performance status, etiology (including hepatitis B, hepatitis C and alcoholic liver disease), TNM stage (stage I: <1% vs. <1%; stage II: 10.4% vs. 8.3%; stage III: 37.8% vs. 43.6%; stage IV: 50.8% vs. 46.9%), absence of both macroscopic vascular invasion and extrahepatic tumour spread (30.1% vs. 30.0%), and BCLC stage (stage B: 18.1% vs. 16.8%; stage C: 81.6% vs. 83.2%; stage D: <1% vs. 0%). Liver function Child-Pugh status was comparable between the Nexavar and placebo groups (A: 95% vs. 98%; B: 5% vs. 2%). Only one patient with Child-Pugh C liver dysfunction was treated in the study. Prior treatment included surgical resection procedures (19.1% vs. 20.5%), locoregional therapies (including radiofrequency ablation, percutaneous ethanol injection and transarterial chemoembolisation; 38.8% vs. 40.6%), radiotherapy (4.3% vs. 5.0%) and systemic therapy (3.0% vs. 5.0%).

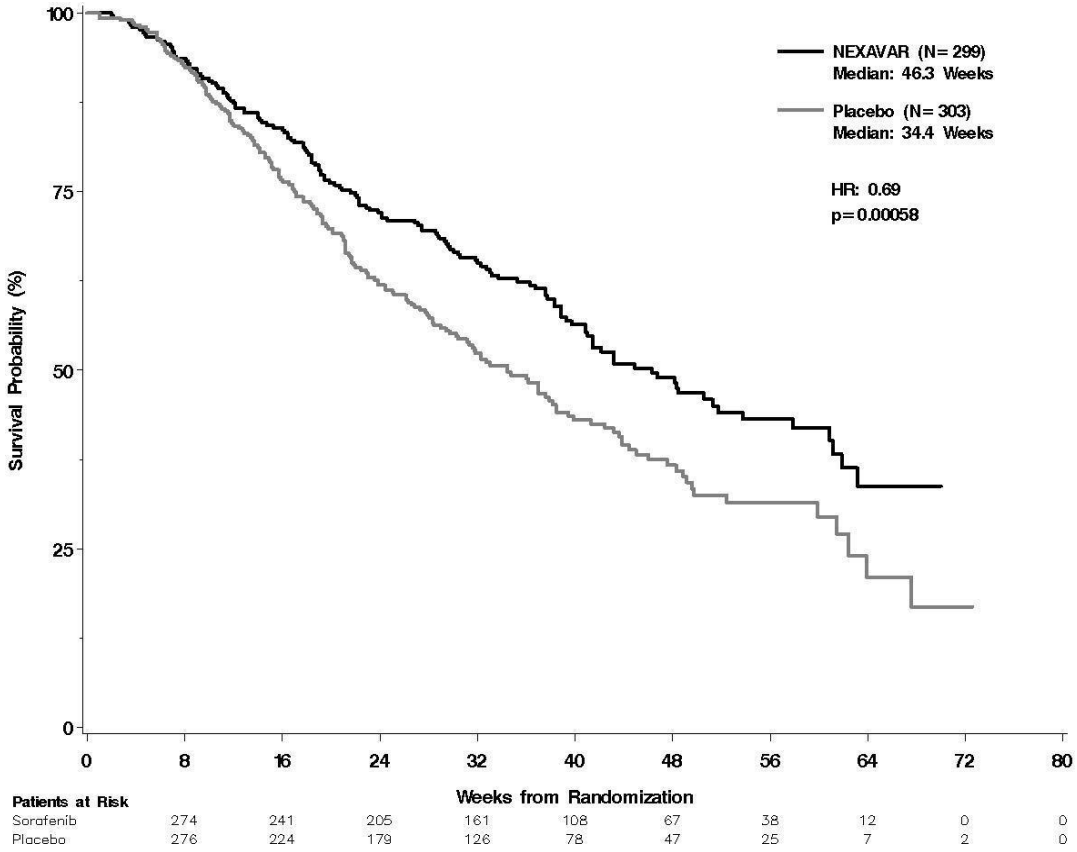
The study was stopped after a planned interim analysis of OS had crossed the prespecified efficacy boundary. This OS analysis showed a statistically significant advantage for Nexavar over placebo for OS (HR: 0.69, p= 0.00058, see Table 8 and Figure 1). This advantage was consistent across almost all subsets analysed. In the prespecified stratification factors (ECOG status, presence or absence of macroscopic vascular invasion and/or extrahepatic tumour spread, and region) the hazard ratio consistently favoured Nexavar over placebo. The time to tumour progression (TTP, by independent radiological review) was significantly larger in the Nexavar Arm (HR: 0.58, p=0.000007, see Table 8).

Table 8: Efficacy Results from Study 3 (study 100554) in hepatocellular carcinoma

Efficacy Parameter	Nexavar (N=299)	Placebo (N=303)	P-value	HR (95% CI)
Overall Survival (OS) [median, weeks (95% CI)]	46.3 (40.9, 57.9)	34.4 (29.4, 39.4)	0.00058*	0.69 (0.55, 0.87)
Time to Progression (TTP) [median, weeks (95% CI)]**	24.0 (18.0, 30.0)	12.3 (11.7, 17.1)	0.000007	0.58 (0.45, 0.74)

CI=Confidence interval, HR=Hazard ratio (Nexavar over placebo)
*statistically significant because the p-value was below the prespecified O'Brien Fleming stopping boundary of 0.0077
**independent radiological review

Figure 1: Kaplan-Meier curve of overall survival in Study 3 (study 100554, intent-to-treat population)



Renal cell carcinoma

The safety and efficacy of Nexavar in the treatment of advanced renal cell carcinoma (RCC) were studied in the following two randomised controlled clinical studies:

Study 11213, TARGET (Treatment Approaches in Renal cancer Global Evaluation Trial)

The TARGET study (Study 11213) was a Phase III, international, multi-centre, randomised, double blind, placebo-controlled study in 903 patients with advanced renal cell carcinoma who had received prior systemic therapy. Primary study endpoints included overall survival and progression-free survival (PFS). Tumour response rate was a secondary endpoint.

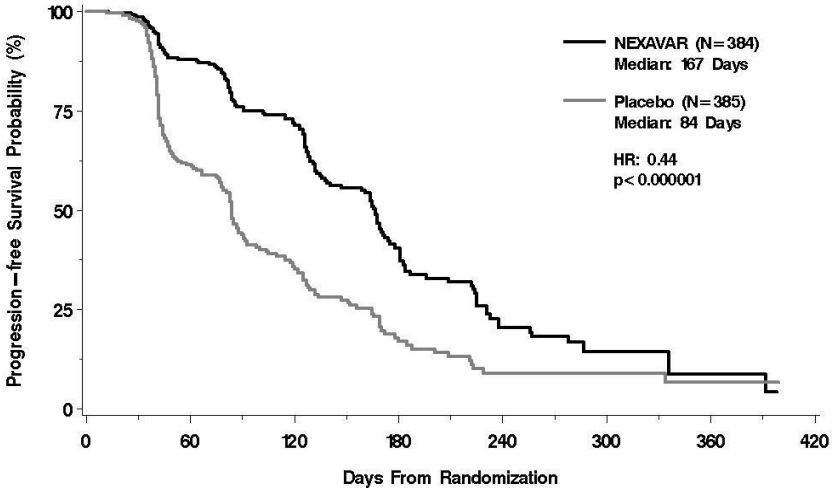
Patients were randomised to NEXAVAR 400 mg twice daily (N = 451) or to placebo (N = 452). Baseline demographics and patient characteristics were well balanced for both treatment groups. Approximately half of the patients had an ECOG performance status of 0 and half of the patients were in the low MSKCC (Memorial Sloan Kettering Cancer Centre) prognostic group.

Two planned interim analyses of survival were conducted. In the first analysis based on 220 deaths, there was an estimated 39% improvement in overall survival for patients receiving sorafenib vs placebo. The estimated hazard ratio (risk of death with sorafenib compared to placebo) was 0.72 (95% CI, 0.55-0.95; p= 0.018. The threshold for statistical significance of the interim analysis was $p < 0.0005$). As of November 30, 2005, 367 deaths were reported, comprising 68% of the protocol-specified 540 survival events, there was an estimated 30% improvement in overall survival for patients receiving sorafenib compared to placebo. A total of 216 placebo patients had crossed over to NEXAVAR treatment. The median overall survival for the sorafenib and placebo group was 19.3 months and 15.9 months, respectively.

The estimated hazard ratio (risk of death with sorafenib compared to placebo) was 0.77 (95% CI: 0.63- 0.95; p=0.015. The threshold for statistical significance of the interim analysis was p < 0.0094).

Figure 2 depicts Kaplan-Meier curves for PFS. The PFS analysis was a two-sided Log-Rank test stratified by Motzer/MSKCC prognostic risk category and country.

Figure 2: Kaplan-Meier Curves for Progression-Free Survival

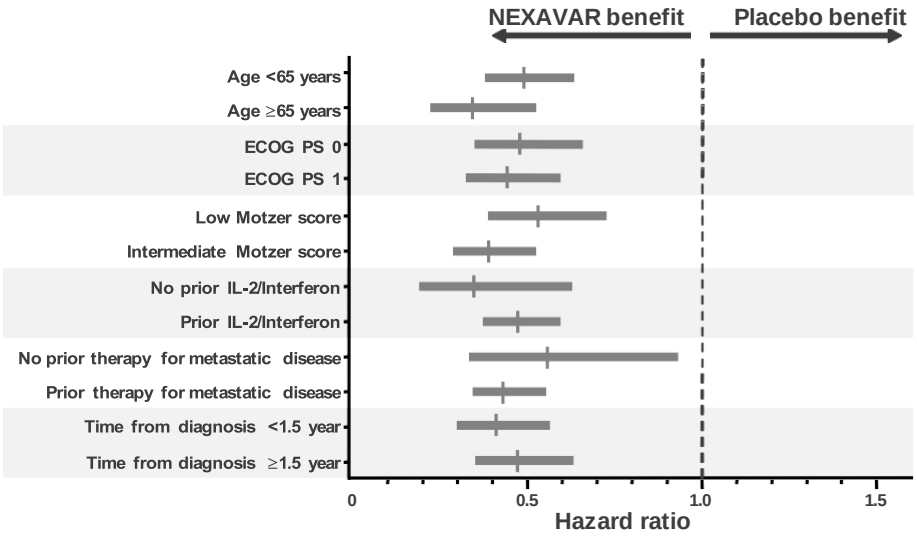


NOTE: HR is from Cox regression model with the following covariates: Motzer/MSKCC prognostic risk category and country. P-value is from two-sided Log-Rank test stratified by Motzer/MSKCC prognostic risk category and country.

The PFS analysis included 769 patients randomised to NEXAVAR 400 mg twice daily (N=384) or to placebo (N=385). PFS was evaluated by blinded independent radiological review using RECIST criteria. The median PFS was double for patients randomised to sorafenib (167 days) compared to placebo patients (84 days), representing a 56% reduction in risk of progression for patients receiving sorafenib compared to placebo. (HR=0.44; 95% CI: 0.35-0.55; p<0.000001).

A series of patient subsets were examined in exploratory univariate analyses of PFS. These results are shown in Figure 3. The effect of NEXAVAR on PFS was consistent across these subsets, including patients with no prior IL-2 or Interferon therapy (N = 137), for whom the median PFS was 172 days on NEXAVAR compared to 85 days on placebo.

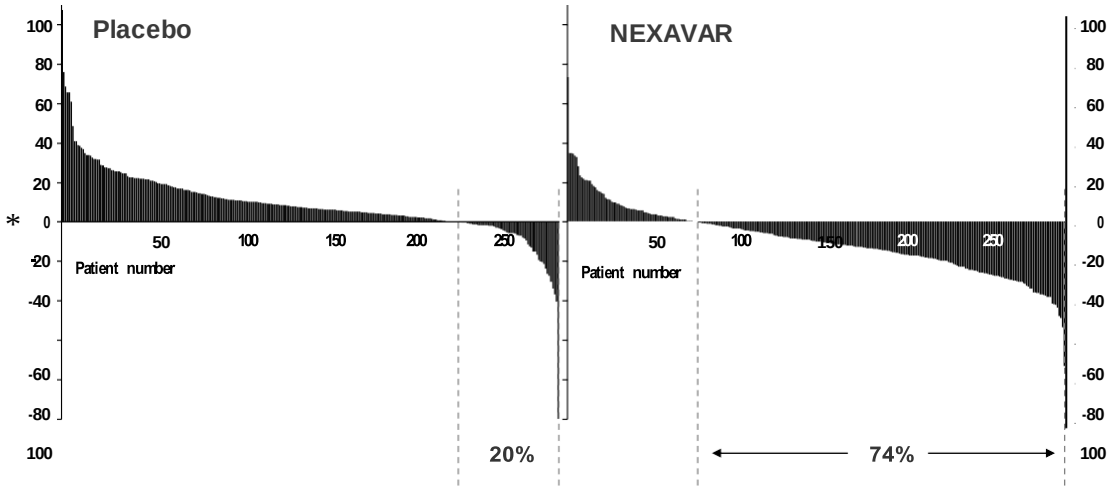
Figure 3:Progression-Free Survival in Patient Subgroups (Hazard Ratio and 95% Cl for NEXAVAR : Placebo)



Best overall tumour response was determined by investigator radiological review according to RECIST criteria. In the sorafenib group 1 patient (0.2%) had a complete response, 43 patients (9.5%) had a partial response, and 333 patients (73.8%) had stable disease. In the placebo group, 0 patients (0%) had complete response, 8 patients (1.8%) had a partial response, and 239 patients (52.9%) had stable disease.

Overall, 293 patients in the NEXAVAR group and 281 patients in the placebo group had at least one post-baseline radiographic tumour evaluation available for independent review; tumour shrinkage was reported in 74% of patients receiving NEXAVAR compared to 20% of patients in the placebo group (see Figure 4).

Figure 4: Maximum Percent Reduction of Target Lesions by Patient, Using Independent Review of Scans in the TARGET Study



* Maximum percentage reduction in tumour burden from baseline for individual patients, each of whom is represented by a bar on the graph. Bars pointing in the positive direction of the Y axis represent patients whose tumours grew, while bars pointing in the negative direction represent patients with tumour shrinkage.

Sorafenib demonstrated no overall deterioration in kidney-cancer specific symptoms (FKSI-10) or health-related quality of life compared to placebo. At 18 and 24 weeks of treatment, more patients receiving sorafenib reported improvement in total FKSI-10 score (55 and 44%,

respectively) and the physical well-being (FACT-G PWB) score (57 and 47%, respectively) versus placebo (FKSI-10, 33 and 21% and FACT-G PWB 37 and 21%, respectively).

Study 100391

Study 100391 was a Phase II randomised discontinuation trial in patients with metastatic malignancies, including RCC. The primary endpoint of the study was the percentage of randomised patients (N=65) remaining progression-free at 24 weeks. Progression-free survival was significantly longer in the sorafenib group (163 days) than in the placebo group (41 days) (p=0.0001, HR= 0.29). The progression-free rate was significantly higher in patients randomised to sorafenib (50%) than in the placebo patients (18%) (p=0.0077).

Differentiated Thyroid Carcinoma

Study 4 was a Phase III, international, multi-centre, randomised, double blind, placebo-controlled trial in 417 patients with locally advanced or metastatic differentiated thyroid carcinoma refractory to radioactive iodine.

Progression-free survival (PFS) was the primary endpoint of the study. Secondary endpoints included overall survival (OS), tumor response rate and duration of response. Following progression, patients were allowed to receive open label Nexavar. Concomitant radioactive iodine treatment was not permitted.

Patients were included in the study if they experienced progression within 14 months of enrollment and had DTC refractory to RAI. DTC refractory to RAI was defined as having a lesion without iodine uptake on a radioactive iodine (RAI) scan, or receiving cumulative RAI $\geq$ 600 mCi, or experiencing a progression after a RAI treatment within 16 months of enrollment or after two RAI treatments within 16 months of each other.

Baseline demographics and patient characteristics were well balanced for both treatment groups. Metastases were present in the lungs in 86%, lymph node in 51% and bone in 27% of the patients. Almost all patients had thyroidectomy (99.5%) and had a median delivered cumulative radioactive activity of approximately 400 mCi. Majority of patients had papillary carcinoma (56.8%), followed by follicular (25.4%) and poorly differentiated carcinoma (9.6%).

The full analysis set included 207 patients randomised to Nexavar 400 mg twice daily and 210 patients randomised to placebo. PFS was evaluated by blinded independent radiological review using RECIST criteria.

Median PFS time was 329 days (10.8 months) in the Nexavar group compared to 175 days (5.8 months) in the placebo group. The relative risk for PFS (disease progression or death) was reduced by approximately 41% in sorafenib-treated patients compared to placebo-treated subjects with a hazard ratio. Hazard Ratio (HR) =0.587; 95% Confidence Interval (CI): 0.454, 0.758; one-sided p <0.0001). (Table 9, Figure 5)

The effect of Nexavar on PFS was consistent across all subsets including geographic region, age above or below 60 years, gender, histological subtype, tumor burden and presence or absence of bone metastasis.

There was no statistical difference in overall survival between the treatment groups (the HR was 0.802; 95% CI:0.539, 1.194, one-sided p value of 0.138, Table 9). The median OS was not reached for either arm. One hundred fifty (71.4%) patients randomised to placebo and 55 (26.6%) patients randomised to Nexavar received open-label Nexavar.

No complete response (CR) according to RECIST were observed. The overall response rate (CR + partial response (PR) per independent radiological assessment was higher in the Nexavar group (24 patients, 11.6%) than in the placebo group (1 patient, 0.5%), one-sided p<0.0001. The median duration of response was 309 days (95% CI:226, 505 days) in Nexavar treated patients who experienced a PR.

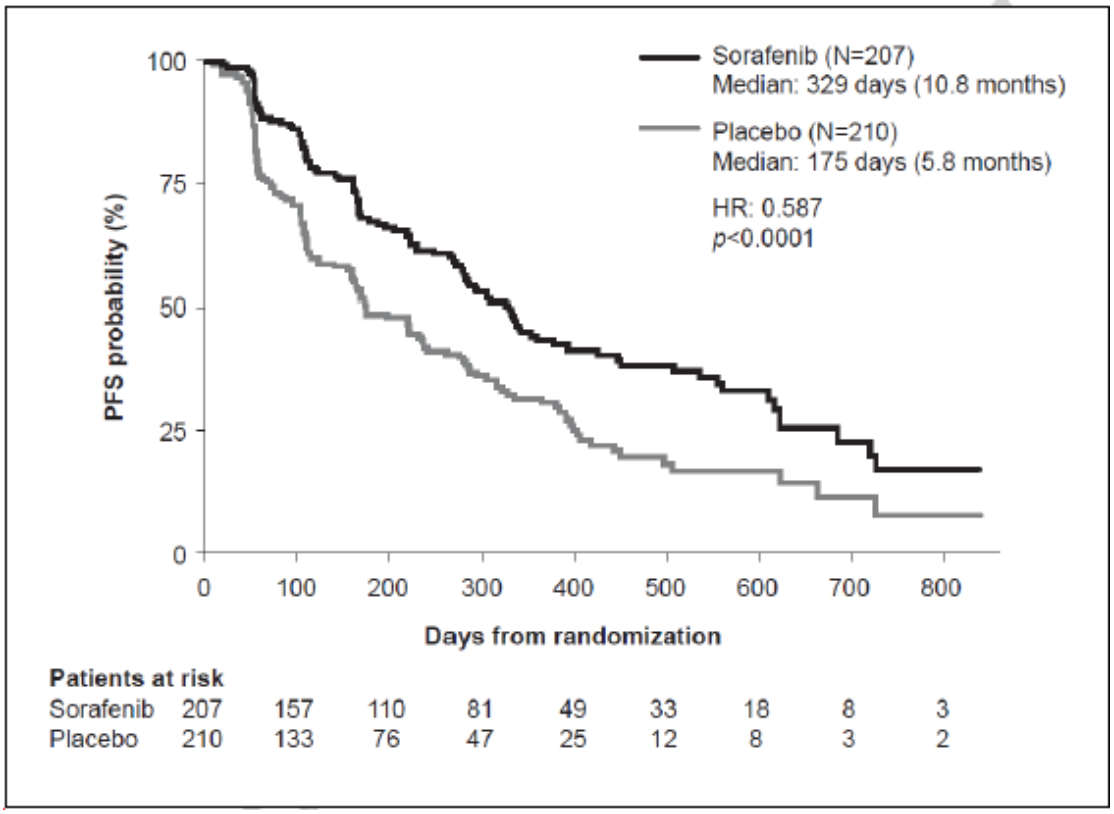
Table 9: Efficacy Results from Study 4 in Differentiated Thyroid Carcinoma

Efficacy Parameter	Nexavar (N=207)	Placebo (N=210)	P-value	HR (95% CI)
Progression-Free Survival	329 (278, 393)	175 (160, 238)	<0.0001	0.587 (0.454, 0.758)

(PFS) [median days (95%CI)]*				
Overall Survival (OS) [median days (95% CI)]	NR	NR	0.1381	0.802 (0.539, 1.194)

NR = Not reached CI=Confidence interval, HR=Hazard ratio (Nexavar over placebo) *independent radiological review

Figure 5: Kaplan-Meier curve of Progression-Free Survival (PFS) in Study 4 Thyroid carcinoma (full analysis set)



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

Steady state plasma sorafenib concentrations are achieved within 7 days, with a peak to trough ratio of mean concentrations of less than 2.

Absorption and Distribution

After administration of sorafenib tablets, the mean relative bioavailability is 38-49% when compared to an oral solution. Absolute bioavailability has not been determined. 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.

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

Metabolism/ 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%.

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 and comprises approximately 9-16% of circulating analytes at steady state.

Elimination/ Excretion

Following oral administration of a 100mg 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 glucoronidated 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 25-58 hours.

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 400mg 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 tumour types. The clinical relevance of the increased AUC in thyroid carcinoma patients is unknown.

Table 10: Steady-state plasma sorafenib AUC(0-12)SS from Differentiated Thyroid Carcinoma, RCC and HCC Patients (geometric mean (%CV) [range])

	Thyroid Cancer Pool	RCC Pool	HCC Pool
AUC(0-12)ss (mg*h/L)	74.99 (45%) [29.03-186.2] N=114	39.36 (45%) [10.69-103.9] N=136	44.98 (52%) [9.94-242.0] N=194

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. In another clinical pharmacokinetic study, concomitant administration of sorafenib 400 mg twide daily with cyclophosphamide, a CYP2B6 substrate, did not result in a clinically meaningful inhibition.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, carboplatin, 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 "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 "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 is unknown. Effects of other antibiotics have not been studied, but will likely depend on their ability to decrease glucuronidase activity.

Combination with proton pump inhibitors

Omeprazole:

Co-administered of omeprazole has no impact on the pharmacokinetics of sorafenib. No dose adjustment for sorafenib is necessary.

Pharmacokinetics in Special Populations

Elderly (above 65 years) and gender

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

Pediatric patients

There are no pharmacokinetic data in pediatric patients.

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 "Special Warnings and Precautions" and "Dosage and Method of Administration").

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 < 30 ml/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 "Dosage and Method of Administration").

5.3 Preclinical Safety Data

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

Repeat-dose toxicity studies revealed mild to moderate changes (degenerations and regenerations) in various organs.

After repeated dosing to young and growing dogs, effects on bone and teeth were observed. Changes consisted in irregular thickening of the femoral growth plate at a daily sorafenib dose of 600 mg/m^2 body surface area (equivalent to 1.2 times the recommended clinical dose of 500 mg/m^2 on a body surface area basis), hypocellularity of the bone marrow next to the altered growth plate at 200 mg/m^2/day, and alterations of the dentin composition at 600 mg/m^2/day. Similar effects were not induced in adult dogs.

Positive genotoxic effects were obtained for sorafenib in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. 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). Sorafenib was not genotoxic in the Ames test (the material contained the intermediate at 0.34%), and in an *in vivo* mouse micronucleus assay.

Carcinogenicity studies have not been performed 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.

Sorafenib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions and an increased number of external and visceral malformations. Adverse fetal outcomes were observed at an oral dose of 6 mg/m^2/day in rats and 36 mg/m^2/day in rabbits (see "Special Warnings and Precautions for Use" and "Pregnancy and Lactation").

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core: croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethyl cellulose, sodium lauryl sulfate magnesium stearate.

Film-coat: hydroxypropylmethyl cellulose, macrogol, titanium dioxide, iron oxide red.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Please refer to labels

6.4 Special precautions for storage and use

Do not store above 30°C.

6.5 Presentation

The tablets are supplied in packs of 60 tablets.

6.6 Manufactured by:

Bayer AG,
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

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